NIH NATIONAL CANCER INSTITUTE

# DIVISION OF CANCER TREATMENT AND DIAGNOSIS

## PROGRAMS AND INITIATIVES (2020-2023)

U.S. Department of Health & Human Services | National Institutes of Health

NATIONAL CANCER INSTITUTE

# DIVISION OF CANCER TREATMENT AND DIAGNOSIS

## **PROGRAMS AND INITIATIVES** (2020-2023)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

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# ACRONYMS

**AACR** – American Association for Cancer Research
**ABTC** – Adult Brain Tumor Consortium
**ACG** – Agreement Coordination Group
**ACR** – American College of Radiology
**ACRIN** – American College of Radiology Imaging Network
**ADME** – absorption, distribution, metabolism, and excretion
**ADTTP** – Advanced Developmental Therapeutics Training Program
**AERS** – Adverse Event Reporting System
**AFRRI** – The Department of Defense Armed Forces Radiobiology and Research Institute
**AHRQ** – Agency for Healthcare Research and Quality
**AI** – Artificial Intelligence
**ALCHEMIST** – Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial
**ALL** – acute lymphoblastic leukemia
**allo HCT** – allogenic hematopoietic cell transplantation
**AML** – acute myeloid leukemia
**APC** – Agent Prioritization Committee
**APEC** – Asia Pacific Economic Collaboration
**ASCO** – American Society of Clinical Oncology
**ASPR** – Office of the Assistant Secretary for Preparedness and Response
**ASTRO** – American Society for Radiation Oncology
**ATR** – ataxia telangiectasia mutated and Rad3-related kinase
**ATRF** – Advanced Technologies Research Facility
**5-aza-T-dCyd** – 5-aza-4'-thio-2'deoxycytidine
**BARDA** – Biomedical Advanced Research and Development Authority
**BBRB** – Biorepositories and Biospecimen Research Branch
**BDP** – Biopharmaceutical Development Program
**BEBPs** – biospecimen evidence-based practices
**BIQSFP** – Biomarker, Imaging, and Quality of Life Studies Funding Program
**BMT CTN** – Blood and Bone Marrow Transplant Clinical Trials Network
**BPV** – Biospecimen Preanalytical Variables Program
**BRC** – Biomarker Review Committee
**BRD** – Biospecimen Research Database
**BRISQ** – Biospecimen Reporting for Improved Study Quality
**BRN** – Biospecimen Research Network
**BRB** – Biological Resources Branch
**BRP** – Biometric Research Program
**BTB** – Biological Testing Branch
**caAERS** – cancer adverse event reporting system
**CADP** – Clinical Assay Development Program
**caDSR** – NCI Cancer Data Standards Registry and Repository
**CALGB** – Cancer and Leukemia Group B
**CAM** – complementary and alternative medicine
**Can-ACT** – Cancer Adoptive Cellular Therapy Network
**CAR** – chimeric antigen receptor
**CATCH-UP 2020** – Create Access to Targeted Cancer Therapy for Underserved Populations
**CBC** – Chemical Biology Consortium
**CBIIT** – NCI Center for Biomedical Informatics and Information Technology
**CCCT** – NCI Director's Coordinating Center for Clinical Trials
**CCDI** – Childhood Cancer Data Initiative
**CCR** – Center for Cancer Research
**CCRIG** – Cancer Cannabis Research Interest Group
**CCSS** – Childhood Cancer Survivor Study
**CCTG** – Canadian Cancer Trials Group
**CDE** – NIH Common Data Elements Repository
**CDK** – cyclin-dependent kinase
**CDMS** – Clinical Data Management System
**CDP** – Cancer Diagnosis Program
**CDR** – Comprehensive Data Resource
**CDRH** – FDA's Center for Devices and Radiological Health
**CDUS** – Clinical Data Update System
**CEP** – Career Enhancement Program
**CGCB** – Clinical Grants and Contracts Branch
**CGH** – NCI Center for Global Health
**cGLP** – current Good Laboratory Practice
**cGMP** – current Good Manufacturing Practice
**CHTN** – Cooperative Human Tissue Network
**CIB** – Clinical Investigations Branch
**CIB** – Consortium for Imaging and Biomarkers
**CIBMTR** – Center for International Blood and Marrow Transplant Research
**CIMAC-CIDC** – Cancer Immune Monitoring and Analysis Centers - Cancer Immunologic Data Commons
**CIN** – Cancer Immunotherapy Network
**CIP** – Cancer Imaging Program
**CIRB** – Central Institutional Review Board
**CIRP** – Co-Clinical Imaging Research Resources Program
**CISC** – Clinical Imaging Steering Committee
**CIT** – NIH Center for Information Technology
**CITN** – Cancer Immunotherapy Trials Network
**CLIA** – Clinical Laboratory Improvement Amendments
**CMC** – chemistry, manufacturing, and control
**cMET** – hepatocyte growth factor receptor
**CMS** – Center for Medicare and Medicaid Services
**CNS** – central nervous system
**COG** – Children's Oncology Group

**CORE** – CTEP Clinical Oncology Research Enterprise
**COTS** – commercial "off the shelf"
**CPP** – Clinical Pharmacodynamics Program
**CPTAC** – NCI Clinical Proteomic Tumor Analysis Consortium
**CPWS** – Centralized Protocol Writing Support
**CR** – complete response
**CRADA** – Cooperative Research and Development Agreement
**CRC** – NIH Clinical Research Center
**CRCHD** – NCI's Center to Reduce Cancer Health Disparities
**CRDC** – Cancer Research Data Commons
**CrD PTMA** – Career Development Project Team Member Applications
**CRF** – Case Reporting Form
**CROB** – Clinical Radiation Oncology Branch
**CRO** – contract research organization
**CRPC** – castration-resistant prostate cancer
**CRS** – Center for Research Strategy
**CRT** – 3D-conformal radiation therapy
**CRTA** – Cancer Research Training Award
**CSB** – Computational and Systems Biology Branch
**CTAC** – Clinical and Translational Research Advisory Committee
**CTB** – Clinical Trials Branch
**CTCs** – circulating tumor cells
**ctDNA** – circulating tumor DNA
**CTEP** – Cancer Therapy Evaluation Program
**CTEP-AERS** – CTEP-Adverse Event Reporting System
**CTEP-ESYS** – CTEP Enterprise System
**CTEP-IAM** – CTEP-Identity and Access Management
**CTMB** – Clinical Trials Monitoring Branch
**CTMB-AIS** – CTMB-Audit Information Service
**CTMS** – clinical trial management service
**CTOIB** – Clinical Trials Operations and Informatics Branch
**CTRP** – Clinical Trials Reporting Program
**CTSU** – Cancer Trials Support Unit
**CTWG** – Clinical Trials Working Group
**DBTB** – Diagnostic Biomarkers and Technology Branch
**DCC** – Data Coordinating Center
**DCEG** – Division of Cancer Epidemiology and Genetics
**DCIDE** – Development of Clinical Imaging Drugs and Enhancers
**DCP** – Division of Cancer Prevention
**DCTD** – Division of Cancer Treatment and Diagnosis
**DDR** – DNA damage repair
**DEB** – Diagnostics Evaluation Branch
**DHS** – Department of Homeland Security
**DIPG** – diffuse intrinsic pontine glioma
**DMG** – diffuse midline glioma
**DNMT1** – DNA (cytosine-5-)-methyltransferase 1
**DOD** – U.S. Department of Defense
**DOE** – U.S. Department of Energy
**DOI** – Digital Object Identifier
**DOT1L** – disruptor of telomeric silencing 1-like histone H3K79
**DRG** – Drug Regulatory Group
**DRSC** – Drug Resistance and Sensitivity Center
**DRSN** – Drug Resistance and Sensitivity Network
**DSC** – dynamic susceptibility contrast
**DSCB** – Drug Synthesis and Chemistry Branch
**DTC** – Developmental Therapeutics Clinic
**DTL** – Delegation of Task Log
**DTP** – Developmental Therapeutics Program
**DWI** – diffusion-weighted imaging
**EBV** – Epstein-Barr Virus
**ECOG** – Eastern Cooperative Oncology Group
**EET** – Early Phase and Experimental Clinical Trials Bank
**EGFR** – epidermal growth factor receptor
**ELSI** – ethical, legal, and social issues of biobanking
**EMR** – Electronic Medical Record
**EORTC** – European Organisation for Research and Treatment of Cancer
**EPA** – Environmental Protection Agency
**ERI** – Exceptional Responders Initiative
**ESI** – early-stage investigator
**ESYS** – CTEP Enterprise System
**ETCTN** – NCI Experimental Therapeutics Clinical Trials Network
**FDA** – Food and Drug Administration
**FDG** – fluorodeoxyglucose
**FES** – fluoroestradiol
**FGF** – fibroblast growth factor
**FISH** – fluorescence in situ hybridization
**FLT** – 18F-fluorothymidine
**FMISO** – fluoromisonidazole
**FMT** – fecal microbial transplantation
**FNLCR** – Frederick National Laboratory for Cancer Research
**FOA** – Funding Opportunity Announcement
**FTV** – functional tumor volume
**GB** – gigabytes
**GBM** – glioblastoma multiforme
**GCP** – Good Clinical Practices
**GDC** – Genomic Data Commons
**GI** – gastrointestinal
**GM-CSF** – granulocyte macrophage colony-stimulating factor
**GPNMB** – transmembrane glycoprotein NMB
**GTEx** – NIH's Genotype Tissue Expression Project
**GU** – genitourinary

**GTN** – Glioblastoma Therapeutics Network
**GYN** – gynecologic
**HCT** – hematopoietic stem cell transplantation
**HER2** – human epidermal growth factor 2
**HGF/SF** – hepatocyte growth factor/scatter factor
**HIV** – human immunodeficiency virus
**HM** – hematologic malignancies
**HR** – hormone receptor
**HTS** – high throughput screening
**IAEA** – International Atomic Energy Agency
**IAM** – Identity and Access Management
**IARC** – International Agency for Research on Cancer
**IB** – Investigator Brochure
**ICD** – informed consent document
**ICDC** – Integrated Canine Data Commons
**ICI** – immune checkpoint inhibitors
**ICN** – Immune Cell Network
**ICSS** – Integrative Cancer Surveillance System
**IDB** – Investigational Drug Branch
**IDE** – Investigation Device Exemption
**IDH-1** – isocitrate dehydrogenase-1
**IDSC** – Investigational Drug Steering Committee
**IGRT** – image-guided radiation therapy
**IHC** – immunohistochemistry
**IL-15** – interleukin-15
**IMAT** – Innovative Molecular Analysis Technologies
**IMRT** – intensity-modulated radiation therapy
**IND** – Investigational New Drug Application
**IO** – immune oncology
**IOM** – Institute of Medicine
**IOTN** – Immuno-Oncology Translational Network
**IP** – Intellectual Property
**IPAD** – Integrated Platform for Agents and Diseases
**irAEs** – immune-related adverse events
**IROC** – Imaging and Radiology Oncology Core
**IRTF** – Imaging and Radiation Treatment Facilities
**ISAC** – Independent Scientific Advisory Committee
**ITB** – Information Technology Branch
**ITCR** – Informatics Technology for Cancer Research Consortium
**ITSA** – Integrated Translational Science Award
**IWRS** – Interactive Web Response System
**LAPS** – Lead Academic Participating Sites
**LDHA/B** – lactate dehydrogenase-A and B
**LDT** – laboratory developed tests
**LOI** – Letter of Intent
**LSC** – Laboratory of Synthetic Chemistry
**Lung-MAP** – Lung Master Protocol
**MDM2** – murine double minute 2
**MDS** – myelodysplastic syndromes
**MDNet** – Molecular Diagnostic Network
**MOA** – mechanism of action
**MoCha** – Molecular Characterization Lab
**MPB** – Molecular Pharmacology Branch
**MPL** – Molecular Pharmacology Laboratory
**MRI** – magnetic resonance imaging
**MSA** – Master Service Agreement
**MTA** – Materials Transfer Agreement
**NaF** – sodium fluoride
**NAM** – novel alternative methods
**NAS** – National Academy of Sciences
**NASA** – National Aeronautics and Space Administration
**NCATS** – National Center for Advancing Translational Sciences
**NCCAPS** – NCI COVID-19 in Cancer Patients Study
**NCI** – National Cancer Institute
**NCI-MATCH** – NCI Molecular Analysis for Therapy Choice
**NCI-MPACT** – NCI Molecular Profiling Based Assignment of Cancer Therapy
**NCL** – Nanocharacterization Laboratory
**NCLN** – National Clinical Laboratory Network
**NCORP** – NCI Community Oncology Research Program
**NCTN** – National Clinical Trials Network
**NCTN-CCSCs** – NCTN Core Correlative Science Committees
**NCTVL** – National Cancer Target Validation Laboratory
**NExT** – NCI Experimental Therapeutics Program
**NGS** – Next generation sequencing
**NHGRI** – National Human Genome Research Institute
**NHLBI** – National Heart, Lung and Blood Institute
**NIAID** – National Institute of Allergy and Infectious Disease
**NIBIB** – National Institute of Biomedical Imaging and Bioengineering
**NIDDK** – National Institute of Diabetes and Digestive and Kidney Diseases
**NIH** – National Institutes of Health
**NIR** – near-infrared
**NIST** – National Institute of Standards and Technology
**NLM** – National Library of Medicine
**NLST** – National Lung Screening Trial
**NNI** – National Nanotechnology Initiative
**NOFO** – Notice of Funding Opportunity
**NP** – natural products
**NPB** – Natural Products Branch
**NPNPD** – NCI Program for Natural Products Discovery
**NPSG** – Natural Products Support Group
**NSCLC** – non-small cell lung cancer
**OAD** – Office of the Associate Director
**OCCAM** – Office of Cancer Complementary and Alternative Medicine
**OEWG** – Operational Efficiency Working Group
**OPEN** – Oncology Patient Enrollment Network
**OS** – overall survival
**PACMEN** – Pancreatic Cancer Microenvironment Network

**PADIS** – Pharmacodynamic Assay Development and Implementation Section
**PARP** – poly(ADP-ribose) polymerase
**PATS** – Protocol Abstraction Tracking System
**PBTC** – Pediatric Brain Tumor Consortium
**PD-1** – programmed cell death protein-1
**PD** – pharmacodynamics
**PDAC** – pancreatic ductal adenocarcinoma
**PDCCC** – PDXNet Data Commons and Coordinating Center
**PDHK1** – pyruvate dehydrogenase kinase 1
**PD-L1** – programmed cell death ligand 1
**PDM** – patient-derived models
**PDTC** – PDX Development and Trial Center
**PDO** – patient-derived organoids
**PDQ** – Physicians Data Query
**PDX** – patient-derived xenografts
**PDX-Net** – Patient-Derived Xenograft Network
**PEP-CTN** – Pediatric Early Phase Clinical Trials Network
**PET** – positron emission tomography
**PFS** – progression-free survival
**PI3K** – phosphoinositide 3-kinase
**PI** – principal investigator
**PIN** – Pediatric Immunotherapy Network
**PIO** – Protocol and Information Office
**PIRB** – Pathology Investigation and Resources Branch
**PIVOT** – Pediatric Preclinical In Vivo Testing Program
**PK** – pharmacokinetics
**PMB** – Pharmaceutical Management Branch
**PO** – Program Officer
**POB** – Pediatric Oncology Branch
**PR** – partial response
**PRB** – Pharmaceutical Resources Branch
**PRECINCT** – PRE-medical Cancer Immunotherapy Network Canine Trials
**PSRC** – Pancreatic Ductal Adenocarcinoma Stromal Reprogramming Consortium
**PTGB** – Preclinical Therapeutics Grants Branch
**PTMA** – Project Team Member Application
**QA** – Qualitative Assurance
**QC** – Quality Control
**QCM** – Quality Control Materials
**QIN** – Quantitative Imaging Network
**QOL** – quality of life
**RA** – 13-cis-retinoic acid
**RAB** – Regulatory Affairs Branch
**RAC** – NIH Recombinant DNA Advisory Committee
**RAID** – Rapid Access to Intervention Development
**rCBV** – relative cerebral blood volume
**RCC** – renal cell carcinoma
**RDB** – Radiotherapy Development Branch
**RECIST** – Response Evaluation Criteria in Solid Tumors
**REMARK** – Reporting Recommendations for Tumor Marker Prognostic Studies
**RFA** – Request for applications
**RFP** – Request for Proposals
**ROADMAPS** – Responses to Onocology Agents and Dosing in Models to Aid Preclinical Studies
**ROBIN** – Radiation Oncology Biology-Integration Network
**RRP** – Radiation Research Program
**RRS** – Radiation Research Society
**RSNA** – Radiological Society of North America
**RSS** – Regulatory Support Services
**RT** – radiation therapy
**SAC** – Senior Advisory Committee
**SBIR** – Small Business Innovation Research
**SCLC** – small cell lung cancer
**SEP** – Special Emphasis Panel
**SITC** – Society for Immunotherapy of Cancer
**SNMMI** – Society of Nuclear Medicine and Molecular Imaging
**SOP** – standard operating procedure
**SPOREs** – Specialized Programs of Research Excellence
**SRL** – Specimen Resource Locator
**START** – Study Abstraction Review & Tracking System
**STTR** – Small Business Technology Transfer
**TAILORx** – Trial Assigning Individualized Options for Treatment
**TCGA** – The Cancer Genome Atlas
**TCIA** – The Cancer Imaging Archive
**TCR** – T cell receptor
**T-dCyd** – 4'-thio-2'-deoxycytidine
**TM** – traditional medicine
**TMB** – Tumor Mutational Burden
**TME** – tumor microenvironment
**TMZ** – temozolomide
**TPB** – Toxicology and Pharmacology Branch
**TRF** – Targeted Radiopharmaceutical Facilities
**TRP** – Translational Research Program
**TVSL** – Target Validation and Screening Laboratory
**VCTO** – Virtual Clinical Trials Office
**VHA** – Veterans Health Administration
**VIEW** – Virtual Imaging Evaluation Workspace
**WES** – whole exome sequencing
**WG** – Working Group

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# PREFACE

**DR. JAMES H. DOROSHOW**
DIRECTOR, NCI DIVISION OF CANCER TREATMENT AND DIAGNOSIS

In these pages, we describe the Programs and Initiatives of the Division of Cancer Treatment and Diagnosis (DCTD), providing a multi-year review of the research activities and achievements of a major component of the National Cancer Institute (NCI). Though not meant to be a complete inventory of the Division's activities, this report covers advances from 2020 through 2023 and outlines important highlights that have helped to improve the diagnosis and treatment of cancer both nationally and internationally.

During the current reporting period, DCTD scientific and administrative staff brought to fruition several new programs to enhance our understanding of both novel diagnostic and therapeutic approaches. These include the formation and expansion of research consortia to:

- probe molecular mechanisms of acquired cancer drug resistance
- develop a national network for the conduct of adoptive cell therapy trials in patients with solid tumors
- develop new cancer immunotherapy models using canines with spontaneous tumors that possess intact immune systems which may be more closely reflective of human malignancies
- develop, standardize, and apply a comprehensive panel of immune-oncology biomarkers to clinical trials supported by the NCI and through industry collaborations
- develop novel approaches to glioblastoma multiforme by developing novel tumor models and pharmacodynamically supported early phase clinical trials

From 2020-2023, these complex scientific networks, all linking multiple academic institutions, were successfully launched, produced novel scientific insights, and have improved our understanding of the therapeutic mechanisms that are essential for success in the treatment of patients with cancer.

One of our greatest challenges is to increase the speed with which new treatments are brought to the millions of Americans with cancer. DCTD has continued efforts to streamline the drug discovery and development process. The NCI Experimental Therapeutics (NExT) Program allows researchers to enter candidate agents into the NCI pipeline at several critical steps, including target development or high throughput screening, the facilitation of chemical optimization of potential lead molecules, preclinical toxicology, formulation, development of biologicals, or pharmacokinetic/pharmacodynamic assay development, and the initiation of early-phase clinical trials. Researchers from academic sites, or from biotechnology concerns, may apply for access to NCI resources and expertise in any of these areas. Our goal is to facilitate the development of novel molecules that are not a major focus of current pharmaceutical research; several projects that have proceeded through the NExT pipeline have been licensed to pharmaceutical and biotechnology concerns for clinical evaluation. Many of these agents are now undergoing first-in-human clinical trials at the NCI and in the broader cancer clinical research community; several are making excellent progress toward eventual approval by the US Food and Drug Administration.

During 2020-2023, DCTD's previous efforts to improve the efficiency of its national clinical trials programs have proven remarkably fruitful. We have implemented a wide range of patient-centered approaches and improved clinical trial efficiency including: reducing data requirements for NCTN trials that do not require an FDA IND, sending oral investigational agents to local oncology sites, enhancing the use of telemedicine in clinical trials, performing data audits virtually, and facilitating electronic patient consulting. The NCI's National Clinical Trials Network (NCTN) has developed new generations of genomically based clinical trials (such as ComboMATCH, MyeloMATCH, and immunoMATCH) to be carried out across a national clinical research infrastructure with enhanced research capabilities. Similar results with respect to the initiation of a new generation of early-phase precision oncology studies that incorporate state-of-the-art immunologic and molecular characterization biomarkers are a consistent feature of all NCI's Experimental Therapeutics Clinical Trials Network (ETCTN) trials.

These major DCTD efforts have been made possible by the many talented and committed scientific and administrative staff members throughout the Division. It is my continuing privilege to work with such dedicated individuals.

# OVERVIEW

DCTD supports the development of novel diagnostic and therapeutic approaches for cancer by expediting the initial and subsequent large-scale testing of new agents, biomarkers, imaging tests, and other diagnostic and therapeutic interventions (radiation, surgery, immunotherapy) in cancer patients.

Within DCTD, the Office of the Director, nine major programs and offices, and a patient clinic work together to bring unique molecules, diagnostic tests, and therapeutic interventions from the laboratory bench to the patient bedside.

The **Office of the Director (OD)** consists of DCTD Leadership and the Functional Operations and Research Operations Teams, which are responsible for coordinating and supporting activities of the division's programs, offices and clinic.

The **Biometric Research Program (BRP)** provides state-of-the-art expertise in the areas of biostatistics, bioinformatics, and computational biology for research areas of the DCTD and other NCI components.

The **Cancer Diagnosis Program (CDP)** stimulates, coordinates, and funds specimen resources, databases related to those specimens, and research on in vitro diagnostics and improved technologies to better characterize tumors, leading to improved patient treatment.

The **Cancer Imaging Program (CIP)** uses new technologies to expand the role of imaging in noninvasive diagnosis, identification of disease subsets in patients, disease staging, and treatment monitoring. Among these are nanotechnologies and artificial intelligence methods to extract comprehensive non-visual information from medical images to predict biological and clinical correlates.

The **Cancer Therapy Evaluation Program (CTEP)** functions as DCTD's primary clinical evaluator of new anticancer agents, radiation treatments, and surgical methods. To accomplish this, the program administers the National Clinical Trials Network (NCTN) and the Experimental Therapeutics Clinical Trials Network (ETCTN) along with several specialty networks in immunotherapy, brain tumors, and pediatric cancers.

The **Developmental Therapeutics Program (DTP)** serves as a vital resource in discovering potential cancer therapeutics and acquiring information pertaining to their preclinical development. The program provides preclinical research materials and pharmacologic services to extramural investigators and manufactures new small molecules and biologics in bulk quantities under GMP conditions for use in clinical studies conducted under U.S. Food and Drug Administration (FDA) Investigational New Drug Applications.

The **Radiation Research Program (RRP)** provides expertise to investigators who perform novel research in radiation oncology, biology, physics and technology, systemic radionuclides and other sources of energy (hyperthermia and photodynamic therapy). The program also assists in establishing future directions for radiation research related to cancer and normal tissue injury.

The **Translational Research Program (TRP)** translates novel scientific discoveries from laboratory and/or population studies to the clinic for testing in cancer patients and determines the biological basis for clinical observations.

The **Office of Cancer Clinical Proteomics Research (OCCPR)** integrates proteomics and proteogenomics into cancer research science to improve cancer diagnosis, treatments, and outcomes.

The **Office of Cancer Complementary and Alternative Medicine (OCCAM)** aims to increase the amount of high-quality cancer research and information about the use of complementary and alternative modalities.

The **Developmental Therapeutics Clinic (DTC)** in the NIH Clinical Center on the Bethesda campus works to perform early phase clinical trials that include development of pharmacodynamic assays for subsequent use in the extramural community as part of the Experimental Therapeutics Clinical Trials Network (ETCTN).

# JAMES H. DOROSHOW
## DIRECTOR

Dr. James H. Doroshow has been the Director of NCI's Division of Cancer Treatment and Diagnosis since 2004. He continues to pursue his own research program as a Senior Investigator in the Developmental Therapeutics Branch of the NCI's intramural Center for Cancer Research. He is the author of over 500 full-length publications in the areas of molecular pharmacology, the role of oxidant stress in tumor cell signal transduction, and novel therapeutic approaches to solid tumors. From 1983 to 2004, Dr. Doroshow was the Chairman of the City of Hope Comprehensive Cancer Center's Department of Medical Oncology and Therapeutics Research, and Associate Cancer Center Director for Clinical Investigation. He has served on the Oncologic Drugs Advisory Committee of the U.S. Food and Drug Administration, the Medical Oncology Board of the American Board of Internal Medicine, and as Chair of two NIH study sections: Experimental Therapeutics II and Subcommittee A, Cancer Centers. He is currently a member of both the Forum on Drug Discovery, Development, and Translation and the National Cancer Policy Forum of the National Academy of Medicine of the National Academies of Science. Dr. Doroshow received his A.B. degree magna cum laude from Harvard College in 1969 and graduated from Harvard Medical School in 1973. Following an Internal Medicine residency at the Massachusetts General Hospital, he completed a fellowship in Medical Oncology at the Medicine and Clinical Pharmacology Branches of the National Cancer Institute, NIH.

# DIVISION OF CANCER TREATMENT AND DIAGNOSIS (2025)

**Dr. James H. Doroshow**
Division Director

**Dr. Toby T. Hecht**
Deputy Director


Additional DCTD information is available at https://dctd.cancer.gov and https://cancer.gov.

PROGRAMS AND INITIATIVES (2020-2023)

# MAJOR INITIATIVES SUPPORTING THE CANCER COMMUNITY

## CURRENT RESEARCH EMPHASIS

DCTD supports research across the entire spectrum of areas related to diagnostic and therapeutic approaches to the treatment of cancer. **Figure 1** depicts the distribution of more than $1.4 billion in grant funding managed by DCTD in 2023 across the 6 Programs and 2 Offices with grant portfolios.

## FUTURE RESEARCH EMPHASIS

Over the recent past, NCI has had the opportunity to participate in two major strategic planning programs (including the Clinical Trials and Translational Research Advisory Committees (CTAC) effort to streamline clinical trials) that have identified major areas of research emphasis that are poised for rapid progress. To do so we have emphasized:

### DEVELOPMENT OF A NEW GENERATION OF PRECISION MEDICINE CLINICAL TRIALS

- MyeloMATCH
- ComboMATCH
- ImmunoMATCH

### DEVELOPMENT OF IMPROVED PATIENT-DERIVED MODELS TO ENHANCE EARLY PHASE CLINICAL TRIALS

- Developing a consortium of NCI-Designated Cancer Centers to produce and standardize the development and molecular characterization of patient-derived xenograft (PDX) models of understudied human tumors
- Developing a novel high-throughput drug screening platform for cancer organoids
- Coordinating testing of novel targeted therapeutic agent combinations in preclinical PDX trials focusing on rare tumors to develop the rationale for subsequent clinical studies in the NCI's Experimental Therapeutics Clinical Trials Network (ETCTN)

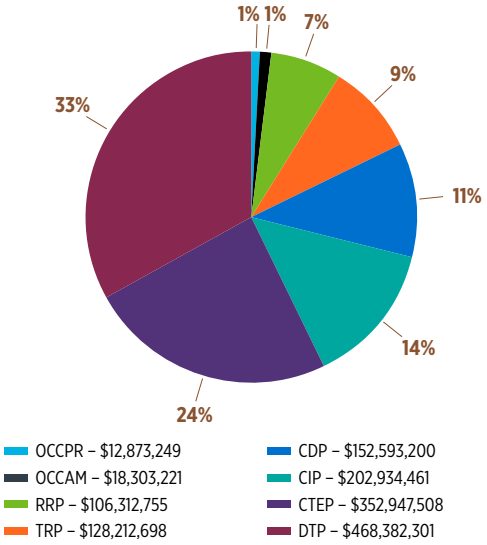



FIGURE 1: DISTRIBUTION OF DCTD 2023 GRANT FUNDING ACROSS PROGRAMS.

### DEVELOPMENT OF CANCER IMMUNOTHERAPIES

- Developing a laboratory consortium to standardize the methodology for analyzing tumor specimens and associated microenvironmental elements for the expression and interaction of immunomodulatory molecules from patients entered on immuno-oncology clinical trials
- Developing novel clinical trials in solid tumors of adoptive cellular immunotherapy

### STREAMLINING THE CLINICAL TRIALS PROCESS FOR NCI – SUPPORTED NETWORKS

- Developing new tools to program electronic health record systems rapidly with the treatment and data collection requirements for new studies
- Developing a virtual clinical trials office and program to facilitate patient screening, data entry, and adverse events tracking at institutions in both rural and urban settings that have been challenged by the inability to retain experienced clinical trials staff

# CURRENT PROGRAMS AND INITIATIVES

## COVID-19 AND CANCER CLINICAL TRIALS

### Clinical Trial Modifications during the COVID-19 Pandemic

The onset of the COVID-19 public health emergency in the U.S. in early 2020 dramatically impacted the conduct of clinical research. Due to concerns about the rapid spread of the novel coronavirus and its negative effect on hospitals, clinics, physician offices, and patients' ability to travel, NCI quickly introduced measures to address challenges for patients enrolled on clinical trials by mitigating immediate hazards to them and ensuring continuity of their care. These measures included:

- Rapidly employing telehealth visits for patient assessments and monitoring in lieu of requiring patients to visit health centers
- Shipping oral IND agents directly from clinical sites to patients
- Incorporating remote consent and auditing processes
- Coordinating care for patients on clinical trials with local providers

These modifications to how trials were conducted helped weekly enrollments in the Cancer Therapy Evaluation Program's (CTEP) clinical trials networks rebound from a 45% decrease in mid-March 2020 to pre-pandemic levels by mid-September 2020. Accrual in November and December 2020 followed similar patterns seen in 2019, with short-term drops around major holidays. Non-white participants were enrolled to CTEP-supported clinical trials at similar monthly rates throughout 2019 and 2020, with slightly higher overall enrollment in 2020 (23.7% vs. 22.7%).

In July 2020, CTEP surveyed 255 investigators from academic and community sites to assess changes in research practices and obtain feedback on NCI's modified processes during the pandemic. Respondents rated the usefulness of the modified trial processes on a scale of 1 to 5, with 5 being the most useful. Respondents rated telehealth as the most useful (avg. 4.6/5), followed by shipping oral IND agents to enrolled patients (4.5/5), remote informed consent (4.2/5), coordinating care with local providers (3.9/5), and remote auditing (3.7/5). CTEP has retained these adaptations as key components of our trial networks and is actively exploring other ways to streamline clinical trial conduct to reduce burdens on clinical research staff and trial participants.

### Effects of COVID-19 on Cancer Clinical Trial Accrual

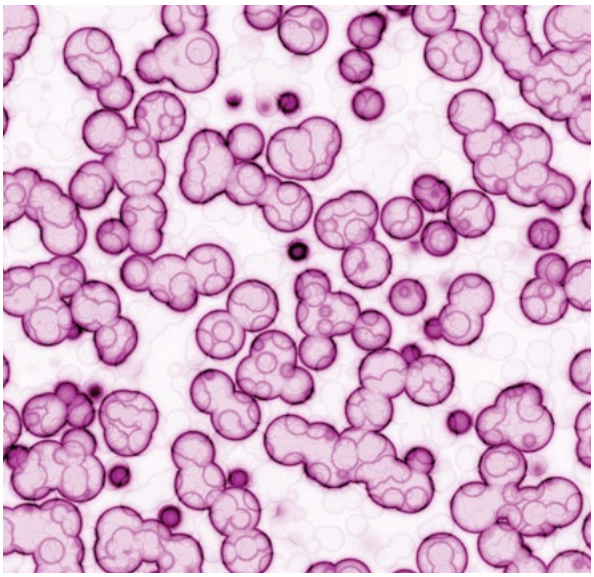
Enrollment of new patients to cancer clinical trials declined sharply beginning in March 2020 and continued throughout the COVID-19 pandemic. Accrual to studies in NCI's National Clinical Trials Network (NCTN), dropped by about 50% in the first week of March 2020. An analysis conducted on the patterns of enrollment in cancer clinical trials during the COVID-19 pandemic at NCI-designated cancer centers revealed the same precipitous drop in enrollment in March 2020 and a nearly 15% decline in annual total enrollment for 2020 compared with 2019. This year-over-year decline was seen in all categories of studies conducted at Cancer Centers (industrial, externally peer-reviewed, and institutional), except for national trials (Prindiville, 2022). The sharp decline in enrollment surrounding the start of the pandemic affected phase 3 trials to a lesser extent than phase 1 and 2 trials, and over time, phase 3 trials have had a stronger recovery than phase 1 and 2 trials.

Multiple factors contributed to the sharp decline in enrollment early during the COVID-19 pandemic including major operational challenges faced by sites:

- Limited ability to conduct in-person study activities, including informed consent, patient visits to receive investigational study drugs, and assessments of patient safety and study adherence
- Requirement for exclusive use of imaging and laboratory facilities specified by trial documents
- Requirement to collect low-grade adverse events despite the potential lack of clinical relevance to study endpoints
- Limited access to cancer care personnel/facilities and reprogramming of clinical research resources to clinical care

NCI's clinical trials programs, in consultation with the U.S. Food and Drug Administration, quickly identified several measures that could be taken to address these barriers and allow for the continuation of care for current patients as well as the ability to offer enrollment to new participants. The response included:

- Use of electronic consenting
- Shipping oral investigational agents directly to local sites
- Initiating electronic, rather than in-person, study audits
- Facilitating the use of telemedicine for study visits



- Limiting the impact of minor study deviations on trial conduct/evaluation for study sites
- Implementing decentralized testing for required lab and imaging studies to reduce the travel burden to patients

The implementation of these public health emergency flexibilities allowed patients already enrolled in a study to continue investigational therapies and new patients to be enrolled. These measures contributed to the rebound in enrollment and demonstrated that certain aspects of clinical trials could be decentralized.

Despite these flexibilities, staff turnover or a decrease in clinical trial staff due to reassignment of clinical trials research staff to other health care activities continued to be a major challenge for sites, affecting their ability to enroll new patients. A survey conducted of the NCI Cancer Centers in November 2021 suggested significant workforce retention challenges that have continued well beyond the early phases of the pandemic. The ongoing lack of enrollment levels recovering to pre-pandemic levels may in part be due to ongoing problems with clinical trials workforce retention.

## The NCI COVID-19 in Cancer Patients Study (NCCAPS)

Most of the clinical trials leading to the approval of vaccines against SARS CoV-2 were conducted in the general population and did not include people with cancer; therefore, it was not known whether individuals with compromised immune systems, such as those undergoing treatment for cancer, could mount an adequate immune response to vaccination. NCCAPS was launched in May 2020 with the goal of describing risk factors, biologic correlates, and outcomes of patients on cancer treatment who were infected with SARS CoV-2. By February 2023 more than 1,700 eligible patients, including 169 pediatric patients, were enrolled in this longitudinal study with up to two years of follow-up. Research blood specimens were collected at multiple timepoints over the first year on the trial, and imaging studies were collected during the first 6 months on study. Information on hospitalizations, treatment received for COVID-19, cancer therapy, and treatment disruptions related to COVID-19 infection was captured.

In an initial publication of NCCAPS analysis (Best, 2023), the association between SARS CoV-2 vaccination and disease severity in cancer patients was assessed. Vaccinated patients with cancer were significantly less likely to develop severe disease (defined as hospitalization for COVID-19 or death within 30 days of SARS CoV-2 infection) compared with unvaccinated patients (odds ratio = 0.44, 95% confidence interval = 0.28 to 0.72, $P < .001$). The results were consistent across subgroups by cancer and treatment type and suggest clinical benefit for COVID-19 vaccination among patients with cancer receiving active immunosuppressive treatment.

One key aspect of the NCCAPS study is the longitudinal collection of both clinical data and biospecimens from patients with a variety of underlying cancer types and treatments,

as this will allow detailed analysis of the immune response to COVID-19 infection in key subgroups. Planned analyses include characterization of immune cell phenotype and cytokine response, development of antibodies and neutralizing antibodies, and assessment of abnormalities in the coagulation cascade. As we transition from the pandemic to the endemic phase of COVID-19, patients with cancer remain at risk for higher morbidity and mortality due to COVID-19 infection. These analyses will improve our understanding of potential risk factors for severe outcomes among patients with cancer and will lead to a better understanding of the immune underpinnings of SARS CoV-2 infection.

## MODERNIZING CLINICAL TRIALS

### The NCI Clinical Trials and Translational Research Committee (CTAC) Working Group Report

Cancer clinical trials have become more complex and expensive to conduct and often collect more data than needed. In October 2019, the NCI CTAC established a Strategic Planning Working Group (WG) charged with re-assessing NCI's strategic vision for its clinical trials system for 2030 and beyond and making recommendations to achieve that vision. The group articulated a bold vision for flexible, faster, simpler, less expensive, and high-impact trials that seamlessly integrate with clinical practice. To achieve this vision, the WG emphasized the need for modernizing clinical trials through streamlining processes for clinical trial design and execution, focusing on essential endpoints, decreasing regulatory hurdles, broadening trial access, and increasing efficiency of data collection. The WG's report[1] outlined 15 recommendations and initiatives centered on the following essential themes:

- Trial complexity and cost
- Decentralized trial activities
- Promoting accrual and access
- New data collection approaches
- Patient-reported data for clinical trials
- Operational burden
- Statistical issues
- Workforce outreach and training

Because the WG's deliberations occurred largely during the COVID-19 pandemic, they were acutely aware of how some of the clinical trials flexibilities initiated at this time reduced operational burden and allowed certain aspects of trials to be conducted closer to patients' homes. The WG's recommendations thus incorporated some of these principles and emphasized that the NCI consider making certain flexibilities in trial procedures permanent.

In July 2022, NCI convened the CTAC Streamlining Clinical Trials Working Group to advise on the implementation of the recommendations from the WG related to data collection and electronic health records. This Streamlining Clinical Trials Working Group issued an interim report[2] in November 2022 (to be updated in 2024) on ways to limit trial data collection in late phase trials to data elements essential for the primary and secondary objectives of the trial. A set of standard practices for data collected in NCI phase 3 and phase 2/3 adult Investigational New Drug-exempt treatment trials was developed for the following categories:

- Adverse events
- Medical history
- Concomitant medications
- Physical exam
- Laboratory tests
- Imaging and other assessment procedures
- Patient-report data

Implementation of the new standard practices is underway and is anticipated to materially reduce the operational burden of participating in the NCI's National Clinical Trials Network (NCTN) trials, which is critical to sustaining a publicly supported late-phase cancer clinical trial enterprise. While the initial focus of the standard practices for data collection is on IND-exempt trials, many of the principles could be extended, in certain clinical and regulatory contexts, to studies being conducted under an IND.

[1] Strategic Planning Working Group Report: https://www.cancer.gov/about-nci/advisory-boards/ctac/working-groups/strategic-planning-working-group/november-2020.pdf
[2] Streamlining Clinical Trials Working Group Interim Report: https://www.cancer.gov/about-nci/advisory-boards/ctac/working-groups/streamlining-clinical-trials-working-group/november-2022.pdf

## Centralized Coordination and Standardization of Electronic Health Record (EHR) Pilot

Multi-institutional clinical trials, like those performed by the NCTN, the Experimental Therapeutics Clinical Trial Networks (ETCTN), and the NCI Community Oncology Research Program (NCORP), use EHRs to support the delivery of both standard-of-care and investigational care and treatments. EHRs are essential, but they are complex. For example, EHR-based care plans may vary considerably for routine therapies between organizations due to differences in EHR systems or in local implementation of the same EHR system.

Treatment plans for investigational therapies can change from study to study, site to site, or even among different commercial insurers. In addition, estimates suggest that 20-30% of clinical trials and 40-50% of treatment plans built in EHRs are never used. This occurs because not all trials activate, or only a few or no patients enroll on a trial. Although it is possible that an EHR will not be used, individual plans must be developed for each trial in preparation to provide support should it be needed. A recent NCTN survey estimated a minimum of 26.5 hours of effort is required to build the treatment plan for a single study arm with a major EHR vendor.

The current process to configure the EHR is inefficient, expensive, and creates a roadblock to study participation. The repetitive efforts to develop and modify instances of EHR systems across potentially hundreds of institutions are inefficient and costly. The EHR study build must be complete to activate the study at a site and enroll a patient, and they must be modified with each study amendment. In addition, the lack of standardization across different EHRs increases the local administrative burden associated with data collection and reporting to an Electronic Data Capture system. The numerous challenges associated with the EHR study build contribute to delayed activation times and inadequate participation in NCI-supported clinical research.

In the summer of 2020, the NCI approved administrative supplements to multiple P30 Cancer Center grants to collaboratively perform exploratory work to facilitate the development of standardized EHR treatment plans for NCI-supported clinical trials applicable across a broad range of clinical research sites. Two consortia received supplements: CTRAC (Clinical Trials Rapid Activation Consortium), led by MD Anderson, and Big Ten EHRC (Electronic Health Record Consortia), led by Indiana University. The consortia worked to:

- Retrospectively identify the tasks across the consortia to analyze and identify the similarities and difference between the SOPs, policies, and workflows associated with EHR treatment plans at each member site for NCI clinical trials
- Identify opportunities for standardization across member sites
- Streamline the work process to develop and maintain study-specific content for clinicians to complete the EHR-mediated tasks at multiple sites

In the spring of 2023, NCI assembled a single consortium and changed the funding mechanism for this project. NCI provided support through the Frederick National Laboratory for Cancer Research (FNLCR) and subcontracts were issued to:

MD Anderson Cancer Center (Lead)
City of Hope
Dana-Farber Cancer Institute
Indiana University
University of Colorado
University of Michigan
University of Wisconsin

The scope of this project is to expand on the work of the P30 Cancer Center grants to:

- Develop standard representations of protocol-specified pharmacotherapy and other required therapeutic and assessment procedures
- Develop an approach to "packaging" the standardized requirements in a form that can either be imported directly into a site's EHR or at least will facilitate local customization
- Build a library of modules that are considered likely to be reusable across trials
- Pilot the central EHR study build, distribute to participating sites with three or four NCI studies, and evaluate the possibility to expand to additional sites at the completion of the pilot

## Expanding Eligibility Criteria in CTEP-Sponsored Trials

Guidelines for clinical trial eligibility are important to provide safety for patients and to ensure that the study population is well characterized. Excessively narrow criteria can be an impediment to achieving progress in the development of cancer therapeutics, potentially excluding many people, and generating study results that may not inform treatment options for the diversity of people with a particular cancer. Therefore, it is vital for investigators to carefully consider whether each eligibility criterion in a clinical trial is too narrow and would unnecessarily exclude patients that might benefit from the study.

The Cancer Therapy Evaluation Program (CTEP) has played a major role towards implementing the American Society of Clinical Oncology / Friends of Cancer Research (ASCO/Friends) initiative for modernizing eligibility criteria in cancer clinical trials (Denicoff, 2022). A CTEP pilot effort was launched after review of the CTEP clinical trials portfolio indicated that most trials did not adopt the ASCO/Friends recommendations in the first several years after publishing. The CTEP pilot implementation team was formed to include specific reviews and requirements for study teams to provide scientific justification for departure from the ASCO/Friends recommendations. This effort led to upwards of 80-90% of trials implementing more inclusive eligibility criteria. Goals now include increasing the number of clinicians offering more diverse patients the opportunity to participate in clinical trials, which will lead to more representative populations participating, and implementing efficient processes to make trial results more generalizable.

The era of precision oncology increases the potential for limitations in clinical trial participation due to molecular profiling of participants' tumors. Therefore, eligibility criteria must be as broad as safely possible to achieve diverse and representative populations in future clinical trials. CTEP will continue to collaborate with investigators and industry partners in our shared responsibility to expand eligibility and access to trials.

## Create Access to Targeted Cancer Therapy for -Underserved Populations (CATCH-UP.2020)

CATCH-UP.2020 was an ETCTN initiative supported by NCI P30 administrative supplement awards at eight NCI-designated comprehensive cancer centers. NCI created CATCH-UP.2020 to enhance access to early-phase NCI ETCTN precision medicine cancer clinical trials for federally underserved populations. NCI funded the following eight NCI-designated cancer centers to support the CATCH-UP.2020 initiative:

- Atrium Health Wake Forest Baptist Comprehensive Cancer Center
- Chao Family Comprehensive Cancer Center–University of California Irvine
- Dartmouth-Hitchcock Norris Cotton Cancer Center
- Karmanos Cancer Institute–Wayne State University
- O'Neal Comprehensive Cancer Center–University of Alabama at Birmingham
- Perlmutter Cancer Center of New York University Langone Health
- Sylvester Comprehensive Cancer Center-University of Miami Health System
- University of Kansas Cancer Center

The eight CATCH-UP.2020 cancer centers were expected to accrue a minimum of 24 patients annually to early-phase NCI ETCTN trials in which at least 50% of patients were required to belong to a federally underserved population. Over the course of 18 months, the CATCH-UP.2020 cancer centers accrued 246 patients to NCI ETCTN trials, and 127 (52%) patients belonged to a federally underserved population. The CATCH-UP.2020 project demonstration led to the formation of new NCI ETCTN Equity-Focused Clinical Investigator Teams (E-FCITs), which allows eligible and former CATCH-UP.2020 cancer centers to further enhance NCI ETCTN infrastructure to advance accrual of patients from underserved populations to clinical trials.

The CATCH-UP.2020 experience has been reported in a peer-reviewed publication (Baranda, 2023), presented at an ASCO program session (2023), and in the ASCO educational book titled Equitable Access to Clinical Trials: How Do We Achieve It? (Acuña-Villaorduña, 2023). The success of the CATCH-UP.2020 program led to a series of competitive supplements to the ETCTN UM-1 grants in 2023 that continues to build E-FCITs. Starting in 2024, the E-FCIs will begin meeting quarterly to share progress and best practices in the recruitment of underserved populations onto early phase clinical trials.

## Pragmatica-Lung

Pragmatica-Lung is a phase 3 clinical trial activated in March 2023 for people with stage 4 non-small cell lung cancer (NSCLC). Patients enrolled in the trial will be randomly assigned to receive either standard chemotherapy or a combination of ramucirumab (Cyramza) and pembrolizumab (Keytruda) (**Figure 2**). Patients aged 18 or older with stage 4 NSCLC whose cancer has continued growing after treatment with immunotherapy and chemotherapy may be eligible. Researchers hope to enroll 700 people to the trial; the enrollment as of December 2023 is 257.

The goal of the trial is to determine if this drug combination can help those with advanced lung cancer live longer than with standard chemotherapy. The combination being studied was tested in an earlier phase 2 clinical trial that was part of the Lung-MAP precision medicine trial. In the Lung-MAP trial, the combination seemed to help certain people with stage 4 lung cancer live longer. Pragmatica-Lung will enroll more and a wider variety of participants than Lung-MAP to confirm if the combination of pembrolizumab and ramucirumab helps patients live longer than if they received standard chemotherapy.

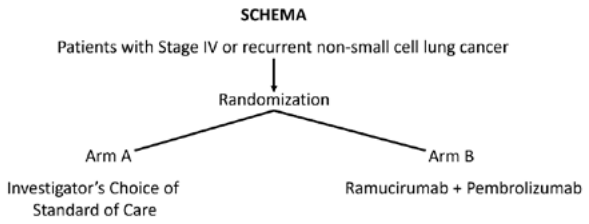



FIGURE 2: LUNG-PRAGMATICA SCHEMA.

Pragmatica-Lung is designed to remove many of the barriers that prevent people from joining clinical trials. Many trials restrict who can join based on performance status, but Pragmatica-Lung allows people with lower performance status who are more representative of people with advanced lung cancer, to participate. The trial was designed to remove many of the extra tests, data collections, and secondary study goals that are often included in clinical trials. Although these other tests may provide important information, they tend to place a large burden on study doctors and patients. Ramucirumab and pembrolizumab are FDA approved, and their side effects are well known; therefore, only severe side effects from the two-drug combination are being recorded.

NCI is sponsoring Pragmatica-Lung, and the trial is being led by the SWOG Cancer Research Network in collaboration with the Alliance for Clinical Trials in Oncology. The study will be conducted with participation from the four US NCTN groups that focus on cancer in adults. The pharmaceutical companies, Merck and Eli Lilly and Co., are each providing one of the study drugs as well as extra funding for the trial. This trial is part of a broader effort by NCI and FDA to modernize clinical trials. The hope is that this type of simplified trial will be less burdensome to patients and investigators and serve as a model for future cancer clinical trials.

## The NCI Virtual Clinical Trials Office (VCTO) Pilot Program

Structural, patient, and provider barriers limit the participation of patients in cancer clinical trials in the United States. This results in <10% of cancer patients enrolling in a clinical study. Low participation is even more pronounced for minority patients and those in rural and underserved areas.

The complexity of trial documentation and patient selection requires highly trained personnel that are coveted by private clinical research organizations (CROs) and are unlikely to remain in smaller academic or private practices. This problem has been further aggravated by the COVID-19 pandemic that precipitated the departure of research personnel from clinical sites to seek greater workplace flexibility and higher pay with larger cancer centers or CROs.

DCTD, through FNLCR, is working to rapidly provide virtual research support to improve accrual to NCI clinical trials, especially for patients from minority and underserved populations, by addressing the shortage of trained personnel at clinical research sites and bringing remote research support teams to the oncology practices/institutions. These virtual research support staff will help identify, screen, and enroll patients on NCI clinical trials and support the data capture and management requirements for the NCI-sponsored clinical sites.

The virtual services will be provided to a limited number of sites and clinical trials during the first year to allow time to develop best practices and procedures for the virtual program. The initial sites will include a combination of NCORP network sites and geographically distinct academic institutions where staffing needs have been identified. Priority will be given to sites with a concentration of minority and underserved populations. The goal is to ensure the virtual services do not interfere with local policies and processes but do support clinical trial activities based on the site's needs. The plan is to continue to add more sites and clinical trials over the course of the pilot, so sites may be selected to join at different points in time.

Remote support will include the following activities:

- Screening patients to identify potential participants for clinical studies
- Working with site physicians to facilitate the enrollment of patients into clinical trials
- Working with site staff to coordinate care and provide education on research needs/requirements and virtual procedures
- Coordinating study visits and procedures, providing reminders, reporting adverse events, and addressing patient questions
- Abstracting data from the local electronic health record system into the NCI Clinical Data Management System (Medidata Rave)

This pilot program is not a funding program; it is being developed to evaluate whether the provision of virtual clinical trials research services could help to remedy workforce shortages that may have been exacerbated by the COVID-19 pandemic.

## NCI'S PRECISION MEDICINE CLINICAL TRIALS

### NCI Molecular Analysis for Therapy Choice (NCI-MATCH)

NCI-MATCH, which opened for enrollment in August 2015, was the largest precision medicine trial in history and completed accrual at the end of 2022. The goal of NCI-MATCH was to determine if treatment based on a tumor's genetic abnormality matched to a molecularly targeted agent is effective for treating tumors, regardless of their tumor type. The ECOG-ACRIN Cancer Research Group, part of the NCI's National Clinical Trials Network, and DCTD's Cancer Diagnosis Program led the trial, with assistance from DCTD's Cancer Therapy Evaluation Program, Biometric Research Program, and additional committees.

The first part of the trial was the screening and enrollment phase, which required the prospective collection of a fresh tumor biopsy followed by targeted next generation screening (NGS) and immunohistochemical (IHC) assays performed in one of four Core Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories. The 250 genes in the NGS panel were carefully selected based on the targeted genetic abnormalities in human tumor cells responsive to the trial agents. Patients could be enrolled under the NCI-MATCH Master protocol umbrella if their tumor contained a genetic abnormality that was the therapeutic target in one of the 24 study arms open at that time. Agent selection based on the molecular findings of the biopsy was rule-driven using a software called MATCHBOX, not by a tumor board. In the event of more than one mutation in a tumor, the MATCHBOX decision rules were used to select which genetic abnormality, and therefore treatment option, would be chosen (**Figure 3**). The NCI-MATCH study reached its accrual goal of screening 6,000 patients 2 years ahead of schedule; however, several of the arms did not complete accrual after the goal of 6,000 biopsies was reached. This led trial leadership to develop the Outside Assay/Rare Variant Initiative, which involved screening patients using standard-of-care NGS to find the rare variants that were eligible for the remaining arms.

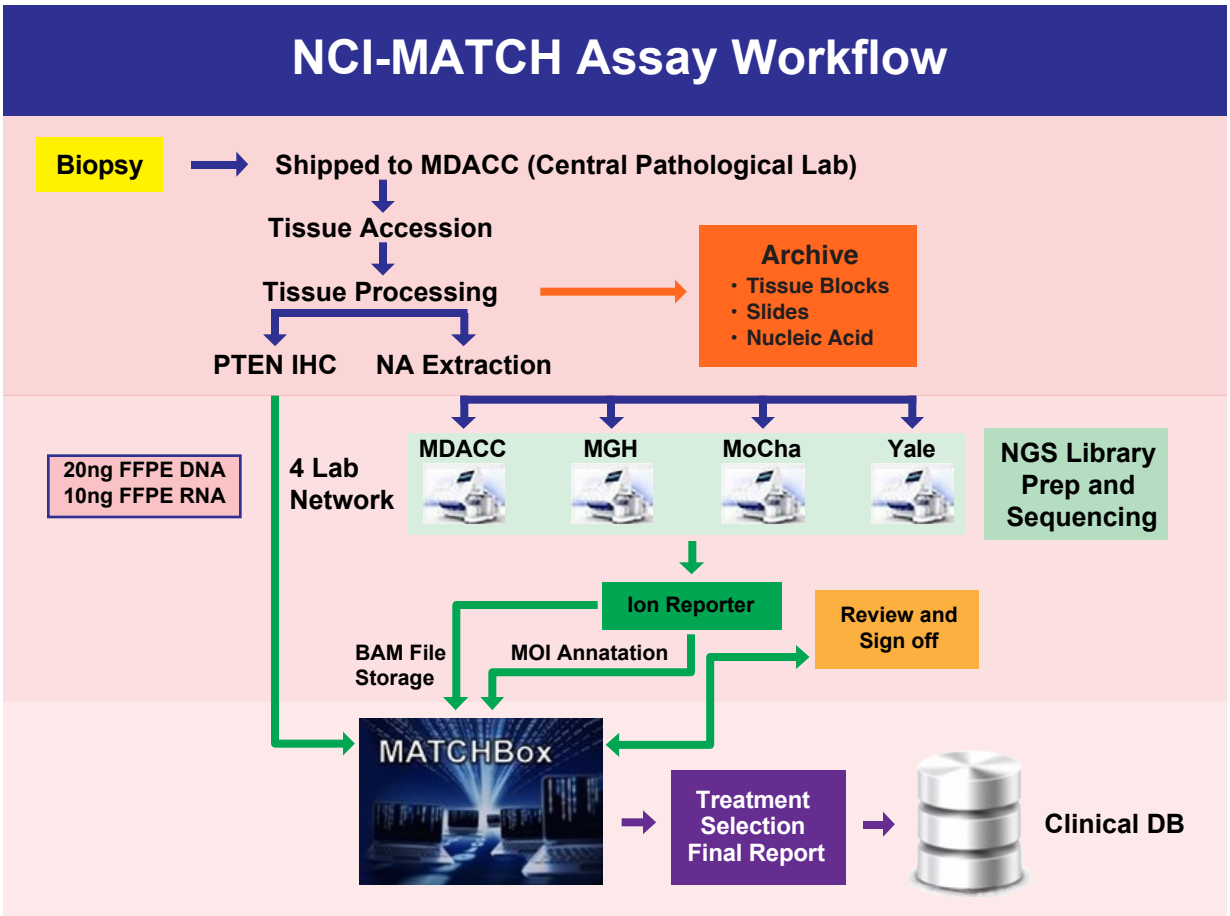



**FIGURE 3: NCI-MATCH ASSAY WORKFLOW WITH MATCHBOX.**

Flow chart based on patient tumor mutation analysis and selection process including MATCHBOX.

NCI-MATCH used Food and Drug Administration (FDA)-approved agents outside of their approved indication, as well as investigational drugs that were not yet approved but had demonstrated evidence of activity against a known target in a specific tumor type. In some trial arms where a tumor type already had FDA approval for the agent being used, or where the agent was known to be ineffective, individuals with those tumor types were excluded. For example, BRAF inhibitors were not given to patients with colon cancer with the V600E mutation as they are known to be ineffective in that setting.

Eligible participants were required to be greater than 18 years of age, have good performance status, adequate organ function, and a metastatic solid tumor, lymphoma, or myeloma that had progressed on all standard therapy or where no standard therapy existed. Patients assigned to a study arm were evaluated for tumor response and progression-free survival. Each arm of the trial accrued enough patients that approximately 31 evaluable patients received the same agent, all of whom met the molecular eligibility criteria. Patients whose tumors continued to progress despite the treatment were removed from the study to pursue other options. Any patient with progressive disease was eligible for re-biopsy to identify potential new actionable mutations for which another targeted study agent would be appropriate.

NCI-MATCH was open at more than 1,100 sites in the US across the four adult NCTN Groups and the NCI Community Oncology Research Program. The initial screening phase of the trial received 6,391 patient referrals (Central Screening Cohort; **Table 1**) and performed molecular profiling for the 5,548 participants who sent in biopsy samples. With a 93% assay success rate, 987 people were matched to a therapy

based on the molecular abnormalities found in their tumors and the available study arms. The high rate of accrual (more than 100 people screened weekly) led to the closure of the initial screening phase of the study in May 2017.

| | Central Screening Cohort | Designated Laboratory Referral Cohort | Total |
|---|---|---|---|
| Enrolled for Screening | 6391 | 762 | 7153 |
| Screen | 5548 | 762 | 6310 |
| Assigned to Treatment | 987 (18%) | 606 (80%) | 1593 |
| Enrolled on Treatment Arm | 686 (70%) | 512 (84%) | 1198 |

TABLE 1: NCI-MATCH ENROLLMENT.

As previously noted, the Outside Assay/Rare Variant Initiative was conceived to help complete accrual to those arms using a different mechanism to obtain molecular profiling. During the time that the screening phase of the NCI-MATCH trial was open, NGS tumor profiling became widely available through commercial companies and some academic laboratories. As many people with cancer were then opting to have their tumor sequenced as a component of routine care, specific laboratories outside of the NCI-MATCH laboratory network were designated as qualified to refer people to the trial. Two commercial companies (Foundation Medicine Inc. and Caris Life Sciences) and three academic laboratories (MD Anderson Cancer Center, Massachusetts General Hospital, and Memorial Sloan Kettering) engaged in a cooperative agreement to work with NCI-MATCH to notify ordering physicians if their patient was potentially eligible for an NCI-MATCH treatment arm.

Once the pilot Outside Assay/Rare Variant Initiative demonstrated the ability to accrue patients with rare mutations, additional laboratories were approved to increase the number of people referred for these rare variant arms. By the end of the study, 28 laboratories comprised the Designated Outside Laboratory Network. Those patients referred to NCI-MATCH through this mechanism and eligible for assignment to a treatment arm had a higher enrollment rate compared to patients randomly screened and found eligible in the initial phase of the trial, (84% vs 18%, respectively) (Designated Laboratory Referral Cohort; **Table 1**). NCI-MATCH closed at the end of 2022, with a total of 38 treatment arms during the study. A table published in *Nature Medicine* (O'Dwyer, 2023) lists the 27 NCI-MATCH arms that published results by early 2023 with links to the data.

Seven of the twenty-seven arms (25.9%) met the prespecified criteria for positivity, suggesting that these agents might be worth pursuing in further studies. As with any clinical trial, even those arms not meeting their primary endpoint provided valuable information, both molecular and clinical data. Examples are rare tumors that responded to the agent or certain types of mutations that were more likely to respond. Each patient enrolled on NCI-MATCH has contributed important information useful in the design of better cancer treatments.

The encouraging initial results of NCI-MATCH have prompted strategies to develop additional precision medicine clinical trials. Follow-up phase 2 studies will be needed to evaluate any active targeted agent(s) in a larger number of patients with both the precise molecular abnormality and the histologies that showed a promising response to determine if and where the agent will be of greatest utility. In addition, combination trials may be suggested in NCI-MATCH studies with limited activity to overcome drug resistance. These studies are now underway as NCI takes precision medicine to the next level with unique approaches to cancer treatment using immunotherapies and combination therapies and treating people diagnosed with rare tumor types. The close collaboration between clinicians, researchers, regulators, pharmaceutical companies, and most importantly patients with cancer, will be necessary to meet these challenges in the years to come.

## NCI-COG Pediatric MATCH

The NCI-COG Pediatric MATCH trial is enrolling children with advanced cancers that have progressed or recurred on standard therapy. As in the adult NCI-MATCH trial, DNA sequencing identifies those children and adolescents between the ages of 1 and 21 whose tumors have a genetic abnormality for which either an approved or investigational targeted therapy exists. Pediatric MATCH, led by the NCTN Children's Oncology Group (COG), opened for accrual in July of 2017 to participants with all types of solid tumors, including central nervous system (CNS) tumors and non-Hodgkin lymphomas as well as histiocytic disorders, as long as tissue from the time of tumor recurrence or progression would be available. In the case of brain stem gliomas, a diagnostic biopsy was acceptable.

The trial opened initially with seven treatment arms and expanded shortly thereafter to thirteen. A minimum of 20 patients is enrolled on each treatment arm, with the ability for expansion if 3 or more responses are observed. After

more than 1,350 pediatric solid tumors had been screened, it was decided that results from outside labs could be used for meeting eligibility requirements for treatment arms. The study was amended at the start of 2022 to use commercial lab results (obtained as part of the standard of care) for enrollment eligibility. More than 1,370 children and adolescents have enrolled into the screening trial. Enrollment averaged around 30 patients/month when all 13 treatment arms were available. Five of the treatment arms met their targeted accrual, two closed for poor accrual, and one closed due to drug supply issues. One treatment arm remains open for patient enrollment, Arm F, with the *ALK* inhibitor ensartinib. Pediatric MATCH is slated to close to enrollment of new patients at the end of 2024.

Pediatric MATCH is unique in that five of the treatment arms include agents (erdafitinib, samotolisib, ensartinib, olaparib, and ulixertinib) that were never formally evaluated in children. Investigators at the NCI, COG, and FDA decided that such agents could be considered for inclusion only after careful review of the toxicities observed in adults, and if an adult recommended phase 2 dose had been identified. The pediatric patients are monitored closely for these and other toxicities. This approach allows Pediatric MATCH to evaluate many more therapeutic agents than would otherwise be available to children. In addition, germline DNA was analyzed on all patients with tumor DNA until 2022. This enabled treating oncologists to determine if a genetic abnormality identified in the tumor was inherited or arose *de novo*, and whether additional genetic testing/genetic counseling to the family should be recommended. Results of the germline DNA testing were presented at AACR in 2021.

Analysis of the first 1,000 children and adolescent patients screened for Pediatric MATCH (Parsons, 2022) showed that 31% had genetic alterations amenable to treatment with an investigational targeted agent on the trial. This is significantly higher than the 10% rate projected when the study was developed. However, 28% of the screened patients were ultimately matched to a treatment arm (some patients were ineligible based on their diagnosis and other factors). The results from two of the treatment arms were published (selumetinib [Eckstein, 2022] and tazemetostat [Chi, 2023]), and the results of three additional completed treatment arms (ulixertinib, palbociclib, and erdafitinib) were presented at ASCO in 2022 and 2023.

This study is successfully facilitating the evaluation of targeted therapies in molecularly defined people with a wide spectrum of childhood solid tumors. The most common diagnoses in the first 1,000 patients screened were sarcomas (50%) (particularly bone sarcomas) and CNS tumors (25%).

## Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST)

Agents targeting the epidermal growth factor receptor (EGFR) or the ALK-EML4 fusion protein in combination with immunotherapies have demonstrated durable responses and an improvement in progression free survival (PFS) in people with advanced lung cancer.

The ALCHEMIST trial, which began in 2014, examined whether the addition of erlotinib (EGFR inhibitor) or crizotinib (ALK inhibitor) to standard adjuvant therapy (when indicated) in people with resectable, early-stage lung cancer (stage 1B – 3A) containing the pathognomonic molecular changes resulted in improved survival. Screening of eligible patients occurred under a common screening study (**Figure 4**). For patients with non-squamous cell lung cancer, EGFR genotyping was performed by sequencing of exons, and ALK FISH was performed using the Vysis break-apart probe. Patients with tumors exhibiting EGFR-activating mutations received standard chemotherapy with or without radiation and were then randomized to erlotinib or observation. Similarly, patients with tumors exhibiting the ALK fusion were randomized to receive crizotinib or observation after completion of standard chemotherapy with or without radiation. Since the EGFR mutation and the ALK fusion occur in only 15% and 5% of people with early-stage lung cancer, respectively, an estimated 8,000 patients were needed to be screened to identify a patient population large enough to power the randomized clinical trials.

As of December 2023, more than 7,100 patients have been screened for ALCHEMIST. All screened patients were evaluated with an epidemiologic questionnaire, and tumor samples from their surgical resection were sent for whole exome sequencing and other "omic" research tests. Patients were followed for 10 years or until death or relapse. At relapse, there was an option of performing another tumor biopsy to evaluate the genomic progression of these treated tumors.

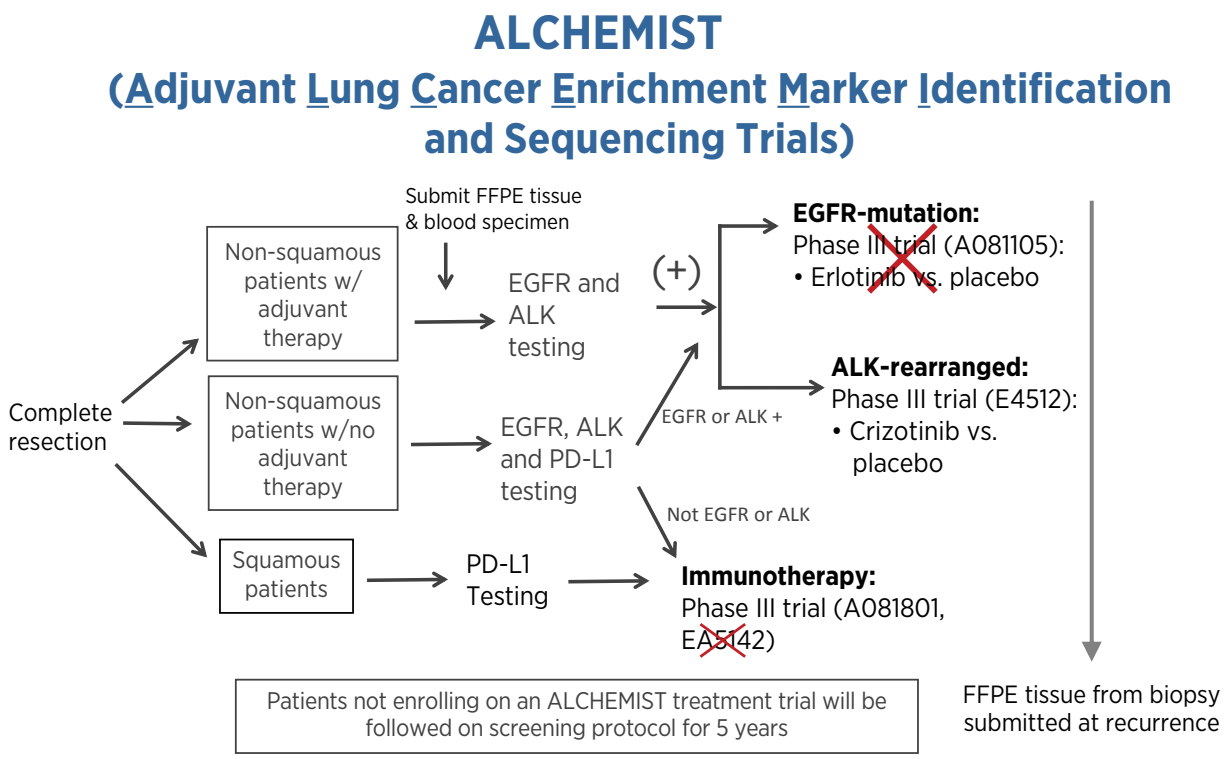



**FIGURE 4: ALCHEMIST TRIAL SCHEMA.**
Flow diagram based on lung cancer diagnosis and results of gene-specific mutation analysis.

ALCHEMIST was amended in 2016 to include a new trial using the PD-1 inhibitor, nivolumab, after it was proven active in patients with advanced non-small cell lung cancer (NSCLC). Unlike the other two trials, which were limited to people with non-squamous cell lung cancer, patients with squamous or non-squamous histology were eligible for the nivolumab trial. This trial was closed to accrual in October 2019 after completing enrollment of 935 participants.

In June 2020 a new immunotherapy trial, Integration of Immunotherapy into Adjuvant Therapy for Resected NSCLC: ALCHEMIST CHEMO-IO, was launched. It was modified in October 2021 to accommodate the FDA approval of atezolizumab as an adjuvant treatment for NSCLC. As of December 2023, the trial has accrued 560/1,210 patients.

After the release of the update, patients are being randomized to Arms B and C only (**Figure 5**). The trial previously had an Arm A, in which patients received only platinum doublet followed by observation, but this arm was stopped with the approval of immunotherapy in this setting. Patients will be followed for up to 10 years or until death, whichever comes first.

After enrollment of 390/450 patients, the EGFR (erlotinib) study was closed to accrual in January 2021 with the FDA approval of Osimertinib (an EGFR inhibitor) in the same patient population. Outcome data from the erlotinib trial are pending as of December 2023.

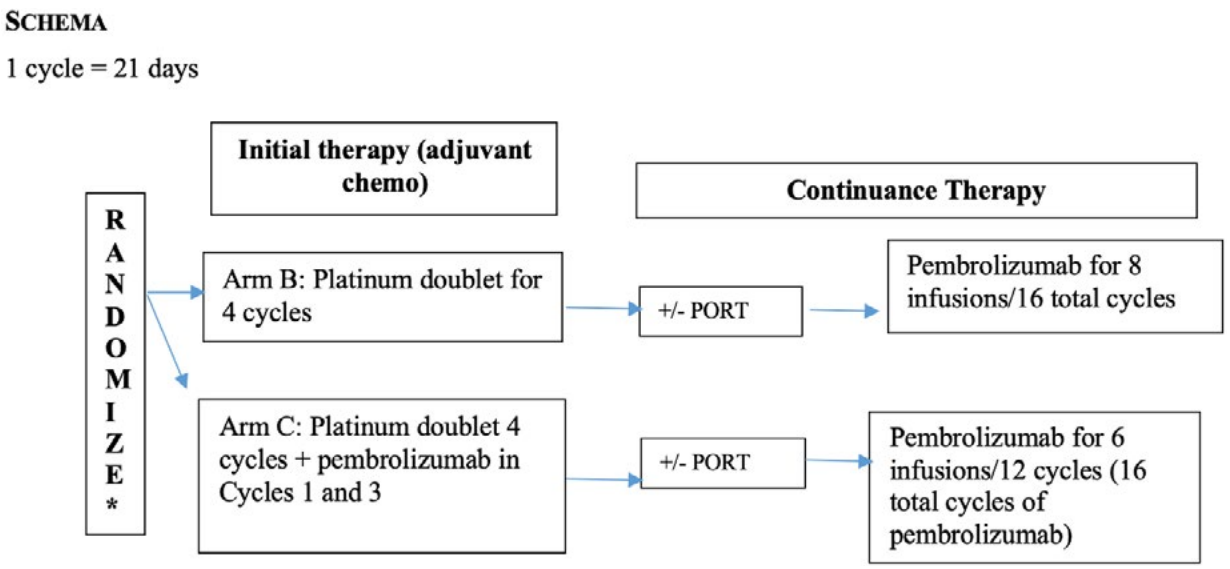
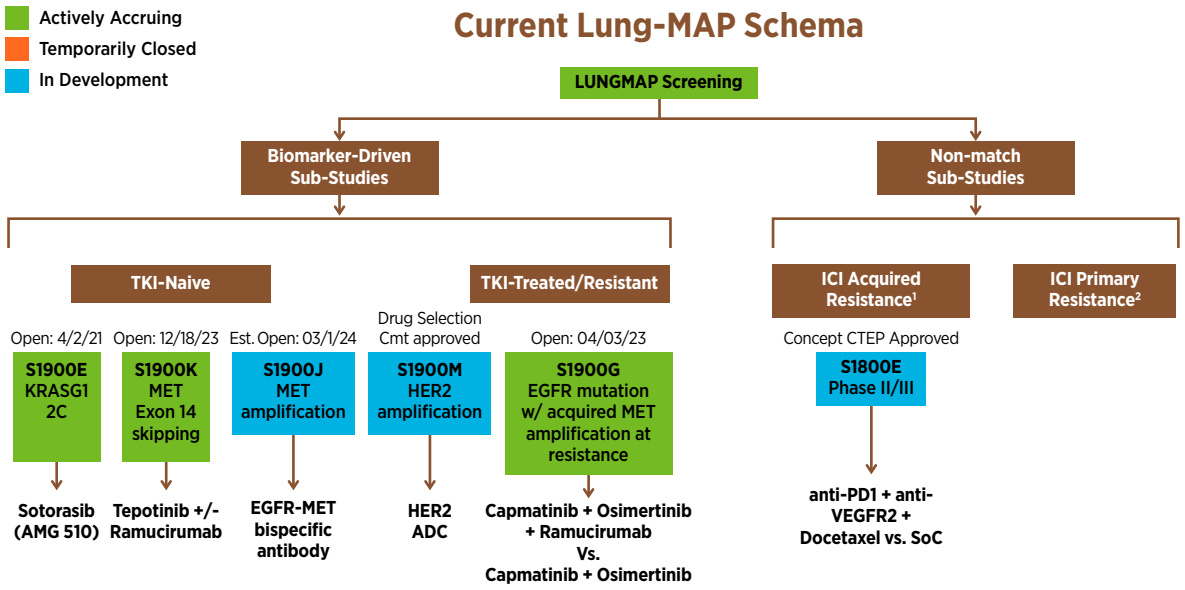



FIGURE 5: ALCHEMIST CHEMO-IO SCHEMA.

## Lung Master Protocol (Lung-MAP)

The clinical trial design for this initiative is a novel approach to drug development and regulatory approval in the evaluation of biomarker-driven therapies and immunotherapies in people with previously treated non-small cell lung cancer (NSCLC). The Lung-MAP study is an umbrella protocol containing both a screening and a clinical trial component (**Figure 6**). Patients whose tumors progress on current therapy or who receive therapy for stage IV or recurrent NSCLC are eligible to participate in the screening component. The clinical trial component consists of sub-studies including biomarker-driven studies evaluating drugs that interact with a particular biomarker and non-match studies that evaluate therapies without any of the study biomarkers. Although included within the umbrella protocol, these sub-studies are independently conducted and analyzed. The protocol is modular to allow for the addition of new sub-studies of interest. A common biomarker-profiling platform is used for determining if a patient is eligible for the biomarker-driven studies.

The Lung-MAP trial opened in June 2014 for second-line treatment of patients with stage IV or recurrent squamous lung cancer. In 2019, the study expanded to allow people with all histologic types of previously treated stage IV or recurrent NSCLC to enroll. Progress in the development of immunotherapies led to a change in the landscape and a subsequent expansion of Lung-MAP. The non-matched category of sub-studies now includes combination immunotherapy agents that are either FDA approved or still investigational; however, small molecule agents or other modalities for which there is a scientific rationale for combining with an immunotherapy agent can be included. All novel combinations continue to be selected through sound scientific rationale, supported when possible with appropriate *in vivo* model systems, to demonstrate anti-cancer activity and to preliminarily assess their clinical tolerability when co-administered. The expansion allowing for all histologic types of NSCLC applies to all the sub-studies. Patients with tumors that do not match one of the active drug-biomarker combinations (i.e., "non-match") will either be assigned to the non-match sub-study for immunotherapy-naïve patients or to a sub-study evaluating immunotherapy combinations for patients previously treated with immunotherapy. As of December 2023, 3,249 patients have been enrolled in the Lung-MAP trial.




[1] Acquired Resistance is defined as progression at least (≥) 84 days from initiation of the most recent line of anti-PD-1/PD-L1 and best response of stable disease, partial response, or complete response.
[2] Primary Resistance is defined as progression less than (<) 84 days from initiation of the most recent line of anti-PD-1/PD-L1 or best response of progressive disease or symptomatic deterioration.

FIGURE 6: LUNG-MAP TRIAL SCHEMA.

## ComboMATCH

ComboMATCH, a successor trial to NCI-MATCH, opened in spring 2023. It is testing combinations of targeted drugs that were effective in preclinical studies. The goal is to overcome drug resistance to single-agent therapy through the development of genetically directed targeted agent combinations.

ComboMATCH is a cross-group collaboration among NCI and all five U.S. clinical trial groups within NCI's National Clinical Trials Network (NCTN). ECOG-ACRIN is managing the overall ComboMATCH registration study, and each NCTN group will run its own treatment trials. The registration protocol contains rules for assigning people to the treatment trials as well as other guidelines. Patients with cancer will be referred to this trial from the Designated Laboratory Network, originally established as part of NCI-MATCH, by using next generation sequencing (NGS) performed as part of clinical care to determine if their tumor reveals a qualifying alteration(s).

## MyeloMATCH

MyeloMATCH is an umbrella trial that will test treatments for acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). The speed at which new, effective, and tolerable treatment options for these cancers are identified must accelerate. The focus of this trial will be to match AML molecular subtypes to therapies in people of different age and fitness groups. SWOG will lead the screening trial, which will complete patients' genetic screening through routine bone marrow biopsy. NCI's Molecular Diagnostic Network (MDNet), an NCI-funded network of laboratories, will perform these molecular tests. MDNet will perform all the molecular and cellular biomarker assays on the new three precision medicine trials for the purpose of assigning patients to treatment. Each of the NCTN Groups will lead treatment sub-studies within myeloMATCH in this collaboration.

## ImmunoMATCH (iMATCH)

iMATCH is NCI's first precision medicine trial focused on immunotherapy. Participants undergo molecular testing for markers associated with response to immunotherapy, which will be used to define immune-based subgroups for patient enrichment or stratification in therapeutic trials. The goal of iMATCH is to enhance further development of immunotherapies, especially combination strategies. iMATCH started as a pilot study to establish feasibility of a central testing platform.

The pilot will test an immunotherapy-based combination, nivolumab (Opdivo) and cabozantinib (Cabometyx), in patients with advanced melanoma or certain types of head and neck cancer that have stopped responding to previous immunotherapies. The primary goal of the pilot is to assess feasibility of molecular testing and patient subgroup allocation, as well as to obtain preliminary evidence of the treatment effect in individual subgroups. MDNet, which provides assay support to DCTD's precision medicine trials, will support the laboratory testing, and SWOG, a member of the NCI National Clinical Trials Network, is leading the pilot study.

## TRANSLATIONAL CONSORTIA AND RESEARCH NETWORKS

### Specialized Programs of Research Excellence (SPOREs)

The SPOREs are a cornerstone of the NCI's efforts to promote collaborative, interdisciplinary translational research. Funded through the P50 or U54 grant mechanisms and managed by the Translational Research Program (TRP), SPORE funding supports state-of-the-art, investigator-initiated translational research contributing to improved prevention, early detection, diagnosis, and treatment of cancer.

Each SPORE achieves this goal by:

- Focusing on a specific organ site, a group of highly related cancers, or cancers that are linked by a common signaling pathway alteration or other novel cross-cutting themes that have potential for innovation and high scientific impact
- Supporting research projects that have the potential to result in new and diverse approaches to the prevention, early detection, diagnosis, and treatment of human cancers
- Encouraging cross-fertilization between various biomedical disciplines by requiring a minimum of three diverse translational research projects per SPORE and involving both basic and clinical or applied scientists in each research project
- Requiring a dedicated biospecimen/pathology specialized resource core to ensure access to clinical materials
- Supporting a developmental research program to promote pilot projects of cutting-edge research (basic, clinical, or translational)
- Supporting a career enhancement program to promote the transition of early-stage or established investigators to translational cancer research in the proposed organ site or theme
- Requiring collaboration among other SPOREs and across NCI-funded networks to promote translational advancement
- Providing flexibility to SPORE investigators to realign resources and substitute research projects if translational objectives are not being met or are completed during the funding period
- Encouraging input and advice from patient advocates and the advocate community

The interdisciplinary and translational nature of SPORE grants requires collaboration. Below are some examples of SPORE investigator engagement in NCI/NIH/Extramural programs, partnerships, and consortia.

Pancreatic cancer SPOREs at the University of Nebraska and Johns Hopkins University have established sophisticated processes through their Rapid Autopsy Programs that allow the acquisition and preservation of biospecimens within 1-3 hours of death. These state-of-the-art procedures minimize postmortem degradation and thus facilitate reproducible downstream analysis. Investigators from multiple SPOREs have contributed more than 135 fresh primary and metastatic tumor samples to the NCI Patient-Derived Models Repository (PDMR) for development of numerous PDX models, as well as 67 PDX models derived by SPORE investigators. In addition, SPORE investigators have worked with the PDMR to develop several SOPs for shipping and handling of both cryopreserved and fresh human tissues.

Several SPORE investigators have accessed NCI's drug development resources such as the NCI-PREVENT program and the NCI Experimental Therapeutics (NExT) Program. The NCI Division of Cancer Prevention runs the NCI-PREVENT program, which uses contract resources to support drug development or therapeutics in cancer prevention. The Mayo Clinic Breast Cancer SPORE used NCI-PREVENT resources to develop a novel six-antigen vaccine for women with premalignant breast cancer and conducted studies for investigational new drug (IND) filing with a clinical trial planned. SPORE investigators at Johns Hopkins University also used NCI-PREVENT resources to aid in the manufacture of clinical grade HPV16 RG1-VLP vaccine and IND supporting preclinical toxicology studies.

Using this vaccine, they plan to develop a GLP freeze-dry protocol and formulation to increase vaccine temperature stability and to increase access to patients, which will help prevent cervical cancer. The NExT Program supports, among other things, cGMP manufacturing and IND-directed toxicology studies of novel investigational agents. For example, the NExT Program supported the development of the SVC112 small molecule by the University of Colorado Head & Neck SPORE to target the eEF2 elongation factor and inhibit protein synthesis.

SPORE investigators are also performing correlative studies to improve the understanding of clinical trials outcomes in terms of fundamental human biology. Some examples of this include the Mayo Clinic Ovarian Cancer SPORE's collaboration with the NCI Clinical Proteomic Tumor Analysis Consortium (CPTAC). CPTAC integrates proteomic and genomic analysis of NCI-sponsored clinical trial samples to better understand the molecular basis of cancer. CPTAC is helping the Mayo SPORE develop a proteomic signature to identify patients with refractory ovarian cancer prior to therapy so that those patients can be offered alternative treatments.

Finally, the focus of SPOREs has expanded to include research in cross-cutting themes, such as pathway-specific themes, pediatric cancers, and cancer health disparities. The Developmental and Hyperactive Ras Tumor SPORE, which consists of a team of investigators from several institutions and the NCI intramural researcher, Dr. Brigitte Widemann, focuses on treatment and survival of children and adults with RASopathy disorders. In partnership with the NCI Center to Reduce Cancer Health Disparities, TRP supports feasibility and planning activities (P20 awards) to develop translational research programs focused on cancer health disparities research with the expectation that the research programs will become competitive for a P50 SPORE award. Twelve SPORE P20s were awarded in 2020-2023, including eight active P20s at Baylor College of Medicine (leukemia), Duke University (gastrointestinal and lung cancer), Fred Hutchinson Cancer Center (gastrointestinal cancer), New York University (head & neck and gastrointestinal cancer), Northwestern University (endometrial and ovarian cancer), University of Washington (gastrointestinal cancer), Virginia Commonwealth University (lung cancer), and Wayne State University (lung cancer).

SPOREs are located at academic centers or consortia in 20 states across the United States (**Figure 7**).

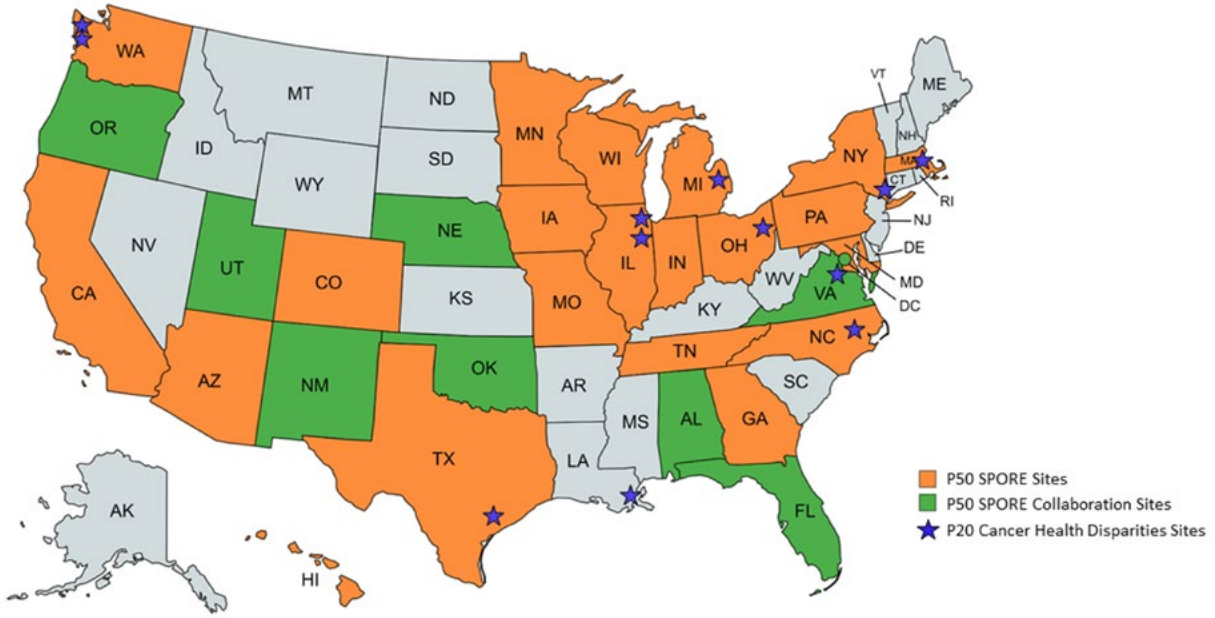



**FIGURE 7: STATES WITH ACTIVE SPORE GRANTS IN FISCAL YEARS 2020-2023.**

Fifty-four SPOREs were funded in 21 states within 30 institutions and collaborated with institutions in 8 additional states and the District of Columbia. Twelve P20 SPORE Planning Grants in cancer health disparities were also funded in represented states.

**SPORE Clinical Trials**

Early phase clinical trials are an indispensable part of the SPORE program. In years 2020-2023, SPORE investigators conducted about 150 trials, most of them phase 1, phase 1/2, or phase 2 clinical trials. More than one third of these trials support industry collaborations, and the rest are collaborations with NIH, other government programs, academia, and nonprofit organizations. The most tested drugs, out of 100 compounds tested in these trials, are listed in **Table 2**.

An important NCI partnership evolved with the Gateway for Cancer Research (Gateway) foundation. Gateway is a nonprofit 501(c)(3) organization committed to funding innovative cancer research, namely phase 1 and phase 3 cancer treatment-based investigator initiated clinical trials. So far, Gateway has funded two SPORE-initiated clinical trials: "SX-682 in combination with Nivolumab for ctDNA positive colorectal cancer" conducted by the MD Anderson GI SPORE, and "The STOP-HER2 Study" led by the Dana Farber Harvard Cancer Center Breast Cancer SPORE. The latter trial assesses circulating tumor DNA as a marker to identify patients with breast cancer who have an exceptional response to Trastuzumab and may therefore safely stop treatment without relapse. More trials are planned.

| Intervention | Number of trials |
|---|---|
| Nivolumab | 18 |
| Pembrolizumab | 13 |
| Olaparib | 11 |
| Enzalutamide | 11 |
| Cyclophosphamide | 10 |
| Carboplatin | 10 |
| Ipilimumab | 8 |
| Prednisone | 7 |
| Docetaxel | 6 |
| Paclitaxel | 5 |
| Doxorubicin | 4 |
| Liposomal compounds | 4 |
| Atezolizumab | 4 |
| Abiraterone | 4 |
| Avelumab | 4 |
| D-Ribose | 4 |

TABLE 2: DRUGS USED IN SPORE CLINICAL TRIALS IN FISCAL YEARS 2020-2023.

**SPORE Scientific Accomplishments**

SPORE researchers were highly productive from 2020-2023 and published more than 4,900 publications with relative citation ratios as high as 96 in leading journals. Several SPORE scientific accomplishments are highlighted in **Table 3**.

| Institution | Organ Site | Summary |
|---|---|---|
| The Robert H. Lurie Comprehensive Cancer Center UNW | Brain | Kumthekar, P., et al., A first-in-human phase 0 clinical study of RNA interference-based spherical nucleic acids in patients with recurrent glioblastoma. *Sci Transl Med*. Mar 10;13(584):eabb3945 (2021). |
| The Robert H. Lurie Comprehensive Cancer Center UNW | Brain | Fares, J., et al., Neural stem cell delivery of an oncolytic adenovirus in newly diagnosed malignant glioma: a first-in-human, phase 1, dose-escalation trial. *Lancet Oncol*. Aug;22(8):1103-1114 (2021). |
| UC San Francisco | Brain | Amen, A., et al., Cancer-specific loss of TERT activation sensitizes glioblastoma to DNA damage. *Proc Natl Acad Sci U S A*. Mar 30;118(13):e2008772118 (2021). |
| Memorial Sloan-Kettering Cancer Center | Breast, Ovarian | Pareja, F., et al., Cancer-Causative Mutations Occurring in Early Embryogenesis. *Cancer Discov*. Apr 1;12(4):949-957 (2022). |
| Dana Farber Cancer Institute | Breast | Baldominos, P., et al., Quiescent cancer cells resist T cell attack by forming an immunosuppressive niche. *Cell*. May 12;185(10):1694-1708 (2022). |
| UNC Lineberger Comprehensive Cancer Center | Breast | Benefield, H., et al., Outcomes of Hormone-Receptor Positive, HER2-Negative Breast Cancers by Race and Tumor Biological Features; *JNCI Cancer Spectr*. Sep 23;5(1):pkaa072 (2020). |
| Dana Farber Cancer Institute | Breast | Barroso-Sousa, R., et al., Prevalence and mutational determinants of high tumor mutation burden in breast cancer. *Ann Oncol*. Mar;31(3):387-394 (2020). |
| Dana Farber Cancer Institute | Colon/Colorectal | Ryan, M., et al., Vertical Pathway Inhibition Overcomes Adaptive Feedback Resistance to KRASG12C Inhibition. *Clin Cancer Res*. Apr 1;26(7):1633-1643 (2020). |
| Dana Farber Cancer Institute | Colon/Colorectal | Wu, Q., et al., EGFR Inhibition Potentiates FGFR Inhibitor Therapy and Overcomes Resistance in FGFR2 Fusion-Positive Cholangiocarcinoma. *Cancer Discov*. May 2;12(5):1378-1395 (2022). |
| Dana Farber Cancer Institute | Colon/Colorectal | Ryan, M., et al., KRASG12C-independent feedback activation of wild-type RAS constrains KRASG12C inhibitor. *Cell Rep*. Jun 21;39(12):110993 (2022). |
| University of Pittsburgh | Head & Neck | Ferris, R., et al., Phase I Trial of Cetuximab, Radiotherapy, and Ipilimumab in Locally Advanced Head and Neck Cancer. *Clin Cancer Res*. Apr 1;28(7):1335-1344 (2022). |
| University of Pittsburgh | Head & Neck, Melanoma, Lung | Somasundaram, A., et al., Systemic Immune Dysfunction in Cancer Patients Driven by IL6 Induction of LAG3 in Peripheral CD8+ T Cells. *Cancer Immunol Res*. Jul 1;10(7):885-899 (2022). |
| University of Pittsburgh | Head & Neck | Cillo, A., et al., Immune Landscape of Viral- and Carcinogen-Driven Head and Neck Cancer. *Immunity*. Jan 14;52(1):183-199 (2020). |
| Beth Israel Deaconess Medical Center | Kidney | Braun, D., et al., Interplay of somatic alterations and immune infiltration modulates response to PD-1 blockade in advanced clear cell renal cell carcinoma. *Nat Med*. Jun;26(6):909-918 (2020). |
| Beth Israel Deaconess Medical Center | Kidney | Yuen, K., et al., High systemic and tumor-associated IL-8 correlates with reduced clinical benefit of PD-L1 blockade. *Nat Med*. May;26(5):693-698 (2020). |
| UT MD Anderson Cancer Center | Leukemia | Morita, K., et al., Clonal evolution of acute myeloid leukemia revealed by high-throughput single-cell genomics. *Nat Commun*. Oct 21;11(1):5327 (2020). |
| Dana Farber Cancer Institute | Leukemia, Kidney | Bhatt, R., et al., KIR3DL3 Is an Inhibitory Receptor for HHLA2 that Mediates an Alternative Immunoinhibitory Pathway to PD1. *Cancer Immunol Res*. Feb;9(2):156-169 (2021). |
| Mayo Clinic | Liver | Kottke, T., et al., Oncolytic virotherapy induced CSDE1 neo-antigenesis restricts VSV replication but can be targeted by immunotherapy. *Nat Commun*. Mar 26;12(1):1930 (2021). |
| UT MD Anderson Cancer Center | Liver | Jiao, J., et al., Circulating Fatty Acids Associated with Advanced Liver Fibrosis and Hepatocellular Carcinoma in South Texas Hispanics. *Cancer Epidemiol Biomarkers Prev*. Sep;30(9):1643-1651 (2021). |

| Institution | Organ Site | Summary |
|---|---|---|
| UT Southwestern Medical Center | Lung | Park, J., et al., Mechanical regulation of glycolysis via cytoskeleton architecture. *Nature*. Feb;578(7796):621-626 (2020). |
| Yale University | Lung | Schalper, K., et al., Elevated serum interleukin-8 is associated with enhanced intratumor neutrophils and reduced clinical benefit of immune-checkpoint inhibitors; *Nat Med*. May;**26**(5):688-692 (2020). |
| UT MD Anderson Cancer Center | Lung | Robichaux, J., et al., Structure-based classification predicts drug response in EGFR-mutant NSCLC. *Nature*. Sep;597(7878):732-737 (2021). |
| Yale University | Lung | Liu, Y., et al., Immune Cell PD-L1 Colocalizes with Macrophages and Is Associated with Outcome in PD-1 Pathway Blockade Therapy. *Clin Cancer Res*. Feb 15;26(4):970-977 (2020). |
| UT MD Anderson Cancer Center | Lymphoma | Liu, E., et al., Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors. *N Engl J Med*. Feb 6;382(6):545-553 (2020). |
| Beckman Research Institute | Lymphoma | Jacobson, C., et al., Axicabtagene Ciloleucel in the Non-Trial Setting: Outcomes and Correlates of Response, Resistance, and Toxicity. *J Clin Oncol*. Sept 20;38(27):3095-3106 (2020). |
| Beckman Research Institute | Lymphoma | Zhang, C., et al., STAT3 Activation-Induced Fatty Acid Oxidation in CD8+ T Effector Cells Is Critical for Obesity-Promoted Breast Tumor Growth. *Cell Metab*. Jan 7;31(1):148-161 (2020). |
| Dana Farber Cancer Institute, MGH | Multiple Myeloma | Castillo, J., et al., Long-term follow-up of ibrutinib monotherapy in treatment-naive patients with Waldenstrom macroglobulinemia. *Leukemia*. Feb;36(2):532-539 (2022). |
| Dana Farber Cancer Institute | Multiple Myeloma | Treon, S., et al., The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19-infected patients. *Blood*. May 21;135(21):1912-1915 (2020). |
| University of Pittsburgh | Ovarian | Orr, B., et al., Phase I Trial Combining Chemokine-Targeting with Loco-Regional Chemoimmunotherapy for Recurrent, Platinum-Sensitive Ovarian Cancer Shows Induction of CXCR3 Ligands and Markers of Type 1 Immunity. *Clin Cancer Res*. May 13;28(10):2038-2049 (2022). |
| UT MD Anderson Cancer Center | Ovarian | Fan, D., et al., A Novel Salt Inducible Kinase 2 Inhibitor, ARN-3261, Sensitizes Ovarian Cancer Cell Lines and Xenografts to Carboplatin. *Cancers (Basel)*. Jan 25;13(3):446 (2021). |
| Multi-center UCLA and PNW | Prostate | Zhao, S., et al., The DNA methylation landscape of advanced prostate cancer. *Nat Genet*. Aug;52(8):778-789 (2020). |
| Memorial Sloan-Kettering Cancer Center | Prostate | Abida, W., et al., Rucaparib in Men with Metastatic Castration-Resistant Prostate Cancer Harboring a BRCA1 or BRCA2 Gene Alteration. *J Clin Oncol*. Nov 10;38(32):3763-3772 (2020). |
| UC Los Angeles | Prostate | Current, K., et al., Investigating PSMA-Targeted Radioligand Therapy Efficacy as a Function of Cellular PSMA Levels and Intratumoral PSMA Heterogeneity. *Clin Cancer Res*. Jun 15;26(12):2946-2955 (2020). |
| University of Michigan | Prostate | Xiang, W., et al., Discovery of ARD-2585 as an Exceptionally Potent and Orally Active PROTAC Degrader of Androgen Receptor for the Treatment of Advanced Prostate Cance. *J Med Chem*. Sep 23;64(18):13487-13509 (2021). |
| Yale University | Skin | Zhang, S., et al., KDM5B promotes immune evasion by recruiting SETDB1 to silence retroelements. *Nature*. Oct;598(7882):682-687 (2021). |
| Weill Cornell Medical College | Skin | Galassi, C., et al., Using epigenetic modifiers to target cancer stem cell immunoevasion. *Cancer Cell*. Dec 13;39(12):1573-1575 (2021). |
| University of Pittsburgh | Skin | Somasundaram, A., et al., Systemic Immune Dysfunction in Cancer Patients Driven by IL6 Induction of LAG3 in Peripheral CD8+ T Cells. *Cancer Immunol Res*. Jul 1;10(7):885-899 (2022). |
| Memorial Sloan-Kettering Cancer Center | Urothelial/Bladder | Carlo, M., et al., Cancer susceptibility mutations in patients with urothelial malignancies. *J Clin Oncol*. Feb 10;38(5):406-414 (2020). |

**TABLE 3: SPORE SCIENTIFIC ACCOMPLISHMENTS 2020-2023.**

## NCI Experimental Therapeutics Clinical Trials Network (ETCTN)

Since the early 1970s, DCTD's Cancer Therapy Evaluation Program (CTEP) has managed an early-phase experimental therapeutics program that has contributed to the clinical development of anticancer agents. Through this program, hundreds of agents, both small molecule and immunologic, have been made available for collaborative development. CTEP currently holds approximately 85 Investigational New Drug Applications (INDs). Effective development of these agents requires a systematic development plan for phase 1 and pilot trials, followed by phase 2 trials that, it is hoped, will conclude in definitive phase 3 trials. Early combination therapy development is another critical component of early-phase development.

NCI has formed partnerships with pharmaceutical companies, academic institutions, and individual investigators for the early clinical evaluation of innovative cancer therapies. In 2014, the ETCTN was created to enhance more rapid evaluation of these therapies using a coordinated, collaborative, and inclusive team-based approach to early-phase experimental therapeutic clinical trials and biomarker/pharmacodynamic assessment (**Figure 8**).

The goals of the ETCTN are to:

- Enhance the science of hypothesis-driven clinical trial design, dose optimization, and drug development of new cancer treatments using NCI IND agents
- Integrate molecular characterization, pharmacology, cancer biology, and imaging into clinical trials
- Enhance accrual using population science applied to underserved/underrepresented communities in clinical trials
- Expand team science approaches in drug development focusing on early career investigators and consolidation of statistical operations to support trial design, conduct and safety monitoring
- Promote collaboration among institutions and investigators

ETCTN clinical sites (**Figure 9**) participate in the Phase 1 and Phase 2 Programs, which are supported by NCI UM1 grants and cooperative agreements as supplements to the existing UM1 grants, respectively. By integrating Phase 1 and Phase 2 Program activities and administrative operations under the UM1 structure, ETCTN awardees have the flexibility to expand phase 1 studies quickly upon the detection of early antitumor activity. The development of a robust infrastructure (**Figure 10**) to support the conduct of trials in the network is critical to the success of the program.

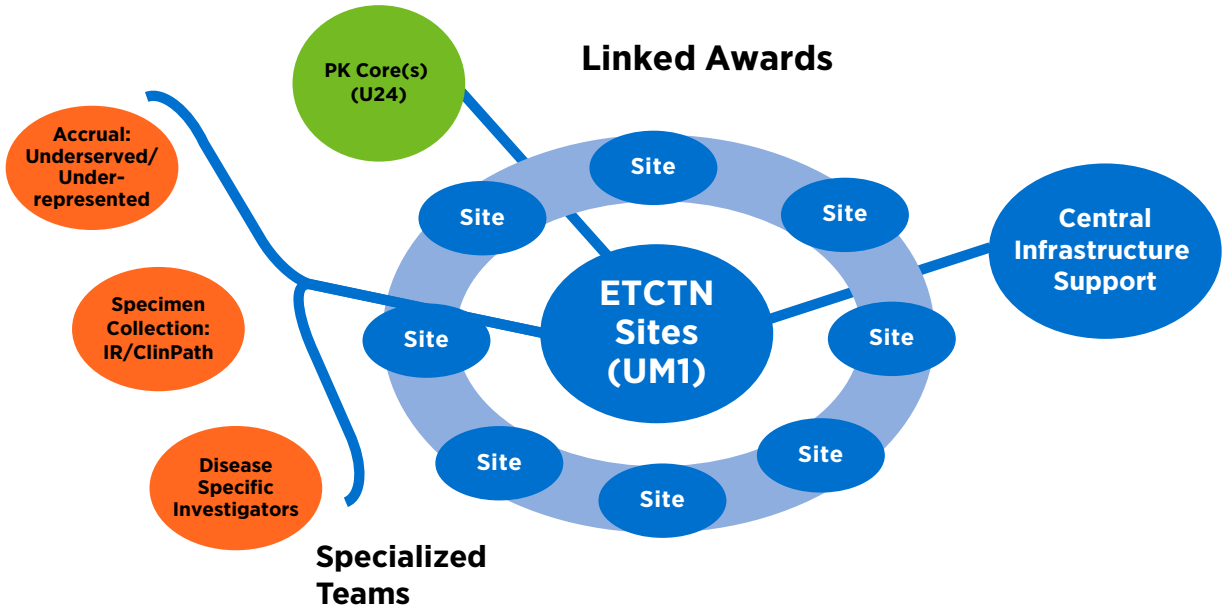



FIGURE 8: COORDINATED AND COLLABORATIVE ORGANIZATION OF THE ETCTN.

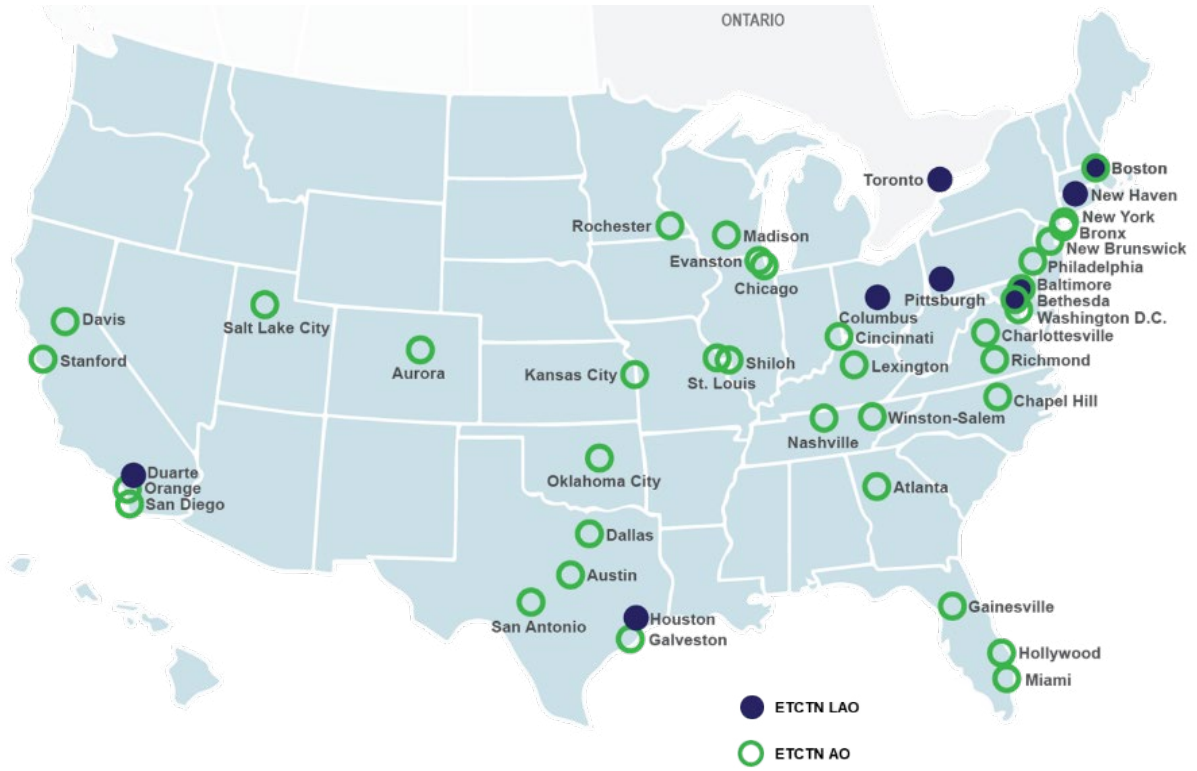



**FIGURE 9: ETCTN PHASE 1 AND PHASE 2 PROGRAM SITES.**
LAO = Lead Academic Organization (closed circles); AO = Academic Organization (open circles).

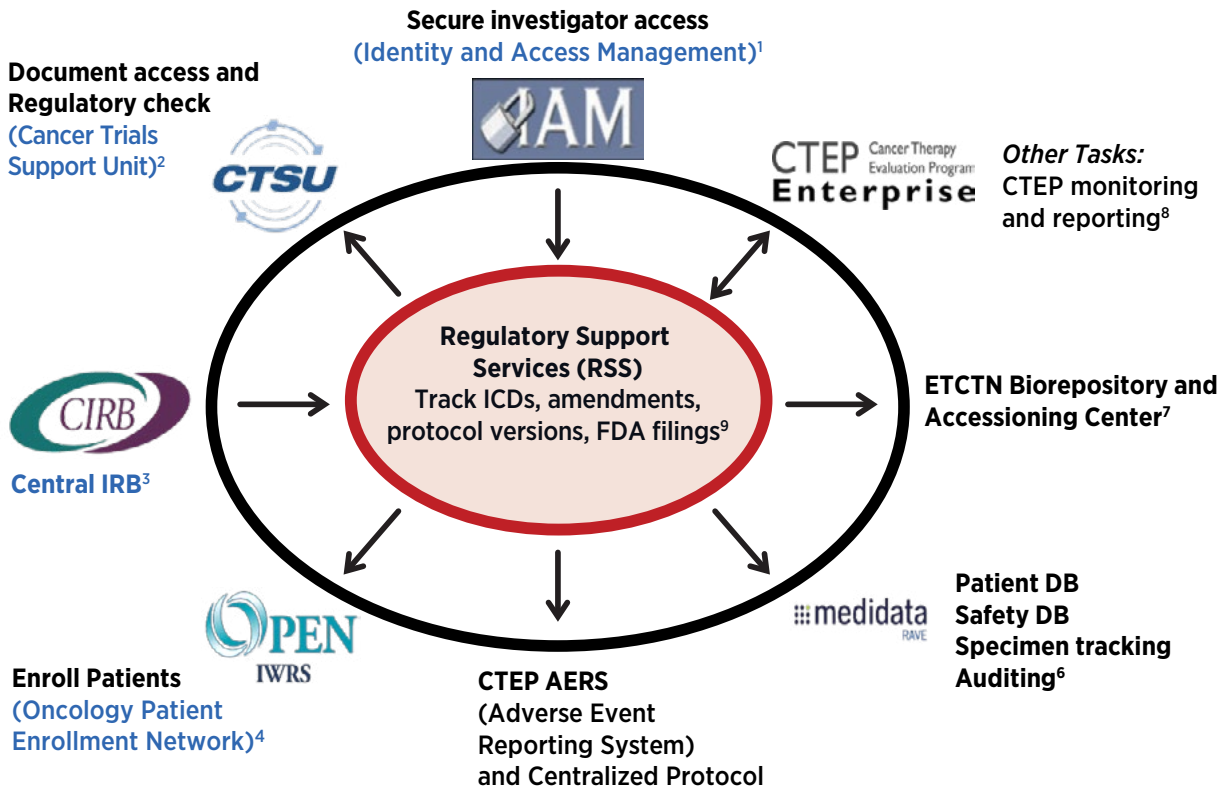



**FIGURE 10: CENTRALIZED SUPPORT SERVICES FOR ETCTN.**
Superscript numbers correspond to the Program Infrastructure described below.

IT data software systems provide the necessary infrastructure to meet the access and reporting requirements of NCI-supported clinical trials.

**Program Infrastructure**

1. CTEP-Identity and Access Management (CTEP-IAM)

   Investigators and Associates register for an account that enables access to the other applications (CTSU, OPEN/IWRS, Rave, CTEP Enterprise).

2. Cancer Trials Support Unit (CTSU)

   Provides services, including a roster of institutions and medical personnel; website support for posting of protocols and other information; and links to other services (OPEN/IWRS, Rave).

3. NCI Central Institutional Review Board (CIRB)

   Conducts IRB review of most early-phase NCI-sponsored trials, including ETCTN studies.

4. Oncology Patient Enrollment Network (OPEN)/Interactive Web Response System (IWRS)

   Linked applications for patient enrollment (OPEN), slot reservations, and cohort management (IWRS). Data are automatically transferred to Medidata Rave.

5. CTEP Adverse Event Reporting System (CTEP-AERS)/Centralized Protocol Writing Support (CPWS) - Safety Reporting and monitor application.

   Administrative and scientific writing support.

6. Medidata Rave

   An application for data entry, data analysis, and clinical trial management.

7. ETCTN Biorepository and Accessioning Center

   The ETCTN Biobank collects, processes, and stores high-quality human biospecimens from people with cancer enrolled in clinical trials. The ETCTN Biobank also provides up-to-date maintenance of specimen inventory and distribution of specimens to qualified, NCI-approved trial investigators and research laboratories.

8. CTEP Enterprise System

   An application for integrated clinical trials management and reporting, including Agent Ordering, shipment, and tracking system; trial monitoring/audits; and Operational Efficiency Working Group (OEWG) reporting.

9. CTEP Monitoring and Reporting Scheduling, tracking, and reporting of audit findings (Regulatory Support Services, RSS).

**Activity Summary**

From 2020 to 2023, investigators submitted 177 letters of intent (LOI). During this reporting period, the following occurred within CTEP-sponsored early-phase trials.

ETCTN awards supported eight sites with the clinical expertise and infrastructure to conduct early phase clinical trials. During this funding period (Mar 1, 2020-August 31, 2023):

- 750 patients were enrolled annually (on average over 3.5 years)
- 80 studies were activated
- 166 studies were ongoing
- 86 studies closed (includes former legacy ongoing studies)
- 135 investigational agent combinations studies were performed
- 16/52 (34.6%) studies used the Bayesian Optimal Interval (BOIN) design (03/1/2020-12/31/2023) – adaptive design in 33% of trials
- 246 Project Team Member Applications (PTMAs) were approved (149 clinician, 50 translational scientist, and 47 basic scientist)
- 26 Drug Development Project Teams with 28 agents were sponsored; of the 92 studies that have gone through these teams, 85% have a young investigator principal investigator/mentor team for leadership
- 55 administrative/biomarker assay development supplements were developed
- 2,654 patients were studied using 85 NCI-IND agents and 62 investigational agent (novel-novel) combinations

**ETCTN Accomplishments**

Investigators submitted and participated in 915 PTMAs for 26 drug development project teams (with 28 agents), and submitted 177 LOIs (48 solicited and 129 unsolicited). Overall, 78% of solicited and unsolicited LOIs had been approved between March 1, 2020, and August 31, 2023. During this same period, 86 trials were closed or completed, and 166 were ongoing in the experimental therapeutics program: 79 (48%) were phase 1, 30 (18%) were phase 1/2, 55 (33%) phase 2, and 1 was phase 0 (0.6%). The CTEP phase 1 trials account for greater than 60% of phase 1 trials (excluding pediatric, NCI Center for Cancer Research, and others) performed under NCI sponsorship.

The agent classes studied under the ETCTN include novel agents that target relevant cancer cell signaling pathways, as well as essential cellular machinery involved in the regulation of cell survival and apoptosis, proliferation, and differentiation. Agents include inhibitors of Phosphoinositide 3-kinase (PI3K), tyrosine kinases, epidermal growth factor receptor, fibroblast growth factor receptor, angiogenesis, mTOR, cell cycle progression, histone deacetylases, the proteasome, heat shock proteins, and poly (ADP-ribose) polymerase (PARP). New agent classes that are now part of the CTEP drug development program include oncolytic viruses, radiopharmaceuticals, antitumor vaccines, antibody-drug conjugates, and cellular therapies.

**Evaluation of Translational Endpoints**

The evaluation of correlative studies in the ETCTN program proceeds in a judicious fashion through collaboration, and with input from the Investigational Drug Steering Committee, the Cancer Diagnosis Program and the Pharmacodynamic Assay Development and Implementation Section (PADIS) and Molecular Characterization laboratories (MoCha) at the FNLCR to assess drug activity using molecular targets or their downstream effectors. The ETCTN has integrated NCI's and NIH's precision medicine and Cancer Moonshot℠ research initiatives through supplemental funding to ETCTN investigators, including launching the Cancer Immune Monitoring and Analysis Centers, Patient-Derived Xenograft Network, Centers for the Study of Drug Resistance and Sensitivity (now Acquired Resistance to Therapy Network) and Partnership for Accelerating Cancer Therapies through the Foundation for the National Institutes of Health to develop standardized immunotherapy biomarkers. Overall, 79 studies incorporated biomarker assays, including 69 with tumor biopsies, 52 assessed target effects, 20 incorporated investigational imaging, and 39 early-phase trials included pharmacokinetics (PK). A number of these studies have included food effect analysis and evaluations for drug-drug interactions that were not being undertaken by the pharmaceutical or academic collaborator.

**Evaluating Combinations of Investigational Agents**

During this reporting period, 135 ongoing trials have tested investigational agent combinations. These trials analyzed combinations of one of NCI/CTEP-IND agents (novel targeting agents) with commercial/older agents or the combination of two investigational agents (97% from different companies). The pharmaceutical industry rarely tests investigational agent combinations from different companies due to intellectual property concerns. Of 150 investigational combination studies abstracted from ClinicalTrials.gov and the literature recently, approximately two-thirds were performed in the early-phase ETCTN Program (approximately 320 combo trials performed in the last 20 years.) These studies continue to be a high priority for the network as part of their assessment of immunotherapy, multiple signaling, regulatory, and metabolic pathway targeting agents.

**Dose Determination/Recommendations in Special Population Patients with Abnormal Hepatic or Renal Function**

The ETCTN provides an important function in conducting uniquely challenging clinical trials with patients who would otherwise be excluded from treatment with specific anticancer agents based on end organ dysfunction. A consortium of sites (across ETCTN) organized to study the effects of anticancer drugs in patients with abnormal kidney and liver function evaluated many IND agents that are now FDA approved. Ten clinical trials have established the safe use of romidepsin, veliparib/carboplatin/ paclitaxel, belinostat, dabrafenib, trametinib, dasatinib, triapine, tazemetostat (EZH2 inhibitor) in cancer patients with end organ dysfunction, and a unique trial of ten groups of patients with autoimmune disorders. These studies provided the PK, pharmacodynamics (PD), toxicity profile, and dose modifications (as appropriate) for these special patient populations.

**Novel Early-Phase Trial Designs**

Novel early-phase trial designs including accelerated titration, Bayesian/BOIN, and other adaptive designs have been employed to optimize the number of patients receiving active doses of an investigational therapeutic. Ten investigational agents that were evaluated in a series of eighteen phase 1 studies employing the accelerated titration design were able to safely achieve their desired endpoints. Of 52 phase 1 and 1/2 trials activated between March 1, 2020 and December 31, 2023, 16 (31%) used a BOIN design and 2 (4%) used a Simon 2-stage design. Of the remaining studies that used a 3+3 design, seven used a modified 3+3 or IQ 3+3 design. The NCI continues to explore these and other adaptive clinical trial designs to further facilitate patient selection and biomarker development.

**Publications**

Since 2020, 156 manuscripts from early-phase and ETCTN trials or related studies supported by this UM1 have been published.

### NCI Early Drug Development Opportunity (EDDOP)

Approval of the ETCTN Phase 2 Cancer Centers supplement in 2016 resulted in the creation of the EDDOP, a collaboration between the ETCTN and the NCI Cancer Centers Program. EDDOP creates ETCTN participation opportunities by using ETCTN program funds to provide supplements to P30 grants. There are two parts of the EDDOP Program:

- Accrual supplements: Eight NCI Cancer Centers successfully competed for supplemental funding that allows them to open select ETCTN studies at their sites. Twenty-three studies were added to the EDDOP Program between March 1, 2020, until August 31, 2023. Unfortunately this resulted in only 60 patients being enrolled, an average of one patient per study per year. Due to poor outcome, the accrual supplements will no longer be offered.
- Study Leadership supplements: There were five recipients of these supplements in the grant cycle.

### NCI Early Drug Development for Underrepresented Communities

As a commitment to enrollment of historically underserved (racial/ethnic/geographic) populations and to decrease cancer treatment disparities, CATCH-UP.2020 (Create Access to Targeted Cancer Therapy for Underserved Populations) program piloted an ETCTN initiative supported through NCI P30 administrative supplement awards to eight NCI-Designated Comprehensive Cancer Centers. Across all sites, 111 protocols were activated. The investigators screened 571 patients and enrolled 373 patients to ETCTN studies during the year this program was active.

### National Clinical Laboratory Network (NCLN)

The ETCTN conducts early phase clinical trials (examples shown in **Table 4**) of investigational anti-cancer agents, and these are arguably the most important trials to facilitate better understanding of the PD, genomic, transcriptomic, and proteomic underpinnings of outcomes in clinical trials. While the ETCTN is well-positioned to conduct these clinical trials, robust and reliable laboratory assays are needed to perform molecular characterization and PD studies. These are often high-complexity assays requiring a combination of specialized specimen collection and preparation, measurement expertise/experience, and test instrumentation to be successful and reliable (**Table 5**). Many components of these molecular assay pipelines are not readily available to most investigators or are not operating under rigorous best practices. The NCLN was established to provide centralized, robust assays and expanded support for ETCTN studies. The NCLN utilizes validated assays, certified operators, and harmonized SOPs to characterize tumors pre- and post-treatment via next-generation sequencing technology and sophisticated, highly quantitative multiplex PD assays.

An NCLN genomics laboratory was established at MD Anderson Cancer Center. When fully operational, it will perform NGS-based assays (**Table 6**) in a manner fully harmonized with the Molecular Characterization Laboratory (MoCha) at the Frederick National Laboratory for Cancer Research (FNLCR). These assays will include a targeted sequencing panel for tumor DNA, whole exome sequencing, RNAseq, and sequencing of circulating DNA on the Illumina platform. Two multiplex PD assays will also be established

| Study Number | Study Name | Accomplishments |
|---|---|---|
| 10005 | Phase II Atezolizumab in Alveolar Soft Part Sarcoma (ASPS) | 2022 FDA approval for the use of atezolizumab, a drug previously approved for patients with other cancer types, for the treatment of advanced ASPS, thereby providing a new treatment option for patients with this rare and aggressive type of cancer which does not respond to chemotherapy. |
| 9681 | Phase I Cabozantinib + Nivolumab +/- Ipilimumab in Advanced /Metastatic Urothelial Carcinoma and Other Genitourinary Tumors | Foundation for CHECKMATE-9ER study that led to 2021 FDA approval of cabozantinib + nivolumab in patients with advanced renal cell carcinoma, providing a new treatment approach for this advanced metastatic disease. |
| 9673 | Phase II Study of Nivolumab +/- Ipilimumab in Refractory Metastatic Squamous Cell Carcinoma of the Anal Canal | - Changed the National Comprehensive Cancer Network (NCCN) guidelines.<br>- First demonstration of anti-PD-1 in squamous cell carcinoma of anal cancer |

TABLE 4: NOTABLE RECENT CTEP-SPONSORED EARLY PHASE TRIALS.

in the NCLN. A quantitative immunofluorescence assay for γ-H2AX and pNBS1 with β-catenin segmentation is being set up at MD Anderson using the SOPs developed by the PADIS group at FNLCR. The Molecular Pathology Laboratory Network, an independently owned company, established the multiplex apoptosis panel for analysis of tumor biopsy extracts by quantitative immunoassay on the Luminex platform. As additional assays undergo development and validation at FNLCR, they may be added to the NCLN test menu.

The NCLN also includes a dedicated biorepository at Nationwide Children's Hospital in Columbus, Ohio, which receives, processes, and distributes the samples collected on the ETCTN clinical trials according to reproducible and standardized SOPs. The centralized support for these complex assays provided through the NCLN will permit comparisons of assay results across trials, which is advantageous for ETCTN project teams that conduct several trials of the same agent in different combinations and clinical settings.

| Biomarker Assay Name(s) | Assay Format | # of Studies | Example |
|---|---|---|---|
| **γH2AX, pNBS1**<br>β-catenin segmentation^ | Multiplex Immunofluorescence Assay (mIFA) | 22 | **Study# 10276**: A Phase I/II Study of M3814 and Avelumab in Combination with Hypofractionated Radiation in Patients with Advanced/Metastatic Solid Tumors and Hepatobiliary Malignancies |
| **γH2AX, pY15-Cdk**<br>β-catenin segmentation^<br>Newly added to NCLN assay menu April 2023 | Multiplex Immunofluorescence Assay (mIFA) | N/A | N/A |
| **Apoptosis***<br>**Panel 1:** BAK, BAX, Lamin-B, Smac, dimer<br>**Panel 2:** BIM, BAD, BAX-Bcl-2 heterodimer, Bcl-xL, Mcl-1<br>**Panel 3:** BAK-Mcl-1 heterodimer, BAK-Bcl-xL heterodimer, Active Caspase 3 (cleaved), Survivin | Multiplex Luminex Assay | 9 | **Study# 10499**: Phase Ib/II Study of ZEN003694 and Entinostat in Advanced and Refractory Solid Tumors and Lymphomas |
| **AKT Panels 3-4***<br>**Panel 1:** AKT1, AKT2, AKT3, rpS6<br>**Panel 2:** pS473-AKT1, pS474-AKT2, pS472-AKT3, pS235-rpS6<br>**Panel 3:** pT308-AKT1, pT309-AKT2, pT305-AKT3, pS240/244-rpS6 | Multiplex Luminex Assay | 2 | **Study# 10492**: Phase Ib/II Study of AKT Inhibitor Ipatasertib with Chemoradiation for Locally Advanced Head and Neck Cancer |
| **AKT Panels 4-5***<br>**Panel 4:** ERK1, ERK2, MEK1, MEK2<br>**Panel 5:** pS218/S222-MEK1, pS222/S226-MEK2, pT202/Y204-ERK1, pT185/Y187-ERK2 | Multiplex Luminex Assay | 3 | **Study# 10496**: A Phase 2 of Ipatasertib in Combination with Pembrolizumab for First Line Treatment of Recurrent or Metastatic Squamous Cell Cancer of the Head and Neck |

**TABLE 5: NCLN PD ASSAYS AVAILABLE FOR ETCTN TRIALS.**

^ Assays performed by NCLN PD Assay Laboratory at MD Anderson

* Assays performed by National Clinical Target Validation Laboratory (NCTVL), Frederick National Laboratory for Cancer Research (FNLCR)

| Biomarker Name | Assay Format | # of Studies | Example |
|---|---|---|---|
| Whole Exome Sequencing (WES)<br>• Tumor<br>• Blood, Germline Control | Next-Generation Sequencing (NGS) on the Illumina platform | 82 | **Study# 10191:** A Phase 2 Study of M6620 (VX-970, Berzosertib) in Combination with Carboplatin Compared with Docetaxel in Combination with Carboplatin in Metastatic Castration-Resistant Prostate Cancer |
| RNAseq | Next-Generation Sequencing (NGS) on the Illumina platform | 65 | **Study# 10217**: A Phase 1b Biomarker-Driven Combination Trial of Copanlisib, Olaprib, and MEDI4736 (Durvalumab) in Patients with Advanced Solid Tumors |
| Oncomine Panel | Targeted NGS (DNA & RNA) | 3 | **Study# 10150**: A Randomized Phase 2 Study of Bevacizumab and Either Weekly Anetumab Ravtansine or Weekly Paclitaxel in Platinum-Resistant or Platinum Refractory Ovarian Cancer |
| Circulating Tumor DNA (ctDNA) | TruSight Oncology 500 cfDNA (TSO500) | 49 | **Study# 10324**: A Phase I/Ib Dose Escalation Study of Pegylated Liposomal Doxorubicin (PLD) with Peposertib (M3814) in Platinum-Resistant or Ineligible Ovarian and Related Cancers with Planned Expansions in High Grade Serous (HGSOC) and Low Grade Serous Ovarian Cancer (LGSOC) |

**TABLE 6: NCLN GENOMICS ASSAYS AVAILABLE FOR ETCTN TRIALS.**
Assays performed by NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research

## NCI National Clinical Trials Network (NCTN)

On March 1, 2014, after several years of extensive consultation and coordination with numerous stakeholders, NCI transformed its longstanding Cooperative Group Clinical Trials program into the NCTN for the conduct of large-scale, national oncology treatment and advanced imaging clinical trials in the era of precision medicine. This transformation was designed to address new and emerging scientific opportunities and to provide a centralized infrastructure for more efficient conduct of clinical trials across a broad, national network, while maintaining a commitment to conducting trials in diverse and special populations. The work of the NCTN continued in 2019 with the successful recompetition of the NCTN grant infrastructure.

The NCTN's integrated and collaborative network infrastructure provides a broad investigator base drawn from NCI-designated Cancer Centers, the NCI Community Oncology Research Program (NCORP), Minority/Underserved NCORPs, and other academic and community hospitals and private practitioners across the U.S. and internationally. The NCTN's Group system is designed to engage hundreds of enrolling sites with central trial registration, data management, and tumor banking processes. The NCTN's Cancer Trials Support Unit provides online access to all protocol and other trial-related materials and the NCI Central Institutional Review Board (CIRB) covers human subject protection for the conduct of all trials conducted at US sites.

The primary focus of the NCTN is the conduct of multi-center, late-phase, clinical treatment and advanced imaging trials. A recent analysis conducted by the US adult NCTN Group grantees found that 162 positive phase 3 randomized trials had been reported out by their groups since 1980, with 87.7% of these trials contributing to changes in cancer care guidelines.[3] The authors estimated that the trials generated 14.2 million additional life years for patients with cancer through 2020 with a federal return on investment of $326 dollars per life-year gained.

The NCTN program is intended to complement, rather than duplicate, research conducted by the private sector. The NCTN's portfolio of trials addresses several types of questions not well supported in a commercial environment, including:

- Radiotherapy, surgery, and multimodality treatment trials

[3] Unger JM, et al. Population, Clinical, and Scientific Impact of National Cancer Institute's National Clinical Trials Network Treatment Studies. *J Clin Oncol*. 2023 Apr 10;41(11):2020-2028. doi: 10.1200/JCO.22.01826. Epub 2022 Dec 8.

- De-escalation trials evaluating whether less treatment can produce disease outcomes that are not worse than more treatment (i.e., that are non-inferior)
- Trials studying the sequence of different agents and other treatments
- Trials requiring an extensive, national patient catchment area
- Trials in special populations, such as children, adolescents, and young adults
- Rare cancer trials

A significant number of NCTN trials are conducted under collaborative agreements with industry partners, including NCTN precision medicine trials, which harness next generation DNA and RNA sequencing methods to screen large numbers of patients to identify appropriate patient populations for evaluation of new therapies. NCTN's national network has been able to screen large numbers of patients to identify those whose tumors exhibit molecular features that may be responsive to new, targeted treatments and/or immunotherapy approaches. In addition to late-phase trials, appropriate preliminary studies needed for development of potential definitive trials, especially umbrella/basket trials and rare tumor trials oriented to discovery, are also conducted within the NCTN when a national patient catchment area is required.

**Selected Recent NCTN Trial Results**

**S1826: A Phase III, Randomized Study of Nivolumab (Opdivo) Plus AVD or Brentuximab Vedotin (Adcetris) Plus AVD in Patients (Age > 12 Years) with Newly Diagnosed Advanced Stage Classical Hodgkin Lymphoma (SWOG Study NCT03907488)**

This collaborative trial brought the pediatric and adult NCTN Groups together to rapidly enroll nearly 1,000 patients, including significant numbers of adolescent and young adult (AYA) patients, between July 2019 and December 2022. The trial found that nivolumab plus AVD was well tolerated and had improved progression-free survival (PFS) compared to brentuximab plus AVD. Results were presented at the 2023 ASCO Plenary Session.[4]

**N1048: A Phase II/III Trial of Neoadjuvant FOLFOX, with Selective Use of Combined Modality Chemoradiation Versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision (Alliance Study NCT01515787)**

This de-escalation trial evaluated whether neoadjuvant FOLFOX could allow some patients with locally advanced rectal cancer to avoid standard chemoradiotherapy without increased risk of recurrence. Nearly 1,200 patients were enrolled at more than 200 NCTN sites, and patients were followed for a median of 58 months to observe the required number of events for the non-inferiority analysis. The trial found that FOLFOX neoadjuvant with chemoradiotherapy used only in select patients was noninferior to standard neoadjuvant chemoradiotherapy, allowing many patients to potentially avoid chemoradiotherapy. Results were presented at the 2023 ASCO Plenary Session and simultaneously published in the *New England Journal of Medicine*.[5]

**NRG-GY018: A Phase III Randomized, Placebo-Controlled Study of Pembrolizumab (MK-3475, NSC #776864) in Addition to Paclitaxel and Carboplatin for Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Cancer (NRG Study NCT03914612)**

This trial found that pembrolizumab given in combination with chemotherapy resulted in significantly improved PFS in advanced and recurrent endometrial cancer patients with both deficient and proficient DNA mismatch repair. Results were presented at the 2023 SGO Plenary Session and simultaneously published in the *New England Journal of Medicine*.[6]

[4] Herrera AF, et al. SWOG S1826, a randomized study of nivolumab(N)-AVD versus brentuximab vedotin(BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL). *J Clin Oncol*. 2023 Jun 41 (17 suppl). doi: 10.1200/JCO.2023.41.17_suppl.LBA4.
[5] Schrag D, et al. Preoperative Treatment of Locally Advanced Rectal Cancer. *N Engl J Med*. 2023 Jul 27;389(4):322-334. doi: 10.1056/NEJMoa2303269. Epub 2023 Jun 4.
[6] Eskander RN, et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. *N Engl J Med*. 2023 Jun 8;388(23):2159-2170. doi: 10.1056/NEJMoa2302312. Epub 2023 Mar 27.

**E1910: A Phase III Randomized Trial of Blinatumomab for Newly Diagnosed BCR-ABL-Negative B Lineage Acute Lymphoblastic Leukemia in Adults (ECOG-ACRIN Study NCT02003222)**

This trial found that blinatumomab added to consolidation chemotherapy led to significantly better overall survival in patients with newly diagnosed B-cell ALL who were MRD negative after intensification chemotherapy. These results represented a new standard for BCR::ABL1 negative ALL patients aged 30-70 years. Results were presented as a Late Breaking Abstract at the 2022 ASH Annual Meeting.[7]

**AHOD1331: A Randomized Phase 3 Study of Brentuximab Vedotin (SGN-35, IND #117117) for Newly Diagnosed High-Risk Classical Hodgkin Lymphoma (cHL) in Children and Young Adults (COG Study NCT02166463)**

This pediatric and AYA trial found that patients receiving brentuximab vedotin with chemotherapy had a superior 3-year event free survival (92.1%) compared to those who did not receive the agent (82.5%) with no increase in toxicity and supported an FDA approval for the indication. Results were simultaneously used in support of the FDA approval and published in the *New England Journal of Medicine*.[8]

**NCTN Organizational Structure**

The NCTN is designed to be a collaborative network made up of the following grant and contract components (**Figure 11**):

- NCTN Network Groups leading trials
- Lead Academic Participating Sites (LAPS) participating in trials along with NCI NCORP and rostered member sites
- NCTN biospecimen banks facilitating biospecimen collection and banking
- Integrated Translational Science Awards (ITSAs) providing translational research expertise
- Imaging and Radiation Oncology Core (IROC) providing quality assurance/control and data collection for radiotherapy and imaging objectives
- Centralized NCI support for key scientific, administrative, and regulatory functions
- Substantial NCI involvement in scientific and programmatic stewardship of these cooperative agreements

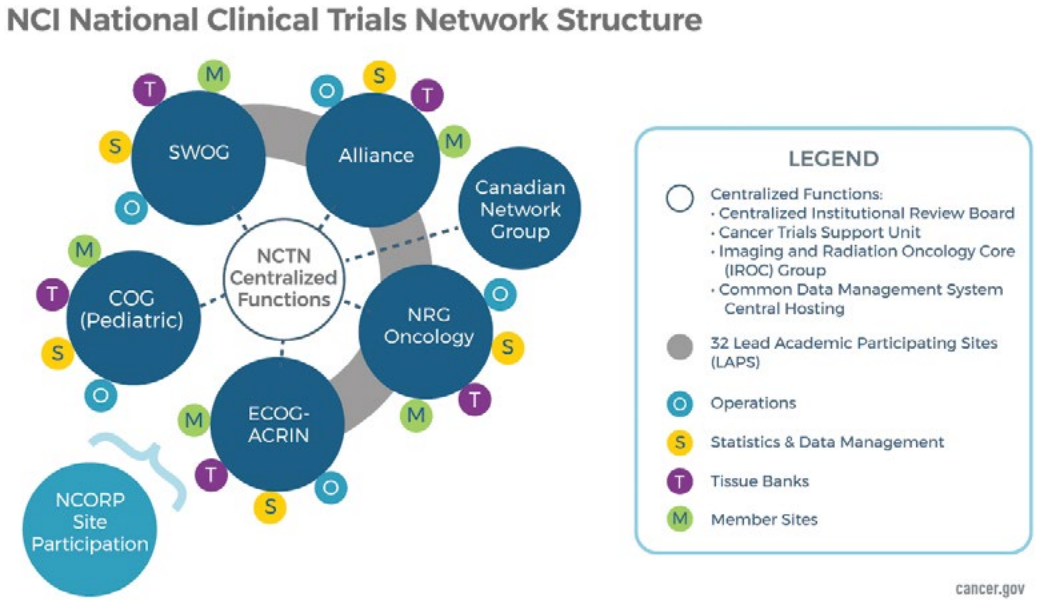



FIGURE 11: NCI NATIONAL CLINICAL TRIALS NETWORK STRUCTURE.

[7] Litzow MR, et al. Consolidation Therapy with Blinatumomab Improves Overall Survival in Newly Diagnosed Adult Patients with B-Lineage Acute Lymphoblastic Leukemia in Measurable Residual Disease Negative Remission: Results from the ECOG-ACRIN E1910 Randomized Phase III National Cooperative Clinical Trials Network Trial. *Blood* 2022 Dec 6;140(Suppl 2):LBA-1. doi: 10.1182/blood-2022-171751

[8] Castellino SM, et al. Brentuximab Vedotin with Chemotherapy in Pediatric High-Risk Hodgkin's Lymphoma. *N Engl J Med*. 2022 Nov 3;387(18):1649-1660. doi: 10.1056/NEJMoa2206660.

**NCTN Network Groups**

The NCTN includes five U.S. Network Groups (one pediatric and four adult focused Groups) and one Canadian Collaborating Network Group. Each U.S. Network Group is supported by multiple cooperative agreements: one grant to the NCTN Group Operations Center, one grant to the Group Statistics and Data Management Center, and one grant to the Group Biobank. The Canadian Collaborating Network Group is supported by a single cooperative agreement and is responsible for partnering with the U.S. Network Groups in the conduct of large-scale, multi-site clinical trials and helping provide regulatory expertise/oversight for the conduct of NCTN trials in Canada.

The NCTN Group Operations Centers provide scientific leadership for developing and implementing multi-disciplinary, multi-institutional trials in a range of diseases and special populations with specific scientific strategy and goals. The Operations Centers are responsible for developing new protocols and managing the regulatory, financial, membership, and scientific committees of each group as well as the conduct of the studies the group leads, including safety monitoring. The Operations Centers are expected to be closely integrated with their corresponding Statistics and Data Management Center in all aspects of trial operations through jointly developed policies and procedures for clinical trial development and conduct.

The NCTN Group Statistical Centers are responsible for providing the statistical expertise required to ensure effective scientific design and conduct of clinical trials as well as leadership in innovation of statistical methodology. These centers are also responsible for data management, data analysis, and statistical analysis for NCTN trials led by their affiliated Network Group Operations Center as well as for translational and other ancillary studies associated with the trials.

NCTN clinical trials are uniquely positioned to provide high-quality biologic specimens associated with detailed treatment histories, recurrence data, and careful follow-up from patients over long periods of time. The NCTN Biobanks constitute a large collection of well-annotated biospecimens from people enrolled on NCTN clinical trials run through the NCTN Groups. Although funding for sites to collect biospecimens is provided under the NCTN Group Operations Center grants along with scientific review for use of biospecimens, funding for the NCTN Group Biobanks is provided by a separate grant program under the oversight of the NCI Cancer Diagnosis Program.

The five U.S. NCTN Groups and the Canadian Collaborating Network are:

- Alliance for Clinical Trials in Oncology
- ECOG-ACRIN Cancer Research Group
- NRG Oncology
- SWOG
- Children's Oncology Group (COG)
- Canadian Cancer Trials Group (CCTG)

Clinical trials led by NCTN Groups may utilize the IROC, ITSAs, and the tissue banks, when appropriate, to support the scientific needs of the trial.

NCTN trials can enroll patients from sites that are LAPS, NCORP sites, or are rostered members of an NCTN Group. Site membership in an NCTN Group is based on criteria as defined individually by each group. Sites can belong to more than one group, and membership in at least one group allows a site to participate in the trials led by any NCTN Group for which their investigators are qualified. Consequently, researchers from the LAPS, NCORP sites, other academic centers, community practices, and international sites that are full members of a Network Group may enroll patients onto any NCTN trial if the site meets all trial-specific requirements. These sites are augmented by member sites from the Canadian Network Group and other international member sites.

**Lead Academic Participating Sites (LAPS)**

As part of the 2019 recompetition, 32 U.S. academic research institutions were selected as LAPS funded through UG1 cooperative agreements. These sites are academic research institutions with fellowship training programs that have demonstrated their ability to enroll high numbers of patients onto NCTN trials, as well as to provide scientific leadership in trial design and conduct. The LAPS grant component of the NCTN provides additional support to the selected institutions for the increased level of patient data management work required because of their high enrollment rate. The current 32 LAPS grantees are:

Case Western Reserve University – Case Comprehensive Cancer Center

Dana Farber/Harvard Cancer Center

Duke Cancer Institute at Duke University Medical Center

Emory University – Winship Cancer Institute

Fred Hutchinson Cancer Research Center

Johns Hopkins University – Sidney Kimmel Comprehensive Cancer Center

Mayo Clinic Cancer Center

Medical College of Wisconsin

Memorial Sloan Kettering Cancer Center

Norris Cotton Cancer Center at Dartmouth Hitchcock Medical Center

Northwestern University – Robert H. Lurie Comprehensive Cancer Center

Ohio State University Comprehensive Cancer Center

Roswell Park Cancer Institute

Sidney Kimmel Cancer Center at Jefferson Health

University of Alabama at Birmingham

University of California Davis Comprehensive Cancer Center

University of Chicago Comprehensive Cancer Center

University of Colorado Cancer Center

University of Michigan Comprehensive Cancer Center

University of North Carolina Lineberger Comprehensive Cancer Center

University of Oklahoma – Stephenson Cancer Center

University of Pittsburgh Cancer Institute

University of Rochester Wilmot Cancer Institute

University of Southern California – Norris Comprehensive Cancer Center

University of Texas MD Anderson Cancer Center

University of Texas Southwestern Medical Center – Harold C. Simmons Cancer Center

University of Utah – Huntsman Cancer Institute

University of Wisconsin Carbone Cancer Center

Vanderbilt University Medical Center – Vanderbilt Ingram Cancer Center

Washington University at St. Louis – Siteman Cancer Center

Wayne State University Barbara Ann Karmanos Cancer Institute

Yale University – Yale Cancer Center

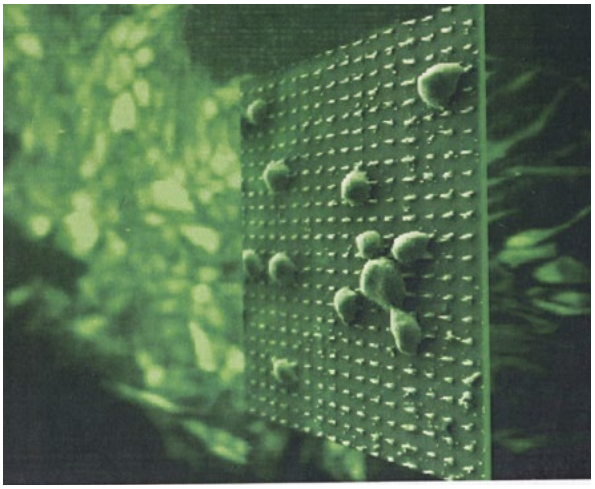
**Integrated Translational Science Awards (ITSAs)**

The NCTN contains a translational component, consisting of five academic institutions funded through ITSA grants to support teams of translational scientists. These teams use innovative genetic, proteomic, and imaging technologies to help identify and qualify potential predictive biomarkers of response to therapy that the NCTN Groups can incorporate into future clinical trials. These awards leverage ongoing work in the investigators' laboratories, which is often supported in part by other NCI grants, to assist the NCTN Groups to bring new laboratory discoveries into clinical trials. These laboratories employ cutting-edge technologies that characterize tumors and identify changes in tumor biology in response to treatment that may help explain mechanisms of treatment resistance. The five current ITSA-funded projects are:

- COG NCTN Integrated Translational Science Center for Hematopoietic Malignancies in Children; Children's Hospital of Philadelphia
- ECOG-ACRIN Thoracic Malignancies Integrated Translational Science Center; Emory University – Winship Cancer Institute
- ECOG-ACRIN Integrated Leukemia Translational Science Center; Memorial Sloan Kettering Cancer Center
- Integrated Translational Science Center for Leukemia for Alliance & SWOG; Ohio State University Comprehensive Cancer Center
- UNC / UT National Clinical Trials Network Group Integrated Translational Science Production and Consultation Center for Alliance & NRG; University of North Carolina Lineberger Comprehensive Cancer Center

**Imaging and Radiation Oncology Core (IROC)**

To help monitor and ensure quality in trials that involve new imaging modalities and/or radiation therapy, the NCTN established a consolidated IROC to assist NCTN Groups using these modalities in their trials. The consolidation of these activities under the leadership of a centralized core team improves efficiency and optimizes the use of these resources by the entire network. This unique Quality Assurance (QA) entity brings together imaging QA leaders and specialists into a single, coordinated program designed to support the NCTN and other NCI-sponsored groups and networks to carry out rigorous oncologic multi-center clinical trials. Within the context of NCI-sponsored trials, the IROC is tasked with providing:



- Scientific expertise in advanced medical imaging, radiotherapy, and information technology to support establishment of appropriate QA procedures
- Consultation to the NCTN Groups in the development of research protocols early in the process to assist with hypothesis generation and trial design that can be supported by effective QA programs
- Resources for the efficient collection, qualification, analysis, archive and transfer of images, radiotherapy plans and associated clinical data
- Qualification and credentialing policies to help ensure the delivery of appropriate protocol-specified radiotherapy and advanced imaging

**NCTN Processes: From Trial Idea to Practice-Changing Results**

The NCTN Groups draw on their robust membership of scientific leaders to identify and develop ideas for trials that are scientifically promising and statistically rigorous. Clinical trial ideas are submitted by the NCTN Groups to NCI for review through two primary pathways: smaller, earlier phase trials are submitted as Letters of Intent (LOIs) and a decision is made by the NCI CTEP Protocol Review Committee, while larger, later phase trials are submitted as Concepts and a decision is made by the NCTN Steering Committees. The LOI or Concept is evaluated by reviewers from across NCI (experts in the disease area, experts who focus on that agent or type of treatment, biostatisticians, and others as needed).

After an LOI or Concept is approved, the Group works on developing the protocol and informed consent based on the approved trial designs. When the protocol and consent have been approved by all NCI DCTD/CTEP reviewers, the study is sent to the NCI CIRB for review. Throughout this process, CTEP contractors work with the lead Group to set up the study in CTEP systems and develop support documents such as the National Coverage Analysis to help sites evaluate what items in the protocol are billable to insurance and, starting in 2023, electronic medical record (EMR) templates to help sites implement the protocol in their local EMR systems. After the protocol is finalized and opens to enrollment, CTEP oversight and collaboration with the lead Group continues throughout the life of the trial.

NCTN trials have changed clinical practice across numerous cancer disease areas, frequently resulting in changes to the National Comprehensive Cancer Network guidelines, which are evidence-based standards for clinical cancer care, and in new approved FDA indications. **Table 7** shows selected NCTN trials supporting FDA approval for an indication.

| Year | Agent | Organizations (Legacy Organizations) | Cancer Site | Type of Indication |
|---|---|---|---|---|
| 2004 | Oxaliplatin | Alliance for Clinical Trials in Oncology (NCCTG) | Colorectal | Secondary |
| 2005 | Nelarabine | Childrens Oncology Group & Alliance for Clinical Trials in Oncology (POG & CALGB) | T-Cell Leukemia/Lymphoma | Primary |
| 2006 | Bevacizumab | ECOG-ACRIN (ECOG) | Colorectal | Secondary |
| 2006 | Bevacizumab | ECOG-ACRIN (ECOG) | Lung | Secondary |
| 2006 | Herceptin | NRG Oncology & Alliance for Clinical Trials in Oncology (NSABP & NCCTG) | Breast | Secondary |
| 2006 | Imatinib mesylate | Children's Oncology Group | Chronic Myeloid Leukemia | Contributing (in pediatric population) |
| 2006 | Rituximab | ECOG-ACRIN (ECOG) | Non-Hodgkins Lymphoma/B-cell Lymphoma | Secondary |
| 2006 | Thalidomide | ECOG-ACRIN (ECOG) | Multiple Myeloma | Secondary |
| 2008 | Imatinib mesylate | Alliance for Clinical Trials in Oncology (ACOSOG) | GI Stromal Tumor | Secondary |
| 2008 | Imatinib mesylate | SWOG | GI Stromal Tumor | Contributing (related to dosing) |
| 2010 | Letrozole | Canadian Cancer Trials Group (NCIC-CCTG) | Breast | Secondary Indication |
| 2011 | Erwinia asparaginase | Children's Oncology Group | Acute Lymphoblastic Leukemia | Primary |
| 2014 | Bevacizumab | NRG Oncology (GOG) | Cervical | Secondary |
| 2015 | Dinutuximab | Children's Oncology Group (CCG) | Neuroblastoma | Primary |
| 2017 | Cabozantinib | Alliance for Clinical Trials in Oncology | Renal Cell | Secondary |
| 2017 | Lenalidomide | Alliance for Clinical Trials in Oncology (CALGB) | Multiple Myeloma | Secondary |
| 2017 | Midostaurin | Alliance for Clinical Trials in Oncology (CALGB) | FLT3 Mutated Acute Myeloid Leukemia | Primary |
| 2018 | Bevacizumab | NRG Oncology (GOG) | Ovarian | Secondary |
| 2018 | Calaspargase | Children's Oncology Group | Acute Lymphoblastic Leukemia | Primary |
| 2020 | Gemtuzumab Ozogamicin | Children's Oncology Group | Acute Myeloid Leukemia | Secondary |
| 2021 | Crizotimib | Children's Oncology Group | Anaplastic Large Cell Lymphoma | Secondary |
| 2021 | Daunorubicin & Cytarabine | Children's Oncology Group | Acute Myeloid Leukemia | Secondary |
| 2021 | Ibrutinib | ECOG-ACRIN (ECOG) | Chronic Lymphocytic Leukemia & Small lymphocytic lymphoma | Secondary |
| 2021 | Rituximab | Children's Oncology Group in collaboration with European Intergroup for Childhood Non-Hodgkin's Lymphoma (EICNHL) | Diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), & mature B-cell acute leukemia (B-AL) | Secondary |
| 2022 | Brentuximab Vendotin | Children's Oncology Group | Hodgkins Lymphoma | Secondary |
| 2022 | Olaparib | NRG Oncology (NSABP) in collaboration with the Breast International Group (BIG) | Breast | Secondary |

**TABLE 7: SELECTED NCTN TRIALS SUPPORTING FDA-APPROVED INDICATIONS.**

### NCTN Steering Committees

The NCI Coordinating Center for Clinical Trials convenes scientific steering committees, which are composed of leading cancer experts, community oncologists, biostatisticians, translational scientists, and patient advocates as well as NCI senior investigators. The NCTN steering committees are committed to increasing the exchange of information at an early stage of clinical trial development and the efficiency of clinical trial collaboration. NCTN Steering Committee activities include:

- Evaluating and prioritizing clinical trial concepts to be conducted through the NCTN at monthly meetings; sharing information at an early stage of trial development
- Reviewing and updating strategic priorities for a given disease or research area
- Assessing the strength of the clinical trial portfolio and its alignment with strategic priorities
- Convening clinical trial planning meetings to plan trials and address other trial-related issues as needed
- Forming task forces or working groups when needed to focus on a specific disease or issue

### NCTN Trial Portfolio and Accrual 2020-2023

*LOI and Concept Approvals*

There were 22 LOIs and 148 concepts approved in the NCTN between January 1, 2020, and December 31, 2023. Of these, the pediatric NCTN group led 25, and the adult groups led 145. The number of LOIs and concepts approved each year by the pediatric or an adult lead group are shown in **Table 8**. The dip in approvals in 2020 is likely attributable to a slowdown in processes during the beginning of the COVID-19 pandemic. The relatively higher number of approvals in 2021 may in part represent a rebound.

| | 2020 | 2021 | 2023 | 2023 | Total |
|---|---|---|---|---|---|
| LOI and Concepts Approved | 31 | 62 | 41 | 36 | 170 |
| Adult Group Approvals | 26 | 53 | 34 | 32 | 145 |
| Pediatric Group Approvals | 5 | 9 | 7 | 4 | 25 |

TABLE 8: NCTN LOI AND CONCEPT APPROVALS BY YEAR AND ADULT OR PEDIATRIC LEAD GROUP.

*Protocol Activations*

There were 169 protocols activated in the NCTN between January 1, 2020, and December 31, 2023. Of these, the pediatric NCTN group led 25 and the adult NCTN groups led 144. The number of protocols activated each year by pediatric or adult lead group are shown in **Table 9**. Following the dip in LOI and concept approvals in 2020, fewer protocols were activated in 2021 and 2022.

Of the activated protocols during this period, 49% were phase 2 trials (n=77), 10% were phase 2/3 trials (n=17), and 36% were phase 3 trials (n=60). Most activated protocols were investigational new drug (IND) trials: 45% of activations were trials where CTEP held the IND with the FDA, 20% were trials conducted under an IND held by an organization other than CTEP, such as the lead group, and 34% were IND exempt trials.

| | 2020 | 2021 | 2022 | 2023 | Total |
|---|---|---|---|---|---|
| **Total NCTN Protocol Activations** | 59 | 36 | 30 | 44 | 169 |
| **Adult or Pediatric Lead Group** | | | | | |
| Adult Group Activations | 49 | 31 | 24 | 40 | 144 |
| Pediatric Group Activations | 10 | 5 | 6 | 4 | 25 |
| **Trial Phase** | | | | | |
| Phase 1, 1/2 or Other | 4 | 1 | 2 | 3 | 10 |
| Phase 2 | 28 | 19 | 15 | 20 | 82 |
| Phase 2/3 or Phase 3 | 27 | 16 | 13 | 21 | 77 |
| **IND Type** | | | | | |
| CTEP IND | 27 | 21 | 12 | 16 | 76 |
| Non-CTEP IND | 12 | 7 | 4 | 11 | 34 |
| IND Exempt | 20 | 7 | 14 | 17 | 58 |

TABLE 9: NCTN PROTOCOL ACTIVATIONS BY YEAR AND ADULT OR PEDIATRIC LEAD GROUP, TRIAL PHASE, AND IND TYPE.

### Active Trials and Accrual in the NCTN

There were 308 protocols with at least one accrual between January 1, 2020, and December 31, 2023. NCI publicly posts PDF documents with diagrams depicting the NCTN trial portfolios by disease area for all trials actively recruiting

across the adult NCTN groups. These are intended to serve as an easy reference for those looking to see what trials were available in a disease area and to increase awareness of trials across groups. The diagrams were designed with input from the CTEP disease experts to aid the medical community in clearly identifying the trials available for a specific patient population. They are updated monthly and include links to the public Clinicaltrials.gov posting with more information about the trial.

The accrual data for the NCTN program are broken out by screening enrollments (when screening is performed as an integral component of the clinical trial or precision medicine initiative) and by intervention enrollments to the treatment/intervention part of the trial. As a result, patients may be counted as both a screening enrollment and an intervention enrollment if they are screened and then continue on a trial to the intervention.

An overall picture of accrual in the NCTN is shown in **Table 10**. Between January 1, 2020, through December 31, 2023, there were 49,550 NCTN intervention accruals and 12,472 screening accruals. Because many patients were screened and then enrolled on an intervention step in the same study, this represents 56,463 patients enrolled to NCTN trials over 4 years.

| | 2020 | 2021 | 2022 | 2023 | Total |
|---|---|---|---|---|---|
| **Protocols with Accrual** | 183 | 203 | 204 | 207 | 308 |
| **Distinct Patients Enrolled** | 15,141 | 15,267 | 13,671 | 12,581 | 56,463 |
| Intervention Enrollments | 12,918 | 13,200 | 12,134 | 11,298 | 49,550 |
| Screening Enrollments | 3,443 | 3,656 | 2,836 | 2,537 | 12,472 |

TABLE 10: NCTN PROTOCOLS WITH ACCRUAL, DISTINCT PATIENTS ENROLLED, INTERVENTION ENROLLMENTS, AND SCREENING ENROLLMENTS BY YEAR (2020-2023) AND TOTAL.

There were 1,590 sites from 27 countries with at least one NCTN accrual between January 1, 2020, and December 31, 2023. More than 1,400 of the enrolling sites are in the United States. These sites are shown in **Figure 12**, with sites designated as LAPS, NCORP, or rostered sites.

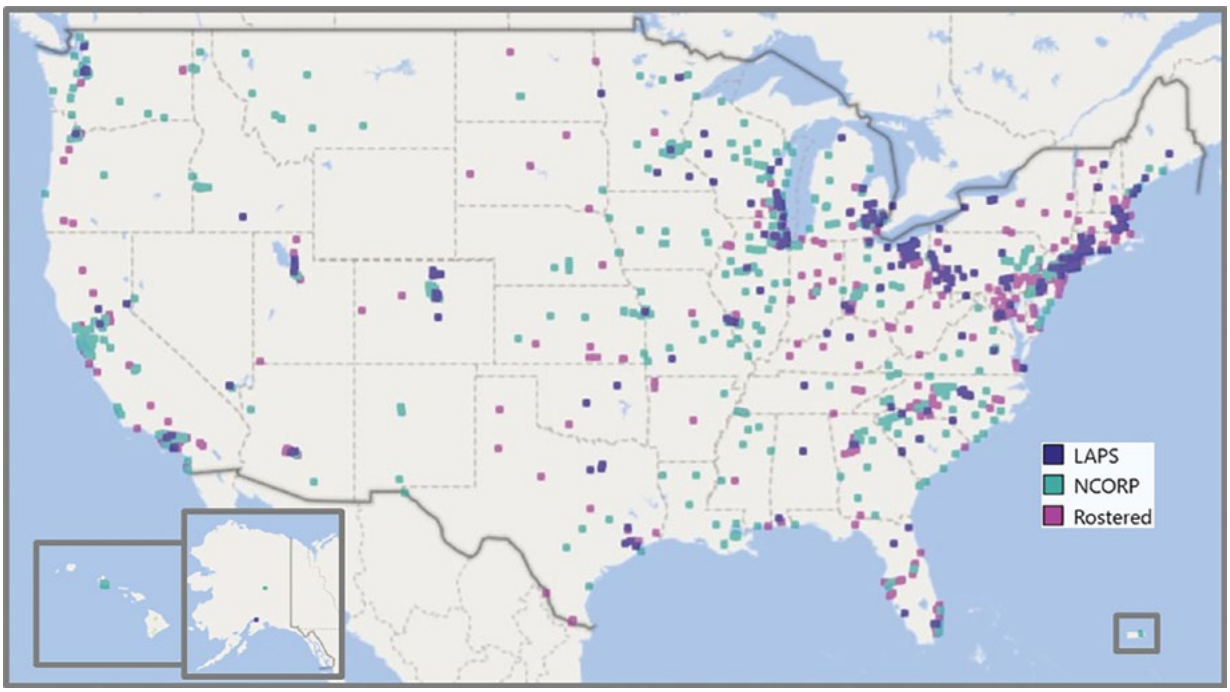



FIGURE 12: US SITES WITH AT LEAST ONE NCTN ACCRUAL 1/1/2020 AND 12/31/2023 BY SITE TYPE.

**Additional Initiatives in the NCTN**

*Specimen Sharing: NCTN Navigator and the NCTN Core Correlative Sciences Committees (NCTN-CCSCs)*

Most oncology biospecimens lack extensive clinical annotation and outcomes data. The biospecimen collections developed from cancer clinical trials conducted by the NCTN are highly annotated with carefully collected clinical data, including outcome data. The NCTN Navigator Clinical Trials Specimen Resource provides the research community, including investigators not affiliated with the NCTN, access to these high-quality, clinically annotated specimens and associated clinical data from a variety of NCTN cancer trials that can be used to test clinically important hypotheses. Remaining biospecimens are made available once the primary trial results have been reported out and materials have been allocated to complete the ancillary correlative studies embedded in the treatment trials.

The Navigator inventory includes specimens from large pediatric and adult treatment trials from which the primary outcome data have been reported. Specimens from newly completed trials are added on a rolling basis. As of December 2023, the Navigator inventory includes 86 trials led by the pediatric NCTN group with 800,595 available specimens and 196 trials led by the adult NCTN groups with 1,899,671 available specimens. The most common trial disease areas with specimens available through Navigator are breast cancer (20 trials), leukemia (16 trials), prostate cancer (12 trials), lung cancer (10 trials), ovarian cancer (13 trials), and head and neck cancer (12 trials).

Investigators interested in conducting research using specimens from NCTN trials can visit the Navigator website and readily explore the available specimens through the query tool. Any investigator interested in obtaining access to specific specimens from the Navigator inventory must submit a brief LOI detailing the specimens in which they are interested. If the LOI is found to be feasible, an investigator then submits a more extensive proposal describing their research project.

The NCTN-CCSCs are composed of NCI and extramural experts in oncology, laboratory science, translational medicine, pathology, statistics, biobanking, and patient advocacy, and perform a scientific review and prioritization of most Navigator proposals. The list of CCSC-approved proposals are publicly available. An expedited review process was developed in 2021 for small, exploratory requests from pediatric trials in Navigator to facilitate developmental research given the lack of available pediatric biospecimens from other resources/biobanks for this type of research compared to the availability of adult biospecimens. Through this process, NCI reviews qualifying proposals submitted through the expedited review process.

*Data Sharing: NCTN/NCORP Data Archive*

The NCTN and the NCORP clinical trials network evaluate therapies, diagnostics, and imaging approaches for the treatment, diagnosis, and prevention of cancer. The results of these NCI-sponsored clinical trials improve and lengthen the lives of individuals with cancer. These trials collect a large amount of information on each patient, including:

- Clinicopathologic data - demographic and pre-treatment clinicopathologic characteristics
- On-treatment information - treatments received and adverse events
- Outcome information - tumor response, quality of life measures, survival, etc.

Although individual trials are designed to provide convincing evidence to address their primary hypotheses, some research and clinical questions can be answered only by much larger datasets consisting of multiple trials. For example, analyzing treatment effects in defined subsets of patients (e.g., patients whose tumors have a specific mutation) or estimating the prevalence of rare adverse events requires pooling data across multiple trials.

The NCTN/NCORP Data Archive (the Archive) was established in 2017 to be a centralized and controlled-access resource to allow the widest availability of patient-level data from completed phase 3 NCTN and NCORP trials. The Archive complements other NCI data sharing activities that focus on genomic or imaging data as well as the sharing of specimens. The Archive primarily contains data from NCTN/NCORP phase 3 trials for which primary publication occurred on or after January 1, 2015. The information submitted to the Archive include patient-level data sufficient to approximately replicate the analyses presented in the primary publications. The data have been cleaned, and each Archive dataset has a comprehensive data dictionary.

Data from 117 NCTN trials and 26 NCORP trials are available in the Archive. The most common disease areas available in the Archive are breast cancer (20 trials), leukemia (16 trials), prostate cancer (12 trials), and lung cancer (10 trials). As of December 2023, 108 publications (presentations, abstracts, and

manuscripts) have been created using data obtained through the Archive, with many more in development.

## Small Cell Lung Cancer Consortium (SCLC-C)

The NCI's Small Cell Lung Cancer Consortium (SCLC-C) was created to address all five priorities established by the SCLC Scientific Framework Report and respond to the Recalcitrant Cancer Research Act of 2012, namely to:

- Build better research tools for the study of SCLC by (a) optimizing the collection of tumor tissue specimens representing distinct phases of SCLC, and (b) developing new tumor models that reflect the phases of SCLC presenting in the clinic
- Expand comprehensive genomic profiling studies of clinically annotated SCLC specimens to improve basic understanding of the frequency, distribution, and range of molecular abnormalities that exist at diagnosis and following therapeutic relapse
- Investigate new diagnostic approaches for populations at high risk of developing SCLC
- Focus therapeutic development efforts on specific molecular vulnerabilities of SCLC
- Examine mechanisms underlying both the high initial rate of response to primary SCLC therapy and the rapid emergence of drug and radiation resistance following completion of treatment

The SCLC-C consists of national and international leaders responsible for many key publications within the past four years spanning several focus areas (**Table 11** features selected papers out of 230). The consortium includes one U24 infrastructure grant, 21 U01 projects in early detection/diagnosis or therapy, 34 Associate Members' grants funded by the NCI in SCLC, and NCI intramural investigators focused on SCLC.

| SCLC-C Milestones | Publications |
|---|---|
| Molecular classification of SCLC | Baine, M.K., et al., SCLC Subtypes Defined by ASCL1, NEUROD1, POU2F3, and YAP1: A Comprehensive Immunohistochemical and Histopathologic Characterization. *J Thorac Oncol*. 15(12):1823-1835 (2020).<br>Tlemsani, C., et al., SCLC-CellMiner: A Resource for Small Cell Lung Cancer Cell Line Genomics and Pharmacology Based on Genomic Signatures. *Cell Rep* 33(3):108296 (2020).<br>Gay, C. M., et al., Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. *Cancer Cell* 39(3): 346-360 e347 (2021). |
| SCLC heterogeneity and plasticity | Ireland, A. S., et al., MYC Drives Temporal Evolution of Small Cell Lung Cancer Subtypes by Reprogramming Neuroendocrine Fate. *Cancer Cell* 38(1): 60-78 e12 (2020).<br>Travaglini, K. J., et al., A molecular cell atlas of the human lung from single-cell RNA sequencing. *Nature* 587(7835): 619-625 (2020).<br>Quintanal-Villalonga, A., et al., Multiomic Analysis of Lung Tumors Defines Pathways Activated in Neuroendocrine Transformation. *Cancer Discov* 11(12): 3028-3047 (2021).<br>Chan, J. M., et al., Signatures of plasticity, metastasis, and immunosuppression in an atlas of human small cell lung cancer. *Cancer Cell* 39(11): 1479-1496 e1418 (2021). |
| Drug resistance in SCLC | Grunblatt, E., et al., MYCN drives chemoresistance in small cell lung cancer while USP7 inhibition can restore chemosensitivity. *Genes Dev* 34(17-18): 1210-1226 (2020).<br>Stewart, C. A., et al., Single-cell analyses reveal increased intratumoral heterogeneity after the onset of therapy resistance in small-cell lung cancer. *Nat Cancer* 1: 423-436 (2020). |
| Immune responses in SCLC | Cai, L., et al., Cell-autonomous immune gene expression is repressed in pulmonary neuroendocrine cells and small cell lung cancer. *Commun Biol* 4(1): 314 (2021).<br>Zhu, M., et al., Evasion of Innate Immunity Contributes to Small Cell Lung Cancer Progression and Metastasis. *Cancer Res* 81(7): 1813-1826 (2021). |
| Therapeutic targets in SCLC | Augert, A., et al., MAX Functions as a Tumor Suppressor and Rewires Metabolism in Small Cell Lung Cancer. *Cancer Cell* 38(1): 97-114 e117 (2020).<br>Coles, G. L., et al., Unbiased Proteomic Profiling Uncovers a Targetable GNAS/PKA/PP2A Axis in Small Cell Lung Cancer Stem Cells. *Cancer Cell* 38(1): 129-143 e127 (2020).<br>Cristea, S., et al., The MEK5-ERK5 Kinase Axis Controls Lipid Metabolism in Small-Cell Lung Cancer. *Cancer Res* 80(6): 1293-1303 (2020). |

**TABLE 11: SELECTED SMALL CELL LUNG CANCER CONSORTIUM PUBLICATIONS.**

## The NCI Glioblastoma Therapeutics Network (GTN)

Treatment for adult glioblastoma (GBM) has not progressed despite large public and private investments into basic, translational, and clinical research. Numerous challenges can explain the lack of progress in GBM treatment including:

- Infiltration of malignant cells beyond the resected contrast enhancing tumor
- Surgical resection that cannot extend to obtain a tumor free margin
- Limited passage of therapeutic agents through the blood-brain-barrier (BBB)
- Reduced radiation therapy (RT) tolerance of the normal brain that limits RT dose
- Intratumoral genetic heterogeneity and plasticity
- An immunosuppressive tumor microenvironment

To address these challenges, NCI established a GBM Working Group (WG) of the Clinical Trials and Translational Research Advisory Committee (CTAC). The WG recommended the establishment of a national infrastructure to support the discovery and development of novel, effective GBM therapeutics. Moreover, the WG report detailed recommendations on the design and conduct of preclinical and early phase clinical trials to optimize GBM therapeutic development. From these recommendations, NCI established the Glioblastoma Therapeutics Network (GTN, RFA-CA-20-047), which was funded in September 2021. The GTN is distinct from the NCI Brain SPORE grant program and the Adult Brain Tumor Consortium. For example, the GTN structure leverages the knowledge and resources of an extensive collaborative network, and it uniquely focuses on late preclinical to early phase clinical studies of novel agents or combinations not previously tested in GBM.

Government staff work toward a shared goal and facilitate the NIH U19 cooperative agreement mechanism that funds the five multi-institutional, collaborative GTN centers (**Figure 13**). The overall goal of the GTN is to improve the treatment of adult GBM by developing and testing novel effective agents in early-stage clinical trials within one or several U19 centers. Each U19 center aims to move a therapeutic agent(s) from preclinical development and IND studies to pilot clinical studies driven by molecular pharmacodynamics (PD). Three structural aspects of the GTN integrate the U19 centers.

1. To harmonize GTN administrative, scientific, and clinical functions, one U19 center includes the Network Coordination Center (NCC). The NCC, located at the Mayo Clinic in Rochester, MN, functions independently of all U19 centers.
2. The Steering Committee assesses the readiness of GBM therapeutic candidates from the GTN (or other NIH programs) to enter clinical studies. It includes representatives from each U19 center, the NCC, NCI staff, and outside experts in GBM.
3. To use the unique and complementary strengths of each team, the U19 centers have budgeted $50,000 in direct costs per year to develop Collaborative Pilot Projects, including sharing of reagents, assays, and patient samples. Importantly, the U19 centers are willing to participate as secondary sites to perform clinical testing of each other's agent(s).

Each GTN U19 center includes at least two Research Projects, at least one Shared Resources Core, and an Administrative Core. Strong preclinical data support the five U19 centers' collective use of a range of small molecule and biological therapeutic agents that have not been tested in adult GBM patients. The centers propose to study combinations of new agents with standard- or non-standard-of-care agents.

The U19 centers have complementary expertise, disciplines, and geographical distribution, increasing the potential for patient recruitment. Each center includes at least two clinical sites with non-overlapping patient populations. Overall, the five centers comprise a balanced set of therapeutic modalities, technologies, and expertise to meet the goal of identifying and testing novel therapies for GBM.

At the end of five years, a successful GTN will be prepared to move to phase 2 studies with at least one agent that has cross-GTN preclinical data support, cross-GTN phase 1 testing, and phase 1 PD outcomes. By engaging GTN members and the GBM community, NCI intends for the GTN to be a hub for preclinical to clinical transit and testing of novel agents for adult GBM.

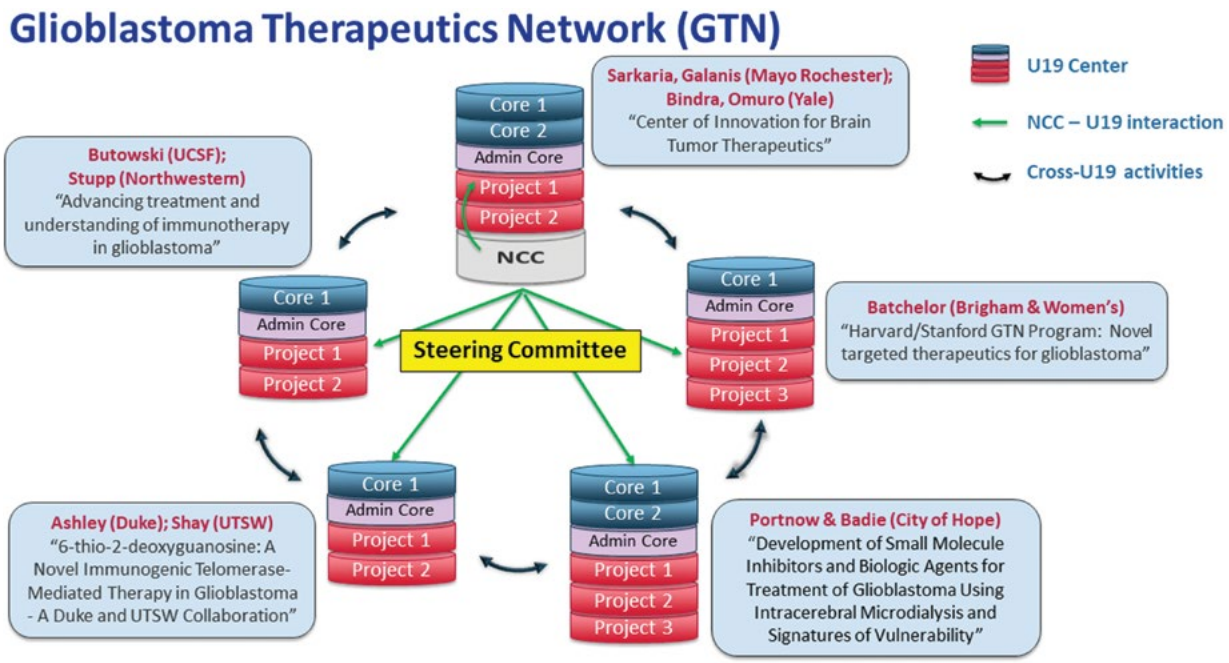



FIGURE 13: STRUCTURE OF THE GLIOBLASTOMA THERAPEUTICS NETWORK (GTN).

Five U19 Center grants include two or three Projects (red discs), one or two Cores (blue discs), and an Administrative Core (lavender disc). Light blue boxes next to each U19 Center include names of PI(s) and their institutions (red) and the title of the U19 grant. The NCC (gray disc), at Mayo Rochester, interacts administratively with all U19 centers (green arrows). Cross-U19 activities (black arrows) include Collaborative Pilot Projects, sharing of resources, and shared clinical studies. The Steering Committee is central in assessing transit of therapeutic agents from preclinical to clinical studies.

## Radiation Oncology-Biology Integration Network (ROBIN)

Human genomic research over the last 20 years has led to the increased availability of functional "-omics", big data, and molecular tools that are now used for precision medicine. However, these discoveries are relatively untapped in radiation oncology. The ROBIN Notices of Funding Opportunity (RFA-CA-21-040; RFA-CA-22-046) allow investigators to apply new biological knowledge to optimize radiation treatment in combination with systemic drugs and other agents.

Historically, most radiobiology research was conducted either in cell lines or in preclinical model systems with limited data derived from intact human tumors. As a result, the pharmaceutical industry has been less likely to support radiation oncology research; therefore, combination therapy involving radiation has not been studied as widely as combinations of pharmaceutical agents. Thus, radiation oncology represents a dichotomy where the technical precision of radiation delivery to tumors continues to improve, but the biological determinants of how tumors and normal tissues respond and adapt to radiation therapy (RT) over time are less understood. This untapped research area has created a knowledge gap and an unmet need to characterize RT so that the biological basis of patient responses and outcomes can be leveraged to both improve the eradication of cancer cells and mitigate toxicity to normal tissues.

In response, the ROBIN network was developed to:

- Prioritize and support research to test translational hypotheses that advance understanding of mechanistic interactions and biologic consequences of RT
- Support longitudinal collection of clinically annotated research biospecimens prior to, during, and after RT

- Facilitate the development of a multidisciplinary workforce
- Engage stakeholders with expertise to conduct studies in translational and preclinical research to inform clinical radiation oncology studies and leverage data science and informatics approaches

Three ROBIN-defining elements were required in the solicitation, which at the time were unique**:**

1. The network must have a central molecular characterization trial focused on longitudinal collection of biospecimens and multimodal data from patients prior to, during treatment, and after RT. The molecular characterization cohorts will be designed as "small n, high-content" studies where each patient serves as their own control over the course of standard-of-care RT with an equal focus on tumor and normal tissue.
2. In addition to having at least two projects and standard cores, the ROBIN U54's must contain a cross-training core whose focus is workforce development in accordance to the CTAC report on radiation oncology.
3. The network must focus on data science that integrates with modern data science methods and aligns with the NCI Cancer Research Data Commons (CRDC), which is a unique contributor of multi-modal data at the intersection of cancer biology and radiation. Also, each center must have a dedicated Data Management Specialist position as key personnel within the relevant core.

The long-term goal of ROBIN is to stimulate the development of radiation and combined modality trial concepts to be further developed in focused grants (R01s), program project grants (P01s), translational large scale grants (SPORE grants), or through the NCI's Experimental Therapeutics Clinical Trials Network or NCI's National Clinical Trials Network. The five members of the ROBIN network committed to accomplishing the long-term goal are summarized in **Table 12**.

| ROBIN Center | Institution | PI or Point of Contact* | Histologies | Date of Award |
|---|---|---|---|---|
| Radiation Oncology-Biology Integration Network on Oligometastasis (ROBIN OligoMET) Center | University of Maryland | Phuoc Tran*<br>Amit Sawant | Prostate | 8/4/2022 |
| | Thomas Jefferson University | Nicole Simone | | |
| Dynamics of Immune Response in Irradiated Rectal Cancer Center (ROBIN ImmunoRad Center) | Cornell University (Weill Medical College) | Silvia Formenti* | Rectum | 9/21/2022 |
| | Memorial Sloan Kettering Cancer Center | Joseph Deasy | | |
| | University of Chicago | Ralph Weichselbaum | | |
| Genomic and Microenvironmental Determinants, Temporal Dynamics, and Treatment Efficacy of Radiation-Based Combination Therapies Center (ROBIN Gen-Rad Center) | Cleveland Clinic Foundation | Timothy Chan* | Bladder | 9/14/2022 |
| | Emory University | David Yu | Head and Neck | |
| MicroEnvironment and Tumor Effects Of Radiotherapy (METEOR) | Washington University | Julie Schwarz* | Pancreas | 8/23/2023 |
| | | Clifford Robinson | Cervix | |
| Radiation Oncology at the Interface of Pediatric Cancer Biology and Data Science (KIDSROBIN) | Dana Farber Cancer Institute | Daphne Haas-Kogan* | Neuroblastoma | 9/19/2023 |
| | | Franziska Michor | Diffuse Midline Glioma | |

TABLE 12: ROBIN NETWORK MEMBERS.

## Pediatric Immunotherapy Network (PIN)

Despite advances in applying immunotherapy to some childhood cancers, there are no effective immunotherapy options for most pediatric patients with solid tumors, including brain tumors. There are several major barriers to the development of immunotherapeutic approaches for pediatric solid tumors such as low mutation burden and hence, less susceptibility to immune checkpoint blockade therapies. Another major limitation is the difficulty in identifying and validating optimal pediatric-specific immunotherapy targets particularly for solid tumors that manifest heterogeneity in target antigen expression. Additionally, effective immunotherapies for solid tumors require strategies to allow therapies to reach the tumor (e.g., reach brain tumors by crossing the blood brain barrier) and disrupt the solid tumor immunosuppressive microenvironment that reduces the effectiveness of immunotherapies.

To address the gaps in immunotherapy for pediatric patients with solid cancers, the NCI Divisions of Cancer Treatment and Diagnosis and Cancer Biology awarded six U01 cooperative agreement research projects in 2023 to establish the PIN (**Table 13**). PIN's overall goal is to investigate basic immune mechanisms and develop and advance novel translational immunotherapy approaches for children and adolescents with solid tumors, including brain tumors.

The primary goals of the PIN are:

- Discover and validate novel pediatric tumor immunotherapeutic targets
- Analyze pediatric-specific immune responses associated with response or resistance
- Molecular and immune profiling of pediatric solid tumors
- Develop strategies to modulate the pediatric tumor immune microenvironment to make immunotherapy agents such as chimeric antigen receptor (CAR) T cells and T cell engagers more effective
- Develop candidate novel immunotherapy agents that can be subjected to preclinical testing as single agents and in combination with other immuno- and non-immunotherapies in anticipation of potential clinical development
- Develop preclinical models for pediatric solid cancers to evaluate novel immunotherapy agents
- Serve as a hub for the broader research community involved in pediatric cancer immunotherapy research

The six U01 cooperative agreement research projects cover a wide breadth and diversity in:

- Childhood and adolescent solid tumor types including Ewing sarcoma, neuroblastoma, Group 3 medulloblastoma (G3MB), and diffuse midline glioma (DMG)
- Distinct and innovative pediatric-specific immunotherapy approaches including neoantigen vaccination strategies, CAR T therapies, T cell receptor (TCR)-based therapeutics and bispecific T cell engagers (BiTEs)
- Novel mechanistic insights into pediatric solid tumor biology using systems immunology approaches such as single-cell and spatial multi-omics profiling, *in vivo* CRISPR-based functional screens, epigenomics and the development and use of novel pediatric preclinical models
- Novel resources to identify and validate neoantigens for cold pediatric tumors and cloud-based data visualization portal

| Project Title | Principal Investigator (s) | Institution | Cancer under Investigation |
|---|---|---|---|
| Enabling Immunotherapy for High-Risk Group 3 Medulloblastoma via Systems Immunology | Chi, Hongbo (contact); Yu, Jiyang | St. Jude Children's Research Hospital | Medulloblastoma |
| Targeting Tumor and T cell DNA Methylomes to improve CAR T cell therapies for diffuse midline glioma | Mack, Stephen (contact); Krenciute, Giedre; Phoenix, Timothy | St. Jude Children's Research Hospital | Diffuse midline glioma |
| Attacking the Immunopeptidome of Ewing Sarcoma | Mackall, Crystal | Stanford University | Ewing Sarcoma |
| Immunotherapeutic Targeting of Gangliosides in Ewing Sarcoma | Majzner, Robbie (contact); Stegmaier, Kimberly | Dana Farber Cancer Center | Ewing Sarcoma |
| Personalized Neuroblastoma Vaccines | Maris, John (contact); Schoenberger, Stephen | Children's Hospital of Philadelphia | Neuroblastoma |
| Bispecific Antibody Therapeutics for Neuroblastoma and Diffuse Midline Glioma | Olson, James (contact); Kalia, Vandana | Seattle Children's Hospital | Diffuse midline glioma and Neuroblastoma |

TABLE 13: PIN U01 COOPERATIVE AGREEMENT AWARDS.

## Stimulation of Cell-Based Immunotherapy Production

### Workshops on Cell-based Immunotherapy for Solid Tumors

Cell-based immunotherapies have had remarkable success in the clinic, specifically in the treatment of hematologic malignancies. However, these strategies have had limited efficacy in patients with solid tumors. To better understand the challenges involved and how to facilitate further progress in the field, DCTD held two workshops on challenges with developing cell-based immunotherapies for solid tumors. These workshops brought together extramural academic researchers, industry scientists, FDA representatives, and NCI staff in December 2018 and December 2020. The goals were to discuss efforts to apply cell-based immunotherapy to solid tumors, obtain insights into the critical knowledge gaps in the field, and receive recommendations for new NCI initiatives to help address major challenges.

The published proceedings (Fogli, 2021) describe the participants' emphasis on seven research areas of unmet need for further developing cell-based immunotherapy for patients with solid tumors:

- Preclinical and translational research to advance cell therapy for solid tumors (tumor targets, immune cell fitness and persistence, cell trafficking, the immunosuppressive tumor microenvironment, development of preclinical models, and others) in both adult and pediatric patients
- Small proof-of-concept studies to rapidly gain knowledge of promising new treatment approaches
- Enhancement of cell manufacturing technologies (new cell expansion methods, genetic engineering including multigene engineering, alternatives to retroviral-based gene delivery, optimization of closed system manufacturing, new strategies for cell product screening, and others)
- Identification of biomarkers and imaging-based detection of response to therapy
- Standardization of cell product characterization through a core laboratory
- Quality Control testing for cell therapy-related reagents (e.g., GMP vectors) needed for manufacturing
- Guidance for investigators on preparing IND submissions

The workshops allowed NCI to identify and begin to respond to these major challenges facing the extramural community, leading to various initiatives to move the cell therapy field forward. A long-term goal of the NCI is to promote greater efficacy and broad-based adoption of cell-based immunotherapies for both hematological and solid tumors.

### Cancer Adoptive Cellular Therapy (Can-ACT) Network

Given the lessons learned at the two NCI Workshops on Cell-based Immunotherapy for Solid Tumors and other known challenges in the field of cell therapy, NCI published three RFAs in 2022 to establish the Cancer Adoptive Cellular Therapy (Can-ACT) Network (**Figure 14**). Can-ACT consists of multiple milestone-driven UG3/UH3 grants (RFA-CA-22-028; RFA-CA-22-029) and a U24 Coordinating Center (RFA-CA-22-030) that are intended to foster innovation and promote early-stage clinical testing of novel state-of-the-art cell-based immunotherapies for solid tumors in adult and pediatric patients, and leverage NCI resources to support the cell therapy community. The goals of Can-ACT are to:

- Develop and enhance immune cellular products modified genetically or through other manipulations for the treatment of adult and pediatric patients with solid tumors
- Support early phase clinical trials
- Explore imaging and biomarker development
- Expand our understanding of the mechanism of action as well as natural and acquired resistance

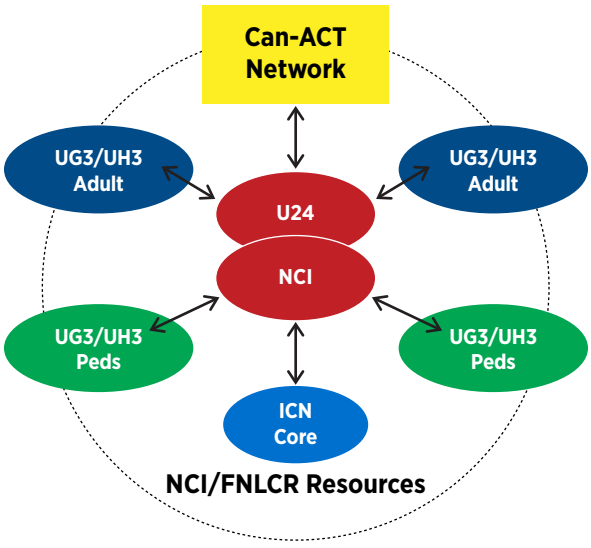



FIGURE 14: STRUCTURE OF THE CAN-ACT NETWORK.

Multi-center trials in the UH3 phase can leverage the Immune Cell Network (ICN) Core, a set of NCI contract resources at the Frederick National Laboratory for Cancer Research (FNLCR) consisting of cGMP manufacturing, clinical trials coordination support, and quality systems and regulatory affairs guidance. As the network becomes established, NCI plans to grant supplement awards to empower collaboration between Cancer Centers and Can-ACT members.

**Cell Therapy Production Facility**

To address the challenges in cell therapy manufacturing faced by researchers, NCI has expanded capacity to produce cell-based immunotherapies at FNLCR, making autologous cell therapy products available to intramural and extramural clinical trial investigators. The NCI Biopharmaceutical Development Program (BDP) at FNLCR commissioned four new manufacturing suites to provide centralized manufacturing of cell-based products in its cGMP facility, ensuring consistent and standardized processes and increasing reproducibility across studies. Clinical sites cryopreserve and ship T-cell source material from each patient to the BDP facility and, after a 2-week manufacturing and testing process, receive cryopreserved clinical product ready for infusion back into that patient. This workflow also allows NCI to help manage product chain logistics, which is a significant challenge for investigators (**Figure 15**).

Current capabilities at FNLCR include production of CAR T-cells using a closed manufacturing system and product-associated lenti- and gamma-retrovirus vector production (**Figure 16**). The expanded manufacturing suites are flexible to accommodate either cell manufacturing or vector production, depending on demand status.

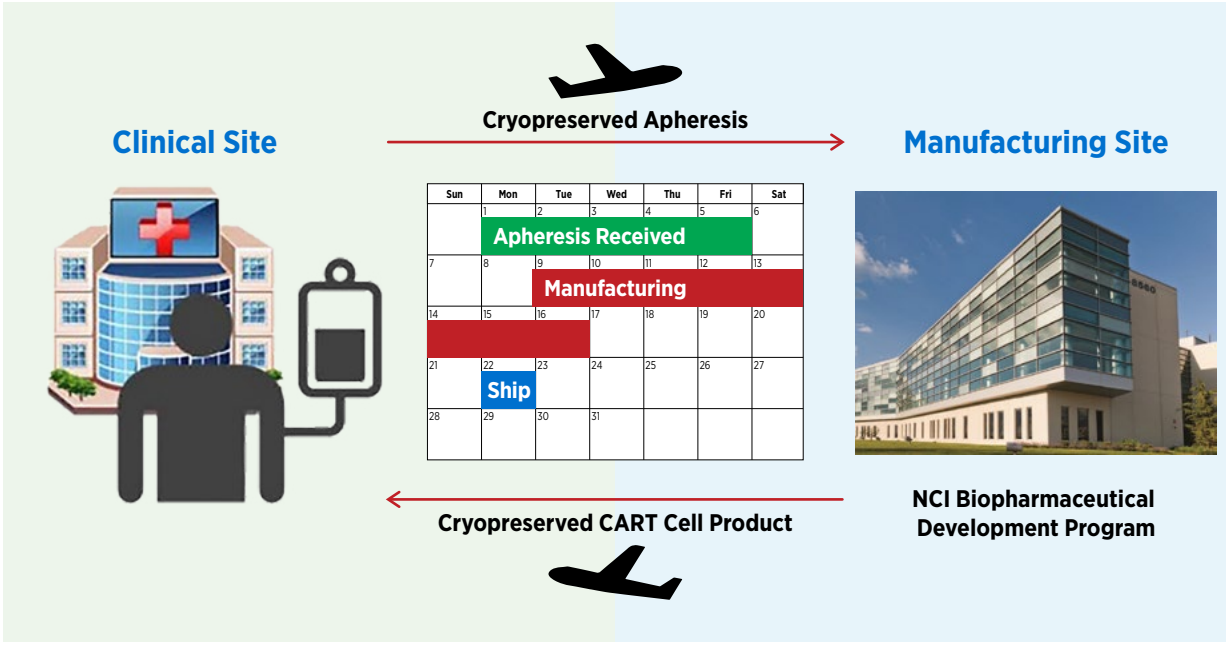



FIGURE 15: OVERVIEW OF BDP/FNLCR CAR T-CELL MANUFACTURING.

FIGURE 16: BIOREACTOR (LEFT) LOCATED IN ONE OF FOUR NEW CELL THERAPY PRODUCTION SUITES (RIGHT) AT FNLCR.

The BDP continues manufacturing support for a multicenter clinical trial of CD33 CAR T-cells in pediatric acute myeloid leukemia (NCT03971799), having produced a total of 30 autologous cell products so far. A second multicenter trial is now underway of GD2 CAR T-cells for pediatric neuroblastoma (NCT04539366) for which six autologous cell products have been produced and administered as of the end of 2023. Through the NCI Experimental Therapeutics (NExT) Program, the BDP is producing cGMP viral vectors for cell therapies targeting GPC2, CD22, STEAP1, and PRODH2 for use in investigator-initiated clinical trials. In addition, NCI is using the facility to generate viral vectors to produce cell therapies targeting mesothelin and CD123, and is planning to leverage this resource in support of the newly established Can-ACT Network.

## Quantitative Imaging Network (QIN)

Quantitative imaging extracts measurable feature information from medical images to enable an assessment of the severity, degree of change, or status of a disease, injury, or chronic condition relative to normal. CIP established the QIN in 2008 to promote the development and clinical validation of imaging data collection methods and software tools for clinical decision making in oncology. The number of member research teams in the QIN is currently nine, down from a peak of 25 teams in 2015 following funding reductions. The network also has 30 associate members from the US and abroad. The geographical location of present members are dispersed throughout the US (**Figure 17**).

The multidisciplinary teams include oncologists, radiologists, imaging specialists, medical physicists, computer informatics scientists, and others. An Executive Committee, consisting of the principal investigators from each member team, oversees the direction and external interactions of the network. External interactions include discussions and presentations to professional societies, cancer centers, global health initiatives, and collaborations with clinical groups, such as the NCTN.

The QIN is moving rapidly from a posture of discovery and development into one of validation and deployment. Tools designed to locate, isolate, and extract information about tumors from medical images are being tested and validated in clinical trials.

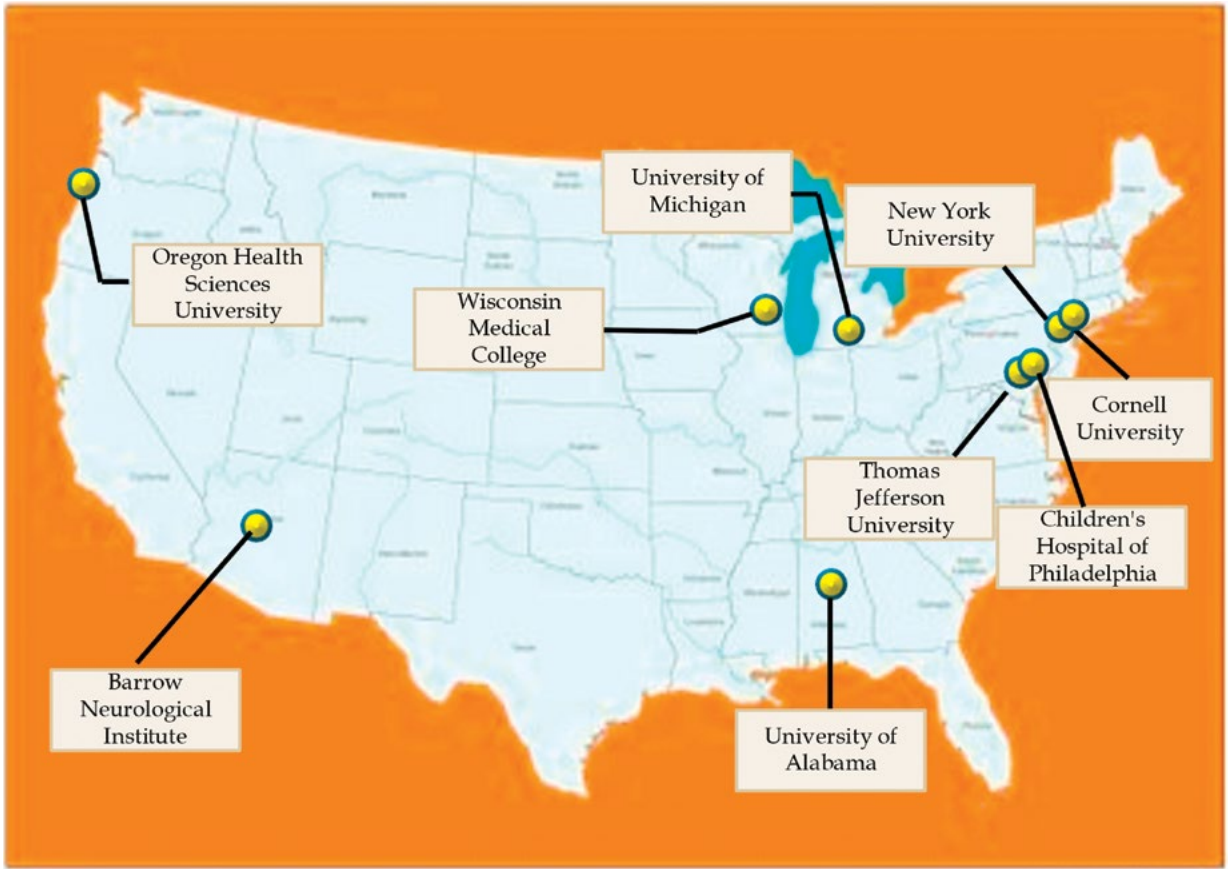



FIGURE 17: GEOGRAPHICAL DISTRIBUTION OF PRESENT QIN TEAM MEMBERS.

**Network Organization**

Networks are generally organized to create avenues for communication and collaboration among its members. A network's value can be measured by the degree of collaboration; however, collaboration can be difficult when teams focus on different technical challenges. Therefore, networks tend to explore activities of common interest that overlap across the goals of each technical team/institution and create a mechanism for emphasizing these common interests. The QIN has achieved these goals through cross-institutional working groups (**Table 14**).

| | |
|---|---|
| **Clinical Trial Design and Development** | Methods for moving software tools into clinical trials, including those the network develops; fostering strong connections with clinical trial groups, such as NCTN |
| **Data Acquisition** | Problems associated with reducing bias and variance in image data collection; phantom circulation among QIN teams to determine sources of error in the various imaging scanners and analysis of results |
| **Bioinformatics and Data Sharing** | Quantitative imaging methods rely on firm informatics infrastructure to support tool comparison, data archiving and visualization, annotation, and statistical methods. This working group considers all projects being conducted within the network and plans for informatics support for them |
| **PET/CT Working Group** | Specific issues in PET/CT data processing |
| **MRI Working Group** | Specific issues in MRI data processing |

TABLE 14: QIN WORKING GROUPS AND FOCUS AREAS.

Moving from discovery and development of clinical decision support tools to their final validation is a complex process. To relate tool performance to the desired clinical outcome, the clinical outcome must be known; however, clinical outcomes data are often missing or of limited value in retrospective datasets and can be difficult to acquire if prospective data are used. In either case, sufficient data must be available to make an accurate assessment of the performance characteristics of the tool or method.

Based on the 2020 QIN progress and strategy update, the NCI Clinical Trials and Translational Research Advisory Committee and QIN members formed a committee to recommend ways to move the more mature QIN imaging tools into the NCTN for integrated testing in specific trials. The QIN initiated a five-step benchmark procedure to chart the technical progress of tools from early-stage development to becoming clinically ready for validation. This process identified several imaging tools ready for NCTN testing. Research teams (early stage, middle stage, and late stage in the network) are progressing in translational efforts. The scale considers basic research to include concept, development, and optimization; early clinical research to include clinical testing or validation using retrospective clinical data; and the final stage to include prospective clinical validation demonstrating clinical functionality and useful clinical utility and workflow.

Not surprisingly, the early-stage teams (fewer than 2 years in the network) are making progress through the basic research tasks, middle-stage research teams (3 or 4 years in the network) have moved past basic research and are working to validate tools or methods, and teams with years of network experience are intent on building collaborations with industrial partners for commercialization. A few past QIN teams have moved their clinical support tools beyond the clinical validation and testing stage into clinical workflow (**Figure 18**).

## PRECISION MEDICINE ONCOLOGY AND 21ST CENTURY CURES ACT-FUNDED RESEARCH NETWORKS

### Immuno-Oncology Translational Network (IOTN)

The IOTN was formed in 2016 in response to the Cancer Moonshot℠ Blue Ribbon Panel recommendation to create a translational science network to advance immunotherapy for adult cancer patients. The goals of the IOTN are to accelerate translation of basic discoveries to clinical applications to:

- Improve outcomes of immune-based therapies and combination approaches for adult patients with cancer
- Prevent cancers before they occur

IOTN research projects for mitigating immune-related adverse events explore ways to eliminate or reduce harmful side effects of immunotherapies. Teams within the IOTN Immuno-Engineering to Improve Immunotherapy Centers use bioengineering and systems biology approaches to discover more effective and safe immunotherapies. The network also includes a Cellular Immunotherapy Data Resource that collects information about patients receiving immune cell-based immunotherapies. A Data Management and Resource-sharing Center provides overall support for the IOTN and integrates the research activities of the IOTN with other Cancer Moonshot programs.

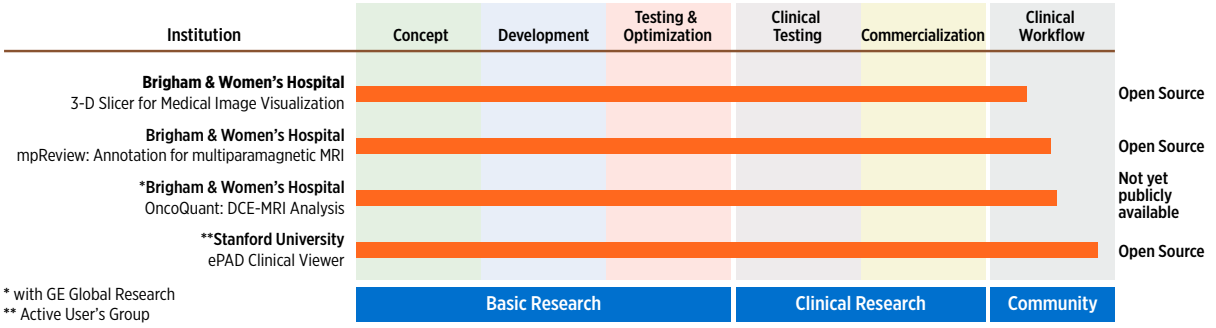



FIGURE 18: A FEW PAST QIN TEAMS ACHIEVING CLINICAL WORKFLOW.

The goals of the IOTN teams' studies include:

- Investigating interactions between tumors and the immune system
- Exploring new targets for immunotherapies
- Studying development of resistance to immunotherapies
- Testing new immunotherapies in preclinical models

Some early IOTN studies were published in the white paper: "Cancer Moonshot Immuno-Oncology Translation Network (IOTN): Accelerating the clinical translation of basic discoveries for improving immunotherapy and immunoprevention of cancer."[9] In addition, a joint IOTN-Accelerating Anticancer Agent Development and Validation-Clinical Trials Task Force Workshop was held in October 2021.

There are several IOTN working groups:

- Immuno-Radiotherapy Working Group
- Translational Cellular Therapy Working Group
- Immune Mechanism and Recognition Working Group
- Clinical Trials Task Force
- Bioinformatics and Computational Biology Working Group
- Immuno-Prevention Working Group

The Immuno-Radiotherapy Working Group published a manuscript in the *Journal for ImmunoTherapy of Cancer*: "Radiation dose and fraction in immunotherapy: One-size regimen does not fit all settings, so how does one choose?" (Demaria, 2021).

IOTN activities have focused on fostering collaborations, outreach, and data and resource sharing. The IOTN website provides Data, Model, and Software Sharing Catalogs. Five collaborative Cancer Moonshot Supplement projects with the NIH intramural research investigators are supported under the trans-NIH Bench-to-Bedside and Back Program. NCI has also supported four supplements for development of an "Immune Radiation Response Index (iRRI)" for immune cells from normal and tumor microenvironments.

## Patient-Derived Xenograft Development and Trial Centers Research Network (PDXNet)

PDXNet comprises centers of excellence that have developed PDX models on a large scale to address the challenges of cancer precision medicine. Increasing the effectiveness of cancer therapy requires honing the assignment of treatments to those cancer indications in which they have the best outcome. As more targeted agents become available, and tumor subtypes are further defined, researchers must prioritize and test optimal combinations of agents in increasingly narrow tumor subsets in early phase clinical trials. New preclinical methods are needed to test novel agents against hundreds of potential tumor subtypes, and in multiple combinations, to identify the most promising strategies for clinical evaluation. Patient-derived models, such as PDXs and patient-derived organoids (PDOs), offer the potential to better represent human tumor biology, in comparison to established cell lines due to their low passage number. Therefore, patient-derived models may serve as better predictive models of tumor response to therapeutic approaches.

PDXNet was formed in 2017 through the issuance of three Cancer Moonshot℠ funding opportunity announcements (**Table 15**). DCTD administers four PDX Development and Trial Centers (PDTCs; U54: (RFA-CA-17-003), one PDXNet Data Commons and Coordinating Center (PDCCC; U24: RFA-CA-17-004), and administrative supplements (PA-18-496 and PA-19-174) to support the access of non-PDXNet NCI-funded investigators to PDXNet resources. The Center to Reduce Cancer Health Disparities (CRCHD) administered two additional PDTCs (U54: RFA-CA-17-032) for the use of patient-derived models from racial and ethnic minority populations to explore the biological reasons behind disparate cancer therapy outcomes in these patient populations. PDXNet sites interact with the NCI Patient Derived Models Repository (PDMR) at the Frederick National Laboratory for Cancer Research (FNLCR) to augment the creation, characterization, and distribution of PDX models to the research community (**Figure 19**).

The primary objective of PDXNet is the performance of large-scale studies that test therapeutic strategies in models representing the molecular diversity of histologies in a context that can lead to feasible clinical validation of the experi-

[9] Annapragada, A., et al., Cancer Moonshot Immuno-Oncology Translational Network (IOTN): accelerating the clinical translation of basic discoveries for improving immunotherapy and immunoprevention of cancer. *J Immunother Cancer*. 2020 Jun;8(1):e000796 (2020).

mental results. Testing of agents for which NCI holds the IND is emphasized, since these are readily available for translation to clinical evaluation in the NCI Experimental Therapeutics Clinical Trials Network (ETCTN).

In addition to pursuing the research interests of individual grantees, PDXNet investigators collaborate on projects to advance PDX science. One collaborative project involved treatment of the same PDX models with a single agent to evaluate the reproducibility of drug response in PDX models across all PDTCs centers. A second project involved multiple methods to determine potential genomic evolution over serial passages to evaluate PDX tumor stability in the context of multiple centers. Both projects required data harmonization and sharing by the PDTCs, and coordination by the PDCCC.

PDXNet was approved for a second grant cycle that began in September 2023 and will continue to be a collaboration between DCTD and CRCHD.

| Activity Code | PI(s) | Grant Title | Lead Institution |
|---|---|---|---|
| U54 | Ramaswamy Govindan (contact); Shunqiang Li; Li Ding | Washington University PDX Development and Trial Center | Washington University |
| U54 | Meenhard Herlyn | Rational Approaches to Melanoma Therapy | The Wistar Institute |
| U54 | Jack Roth (contact); Funda Meric-Bernstam | University of Texas PDX Development and Trial Center | University of Texas MD Anderson Cancer Center |
| U54 | Alana Welm (contact); Bryan Welm; Michael Lewis | PDX Trial Center for Breast Cancer Therapy | University of Utah |
| U54 | Chong-Xian Pan (contact); Luis Carvajal-Carmona; Moon Chen | University of California Minority Patient-Derived Xenograft (PDX) Development and Trial Center (UCaMP) to Reduce Cancer Health Disparities | University of California-Davis |
| U54 | Nicholas Mitsiades | Minority PDX Development and Trial Center: Baylor College of Medicine and MD Anderson Cancer Center Collaboration on Mechanistic Studies to Dissect and Combat Health Disparities in Cancer | Baylor College of Medicine |
| U24 | Jeffrey Chuang (contact); Brandi Davis-Dusenbery | Data Coordination Center for PDXNet | The Jackson Laboratory |

TABLE 15: U54 AND U24 PDXNET AWARDS.

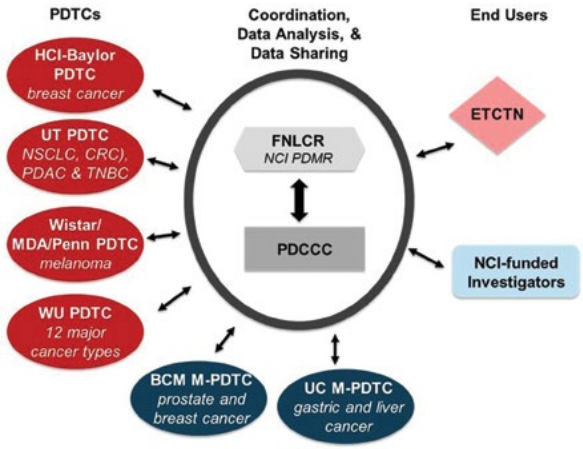



**FIGURE 19: PDX DEVELOPMENT AND TRIAL CENTERS NETWORK (PDXNET).**
HCI=Huntsman Cancer Institute; UT=University of Texas, MD Anderson Cancer Center; MDA/Penn=MD Anderson/University of Pennsylvania; WU=Washington University, St. Louis; BCM=Baylor College of Medicine; UC=University of California, Davis; PDTC=PDX Development and Trial Center; M-PDTC=Minority-PDTC; PDCCC= PDX Data Commons and Coordinating Center; FNLCR=Frederick National Laboratory for Cancer Research; ETCTN=Experimental Therapeutics Clinical Trials Network.

## Mechanisms of Cancer Drug Resistance and Sensitivity Network (DRSN)

The DRSN, launched through the Cancer Moonshot℠ and funded by the 21st Century Cures Act, was a network of centers formed to conduct preclinical research focused on innovative strategies to understand and combat mechanisms of tumor resistance (intrinsic or acquired) and to exploit tumor sensitivity to anti-cancer therapies. The goal of the DRSN was to develop preclinical data to support novel concepts in cancer drug resistance that have a feasible path for clinical validation. The DRSN centers used sophisticated laboratory techniques, preclinical models, and human-derived biospecimens to study methods of overcoming clinical cancer drug resistance.

The DRSN comprised five U54 Drug Resistance and Sensitivity Centers (DRSCs) awarded in 2017 (**Table 16**), eight collaborative administrative supplement projects awarded over the five-year project period (**Table 17**), a U24 Coordinating Center, and eleven drug resistance revision awards in 2020-2022 (**Table 18**). The components of the DRSN are depicted in **Figure 20**.

**MGH/MIT/Broad Institute DRSC (PI: Corcoran)**

The MGH/Broad U54 defined key mechanisms of bypass resistance over three tumor types - lung, melanoma, and GI cancer - involving three of the most important classes of anti-cancer agents - MAPK pathway inhibitors, Receptor Tyrosine Kinase inhibitors, and Immune Checkpoint inhibitors.

**MSKCC/University of Washington/Fred Hutchinson Cancer Research Center DRSC (PI: Sawyers)**

The MSKCC/Fred Hutch U54 applied diverse model systems such as castration-resistant prostate cancer (CRPC) human cell lines, organoids, and PDX models (many developed in-house) to dissect and target various mechanisms of resistance to androgen receptor pathway therapy. The investigators used these model systems to conduct preclinical evaluation of promising, rationally designed combination therapies by screening clinical grade compounds to maximize translation to the clinic.

**Mayo Clinic (Arizona & Rochester)/University of Minnesota DRSC (PI: Stewart)**

The Mayo/UMN U54 used primary patient tumor samples, human myeloma cell lines, and newly engineered humanized multiple myeloma mouse models to elucidate underlying genetics and biology of the tumor to identify sensitivity and resistance mechanisms to current and future drugs.

**OHSU DRSC (PI: Tyner)**

The OHSU U54 leveraged the tumor intrinsic and microenvironmental biology of acute myeloid leukemia to evaluate and identify new drug combinations that may lead to more effective therapies and prevent disease resistance. The investigators used cutting edge technologies, such as genome-wide CRISPR screens, high throughput imaging with single cell granularity, CyTOF, and computational models (many developed in-house) to assess novel drug combinations and the contribution of tumor-intrinsic and microenvironmental pathways to resistance.

**UCSF/Stanford University DRSC (PI: Bivona)**

The UCSF/Stanford U54 focused on dissecting the molecular and cellular basis of incomplete response and resistance in lung cancer with emphasis on targeted therapy and immune checkpoint inhibitor therapy. Cutting-edge technologies including a novel air-liquid interface organoid culture methodology (developed in-house) and a digital droplet-based single cell RNA sequencing analyzed primary patient samples, patient and cell-derived organoids, and xenografts to develop new treatment strategies for lung cancer.

Over its 5-year project period, the DRSN's research activities were linked to 35 clinical trials with mostly best-in-class agents, indicating that DRSN research informed clinical trial translation with the goal of improving patient outcomes. At least 14 clinical trials (subset of the 35 trials) were directly associated with DRSN-generated research.

Collaborations between non-DRSC- and DSRC-supported investigators to perform research within the scientific scopes of their active parent projects and/or cooperative agreement awards led to improved preclinical evaluations of novel discoveries in cancer drug resistance (**Table 17**).

To leverage expertise in the broader NCI-funded project portfolio (R01/U01/U54/P01/P50) to tackle drug resistance in cancer, NCI program staff added new aims and directions to current NCI-funded awards in underexplored areas of basic and preclinical evaluation of therapeutic resistance using revision awards. These revision awards were expected to complement (but not duplicate) ongoing research activities within the DRSN and to accelerate the translational success of current and future clinical trials. Competing revision awardees have expanded DRSN activities into new directions, including incorporating non-immune tumor microenvironment parameters, treatment modalities like chemoradiation, and under-explored mechanisms of acquired resistance (e.g., microbiome influence on therapy efficacy). Eleven DRSN revision recipients awarded between 2020-2022 were associate members of the DRSN (**Table 18**) and transitioned to be associate members of the Acquired Resistance to Therapy Network (ARTNet; see below), a successor to the DRSN.

| Funding Opportunity | Grant/Project Title | Awardee Organization | Principal Investigator(s) |
|---|---|---|---|
| Drug Resistance and Sensitivity/ Research to Identify and Treat Cancer Sensitivity or Resistance to Anticancer Therapy (RFA-CA-17-009) | An Integrated Translational Approach to Overcome Drug Resistance | Massachusetts General Hospital | Ryan B. Corcoran |
| | Overcoming Drug Resistance in Multiple Myeloma | Mayo Clinic Arizona | Peter L. Bergsagel |
| | The MSKCC-UW/Fred Hutch Prostate Cancer Drug Resistance and Sensitivity Center | Sloan-Kettering Institute for Cancer Research | Charles L. Sawyers |
| | Tumor Intrinsic and Microenvironmental Mechanisms Driving Drug Combination Efficacy and Resistance in AML | Oregon Health & Science University | Jeffrey W. Tyner |
| | Bay Area Team Against Resistance | University of California, San Francisco | Trever G. Bivona |

TABLE 16: FIVE U54 DRUG RESISTANCE AND SENSITIVITY CENTERS (DRSCs).

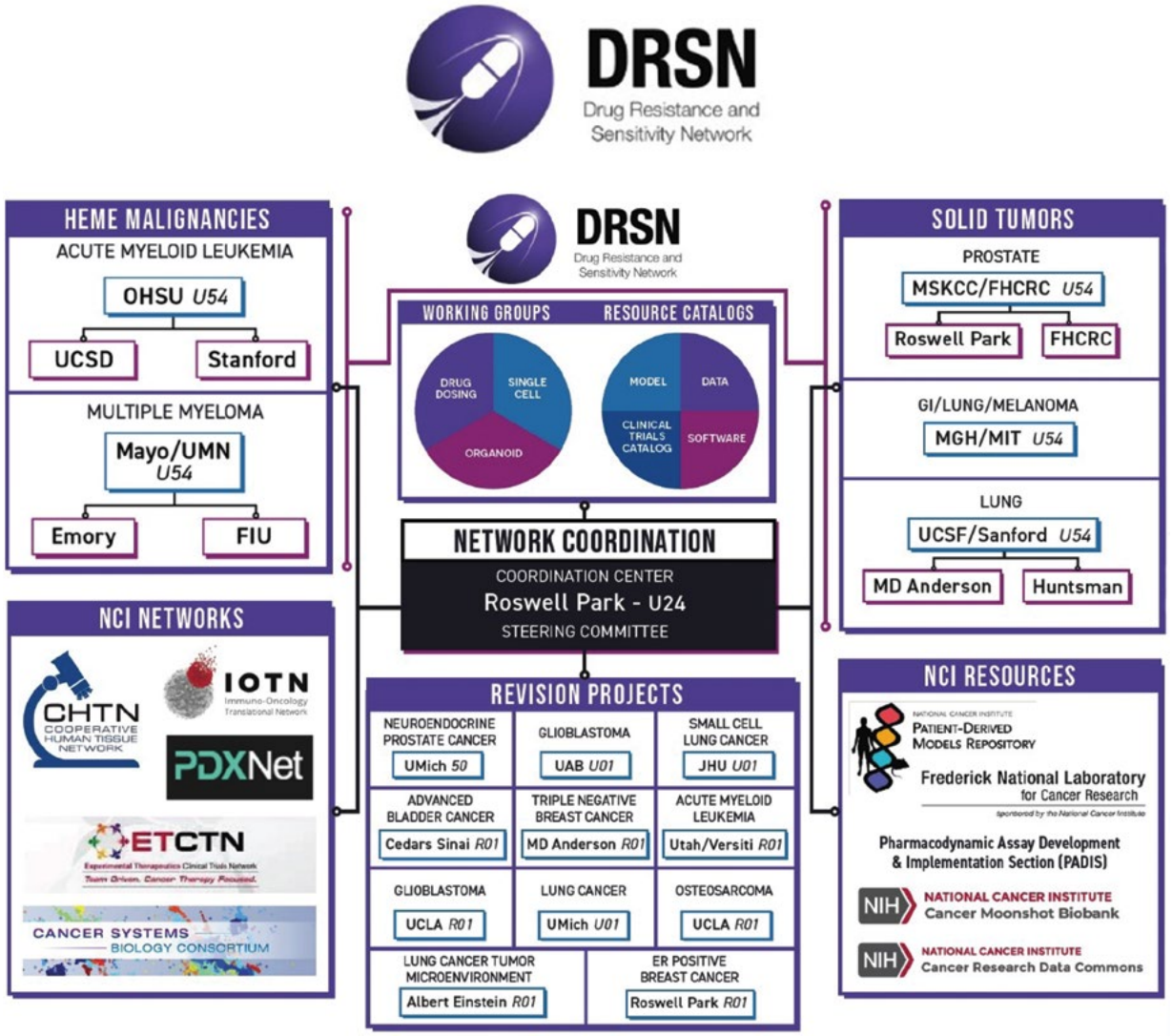



FIGURE 20: DRSN INTERACTOME.

| Funding Opportunity | Grant/Project Title | Awardee Organization | Principal Investigator(s) |
|---|---|---|---|
| Administrative Supplements to NCI Grant and Cooperative Agreement Awards to Support Collaborations with the Drug Resistance and Sensitivity Network (DRSN)(Admin Supp Clinical Trial Not Allowed) (PAR-18-752) | Exploiting RB1 deficiency for the treatment of lethal neuroendocrine prostate cancer | Roswell Park Cancer Institute Corp | David W. Goodrich |
| | Identifying the Molecular Mechanisms of the Regulation of Integrin B3 Expression by the MAP Kinase | University of Utah | Martin McMahon |
| Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Parent Admin Supp Clinical Trial Optional) (PA-18-591) | Combined Natural Killer Cell and Targeted Drug Therapy to Treat AML | University of California San Diego | Dan S. Kaufman |
| | Overcoming Resistance to Tyrosine Kinase Inhibitors in Epidermal Growth Factor Receptor Mutant Non-Small Cell Lung Cancer | University of Texas MD Anderson Cancer Center | Jack A. Roth |
| | The Role of CD86 in Multiple Myeloma | Emory University | Lawrence H. Boise |
| | Hormone Signaling and Translation Control in Advanced Prostate Cancer | Fred Hutchinson Cancer Research Center | Andrew C. Hsieh |
| Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Parent Admin Supp Clinical Trial Optional) (PA-20-272) | Dissecting Single-cell Response or Resistance to Novel Combination Therapy in AML using Mass Cytometry | Stanford University | Kara L. Davis |
| | Analysis of E-selectin Ligands of Human Acute Leukemia Cells and their Biology in Leukemogenesis | Florida International University | Robert Sackstein |

TABLE 17: DRSN COLLABORATIVE ADMINISTRATIVE SUPPLEMENT PROJECTS.

| Funding Opportunity | Grant/Project Title | Awardee Organization | Principal Investigator(s) |
|---|---|---|---|
| Revision Applications for Mechanisms of Cancer Drug Resistance (P50 Clinical Trial Not Allowed) (RFA-CA-19-053) | Michigan Prostate SPORE | University of Michigan, Ann Arbor | Joshi J. Alumkal |
| Revision Applications for Mechanisms of Cancer Drug Resistance (U01 Clinical Trial Not Allowed) (RFA-CA-19-050) | Glioblastoma Tumor Microenvironmental Influence on Acquired and Inherent Cancer Therapy Resistance | University of Alabama at Birmingham | Christopher D. Willey |
| | Tumor-barcoding coupled with high-throughput sequencing of a novel chemoradiation resistant SCLC mouse model | Johns Hopkins University | Christine L. Hann |
| Revision Applications for Mechanisms of Cancer Drug Resistance (R01 Clinical Trial Not Allowed) (RFA-CA-19-049) | A Vicious Cycle of Pyroptotic Cancer Cells and Fibroblasts Fuels Chemoresistance | Cedars-Sinai Medical Center | Keith S. Chan |
| | Long Noncoding RNA Advocates Immune Resistant Microenvironment | University of Texas MD Anderson Cancer Center | Chunru Lin |
| | Targeting the Metabolic Regulator SIRT5 in Acute Myeloid Leukemia | University of Utah | Michael W. Deninger |
| | Development of a First-in-class mEGFR Dimerization Inhibitor | University of Michigan, Ann Arbor | Mukesh K. Nyati |
| | Tumor-expressed immune checkpoint B7x-mediated resistance to anti-CTLA-4 therapy | Albert Einstein College of Medicine | Xingxing Zang |
| | RB tumor suppressor as a therapeutic target in ER-positive breast cancer | Roswell Park Cancer Institute Corp | Erik Knudsen |
| | Signaling Drivers of Sarcoma Drug Resistance | University of California Los Angeles | Alice Soragni |
| | Drivers of Metabolic Plasticity Promote Radiation Resistance in Glioblastoma Multiforme | University of California Los Angeles | Erina Vlashi |

TABLE 18: MECHANISMS OF CANCER DRUG RESISTANCE COMPETING REVISION.

## Acquired Resistance to Therapy Network (ARTNet)

ARTNet (RFA-CA-21-052; RFA-CA-21-053) was launched in 2022 as an interdisciplinary center-based effort to understand the biological underpinnings of acquired resistance to therapies and translate these findings into innovative effective strategies that leverage research discoveries (**Figure 21**).


**FIGURE 21: ARTNET'S PROGRAMMATIC GOAL.**
Establish an iterative bridge between basic-mechanistic, preclinical, and clinical-translational science to overcome challenges in acquired resistance to cancer therapies.

The adaptive and heterogeneous nature of cancers presents fundamental barriers to achieving curative treatment outcomes for most patients. ARTNet investigators view tumors as an ecosystem of diverse cell types that interact through adaptive genetic and non-genetic processes in response to treatments, which enable cancer cell survival and disease recurrence.

Several features of the ARTNet organizational structure are notable:

- Unified "center-based" approach where a central scientific theme focused on addressing challenges in acquired resistance and cancer recurrence defines the projects
- Collaborative team science bridges basic, preclinical, and translational research within center projects and across the network
- Evidence along the shared tumor-tumor microenvironment (TME) continuum informs new treatment strategies that translate into future clinical trial designs

ARTNet, which builds upon the DRSN, is the first collaborative research center network dedicated to addressing the challenges of acquired resistance. ARTNet consists of five research centers and a coordinating-data management center (**Table 19**) that are examining cancer types where acquired resistance and disease recurrence pose significant obstacles. The investigative teams coordinate to use state-of-the-art approaches that combine -omics, imaging, immunology, and cancer biology modeling and engage in trans-network collaborative research projects that seek to further drive data sharing and progress across cancers and modes of treatment.

| PI(s)/Institution | Center Title/Project Information | Funding Mechanism |
|---|---|---|
| Alan Hutson (contact); David Goodrich; Song Liu; Martin Morgan/ Roswell Park Cancer Institute Corporation | Coordinating and Data Management Center for Acquired Resistance to Therapy Network | U24 |
| Trever G. Bivona (contact); Jack Roth/University of California, San Francisco | Bay Area & Anderson Team against Acquired Resistance – U54 Program (BAATAAR-UP) | U54 |
| Boyi Gan (contact); Albert Koong/University of Texas MD Anderson Cancer Center | Acquired Resistance to Therapy and Iron (ARTI) Center | U54 |
| Pankaj Singh/University of Nebraska Medical Center | Pancreatic Cancer ARTNet Center | U54 |
| Jeffrey Myers (contact); Vlad Sandulache/University of Texas MD Anderson Cancer Center | The Houston Center for Acquired Resistance Research (H-CARR) | U54 |
| Jeffrey Tyner (contact); Brian Druker; Shannon McWeeney/Oregon Health & Science University | Architecture and Trajectory of Acquired Resistance to Therapy in AML | U54 |

**TABLE 19: SIX ARTNET CENTERS.**

## PRE-medical Cancer Immunotherapy Network Canine Trials (PRECINCT)

Cancers in pet dogs arise spontaneously (as in humans), and dogs have similar genomes, immune responses, living environment, and tumor complexity to humans. In 2017, NCI granted five teams U01 (RFA-CA-17-001) awards to perform canine immunotherapy trials and correlative analyses to provide validation for initiating human clinical trials and ultimately determine the utility of canine cancers as predictors of human cancer therapy response. PRECINCT (**Figure 22**) was launched through the Cancer Moonshot℠, funded by the 21st Century Cures Act, and was associated with the Immuno-Oncology Translational Network.

The PRECINCT 2017 teams have largely completed their clinical trials and correlative studies of novel immunotherapeutics and combination therapies. Of note, one of the studies (Dow and London) - a losartan plus toceranib canine trial for osteosarcoma - led to a pediatric clinical trial testing a new analogous combination therapy. Canine clinical trial data from another study (Pluhar) was included as part of a package that led to a phase 1 clinical trial with tumor lysate and a human version of the CD200 peptide for human patients with recurrent high grade brain tumors. Comparative analysis from these studies is aiding in the discovery of factors driving canine and human carcinogenesis and is providing rationale for novel therapeutic strategies.

In 2022, the program was renewed with U01 awards (RFA-CA-21-051) issued to five new universities as well as a single U24 for a coordinating center (RFA-CA-17-002; RFA-CA-21-050) (**Figure 23**). The PRECINCT 2022 teams are investigating diverse immunotherapies in dogs: checkpoint inhibitor, cytokine, vaccination, oncolytic virus, and adoptive CAR-iNKT cell therapies. The U01 and U24 investigators, DCTD staff, NCI intramural Comparative Oncology Program staff, and a wide range of canine cancer researchers who are funded from sources inside and outside the network attend monthly PRECINCT steering committee meetings.

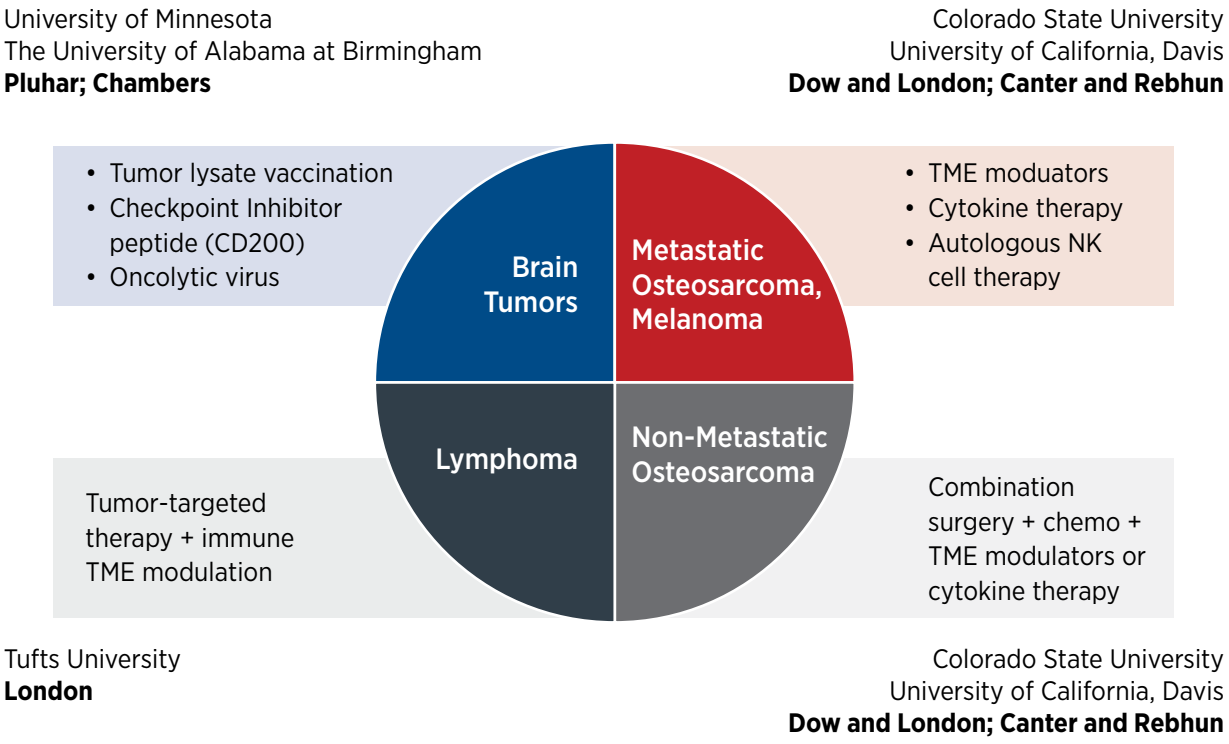



**FIGURE 22: PRECINCT 2017 U01 CANINE IMMUNOTHERAPY AWARDS.**
Principal Investigators are in bold.

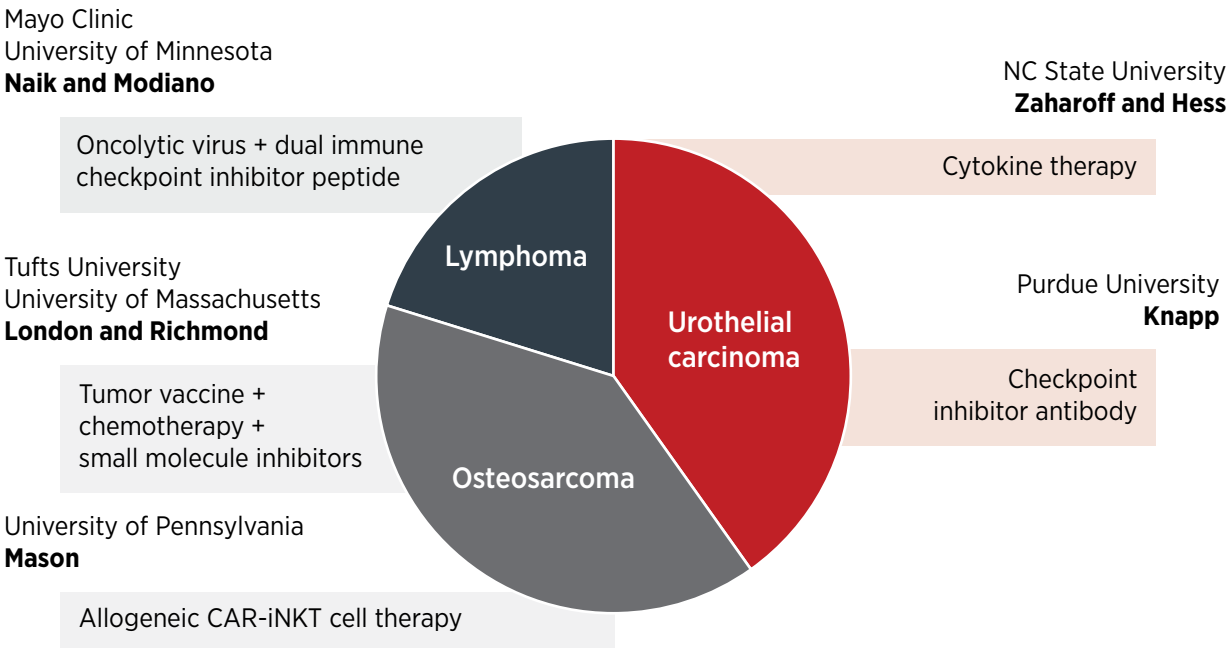



**FIGURE 23: PRECINCT 2022 U01 CANINE IMMUNOTHERAPY AWARDS.**
Principal Investigators are in bold.

### Cancer Immune Monitoring and Analysis Centers – Cancer Immunologic Data Commons-Partnership for Accelerating Cancer Therapies (CIMAC-CIDC-PACT) Network

The CIMAC-CIDC Network was launched through the Cancer Moonshot℠ in September 2017 and was funded by the 21st Century Cures Act. The network was renewed for an additional five years starting in July 2023 (RFA-CA-22-038). This network will continue to address the critical importance of improving management of cancer in patients by identifying biomarkers for optimizing immunotherapeutic strategies.

In February 2018, through the efforts of the Foundation for the NIH, the CIMAC-CIDC Network formed a collaboration with the Partnership for Accelerating Cancer Therapies (PACT), a public-private partnership involving 12 leading biopharmaceutical companies, the NIH, and the FDA. PACT provides support for the CIMAC-CIDC infrastructure as well as correlative analyses in clinical trials, including NCI, academic, and industry-sponsored trials that focus on immunotherapy agents or their combinations.

CIMACs, CIDC, and clinical trial investigators design and conduct analyses correlating biomarkers with clinical data, including outcomes, from NCI-supported immunotherapy trials as well as trials that PACT solicits (**Figure 24**). Each CIMAC encompasses a multidisciplinary group of investigators with basic, translational, clinical, and computational research expertise. The centers provide a wide range of state-of-the-art analyses for genomic, phenotypic, and functional characterization of responses of patients treated in immunotherapy trials, using analytically validated and standardized platforms. The CIDC facilitates the network activities by:

- Optimizing data collection methodologies suitable for immune-related biomarkers
- Integrating clinical and assay data
- Building a centralized immune-oncology database platform containing biomarker and clinical data
- Sharing data with the general research community

The long-term goal of the CIMAC-CIDC-PACT Network is to develop a database of molecular signatures that define immune response categories correlated with the clinical outcomes of immunotherapy in cancer. Collectively, the outcome of the network's activities should lead to the identification of biomarkers with translational potential for optimizing therapeutic strategies and improving outcomes of treatment for people with cancer.

In response to the renewal (RFA-CA-22-038), U24 grants were awarded to four academic centers as CIMACs (**Table 20**). NCI issued subcontracts for the establishment and maintenance of the CIDC, as well as for centralized operational support for the network during the 5-year CIMAC-CIDC renewal period. The augmented structure of the CIMAC-CIDC-PACT Network is provided in **Figure 25**.

| Activity Code | PI(s) | Grant Title | Lead Institution |
|---|---|---|---|
| U24 | Catherine Ju-Ying Wu (contact); Frank Stephen Hodi | Cancer Immune Monitoring and Analysis Center | Dana-Farber Cancer Institute |
| U24 | Sacha Gnjatic (contact); Seunghee Kim-Schulze | High-Dimensional Immune Monitoring of NCI-Supported Immunotherapy Trials | Icahn School of Medicine at Mount Sinai |
| U24 | Ignacio Wistuba (contact); Gheath Al-Atrash; Cara Haymaker | Translational Cancer Immune Monitoring and Analysis Center | University of Texas MD Anderson Cancer Center |
| U24 | Holden Maecker (contact); Sean Curtis Bendall | Immune Monitoring and Analysis of Cancer at Stanford | Stanford University |

TABLE 20: AWARDEES IN THE RENEWED CIMAC-CIDC NETWORK.

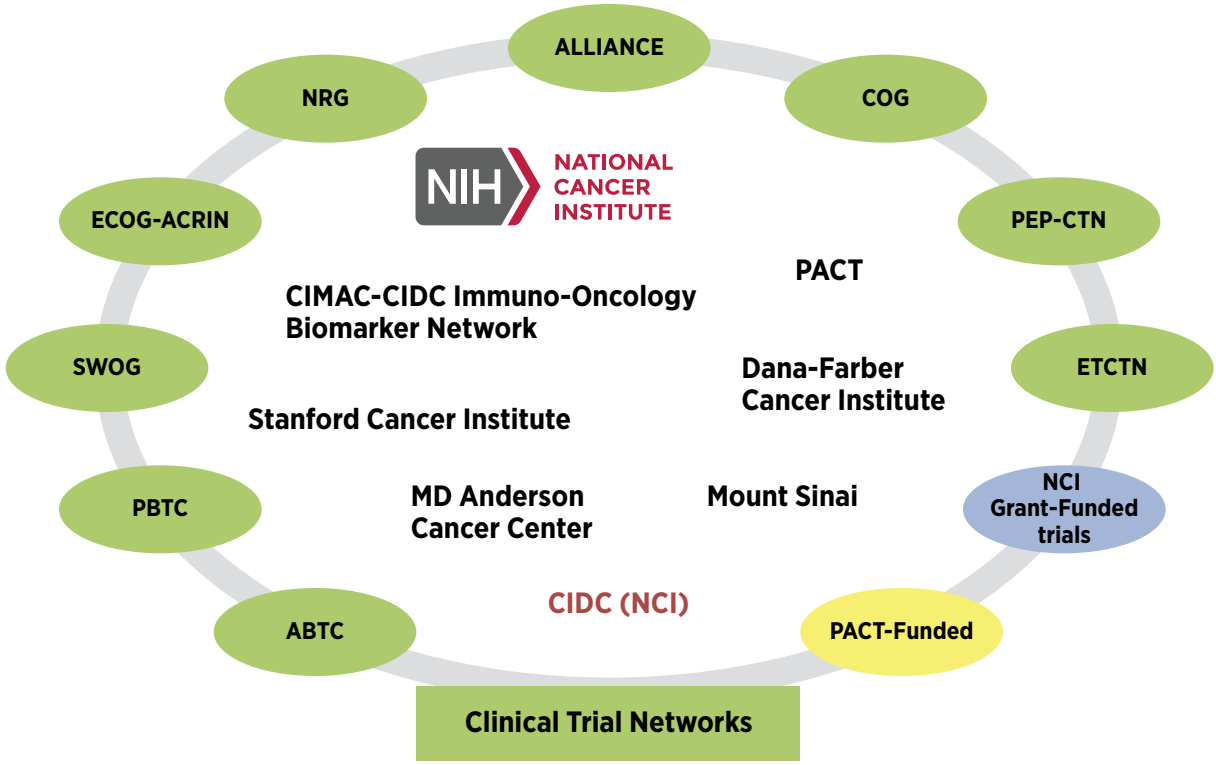



FIGURE 24: CENTERS IN THE 2023 CIMAC-CIDC, NCI, AND PACT CLINICAL TRIALS NETWORKS.

PEP-CTN=Pediatric Early Phase Clinical Trials Network; ETCTN=Experimental Therapeutics Clinical Trials Network; ABTC=Adult Brain Tumor Consortium; PBTC=Pediatric Brain Tumor Consortium.

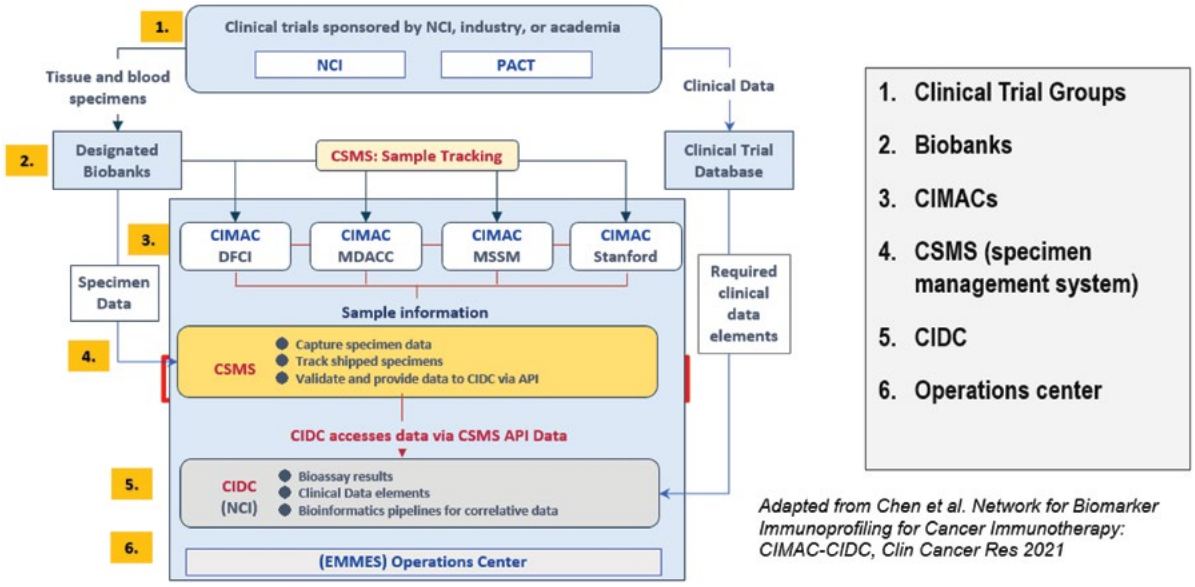



FIGURE 25: ORGANIZATIONAL STRUCTURE OF THE CIMAC-CIDC-PACT NETWORK.

## Pancreatic Cancer Microenvironment Network (PaCMEN) and the Pancreatic Ductal Adenocarcinoma Stromal Reprogramming Consortium (PSRC)

The PaCMEN consortium consisted of five U01 research project grants and one U24 resource center (**Table 21**). The NCI awarded these grants as a pancreatic cancer-directed initiative in response to the Recalcitrant Cancer Research Act of 2012. The intent was to stimulate research to understand the interaction between pancreatic ductal adenocarcinoma (PDAC) and its microenvironment. The grants were preceded by a series of NCI Cancer Center one-year supplements in support of this research.

The goals of the PaCMEN consortium were to:

- Study tumor-microenvironment (TME) interactions in PDAC
- Discover vulnerabilities in these interactions that could be exploited in the design of immunotherapies
- Develop interventions that could lead to improved responses in preclinical models and clinical evaluation either in NCI-based early-phase networks, by industry, or NCI Cancer Centers
- Serve as a hub for the broader research community involved in studies of the PDAC microenvironment

Through the Associate Membership status, several groups joined the consortium and periodically participated in its activities, calls, and meetings. Several collaborative studies evolved from these interactions. The consortium has already published more than 160 scientific papers (118 in the period 2020-2023), including the following topics:

- Definition of pancreatic cancer through biomarkers in extracellular vesicles[10]
- Altering the tumor microenvironment and acceleration of pancreatic carcinogenesis by regulatory T-cell depletion[11]
- Neoantigen quality predicts immunoediting in survivors of pancreatic cancer[12]

[10] Hoshino, A., et al., Extracellular Vesicle and Particle Biomarkers Define Multiple Human Cancers. *Cell.* 2;182(4):1044-1061.e18 (2020).
[11] Zhang, Y., et al., Regulatory T-cell Depletion Alters the Tumor Microenvironment and Accelerates Pancreatic Carcinogenesis. *Cancer Discov.* Mar:10(3):422-439 (2020).
[12] Luksza, M., et al., Neoantigen quality predicts immunoediting in survivors of pancreatic cancer. *Nature.* Jun;606(7913):389-395 (2022).

| Activity Code | PI(s) | Grant Title | Lead Institution |
|---|---|---|---|
| U01 | Vinod Balachandran | Defining Neoantigen Immunodominance for Antigen Selection and Biomarker Discovery in Human Pancreatic Cancer Immunotherapy | Sloan-Kettering Institute for Cancer Research |
| U01 | Howard Crawford, Marina Pasca di Magliano | Interrupting Cellular Crosstalk in the Immunosuppressive Microenvironment of Pancreas Cancer | University of Michigan |
| U01 | William Hahn | Systematic Interrogation of the Pancreatic Cancer Microenvironment in Patient-Derived Specimens | Dana-Farber Cancer Institute |
| U01 | Sunil Hingorani | Disrupting the Immune and Drug-Privileged Microenvironment to Improve Immunotherapy | Fred Hutchinson Cancer Research Center |
| U01 | Rakesh Jain | Reprogramming PDAC Tumor Microenvironment to Improve Immunotherapy | Massachusetts General Hospital |
| U24 | Anirban Maitra, Subrata Sen | Pancreatic Ductal Adenocarcinoma Translational Resource Center (PATReC) | University of Texas MD Anderson Cancer Center |

TABLE 21: SIX PACMEN CONSORTIUM MEMBERS.

- Composition, spatial characteristics, and prognostic significance of myeloid cell infiltration in pancreatic cancer[13]
- Commitment and oncogene-induced plasticity of human stem cell-derived pancreatic acinar and ductal organoids[14]
- Apolipoprotein E promotes immune suppression in pancreatic cancer through NF-κB-mediated production of CXCL1[15]
- Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer[16]

After five years of PaCMEN, a new Cancer Moonshot℠ initiative was launched in 2022 - the Pancreatic Ductal Adenocarcinoma Stromal Reprogramming Consortium (PSRC). The goals of the PSRC were to:

- Develop a community of PDAC researchers that will expand upon traditional tumor-centric studies and ongoing immuno-oncology efforts by emphasizing additional TME elements driving PDAC progression and response to therapy
- Adopt a comprehensive "Tumor-TME Co-Organizer" research model in the pursuit of novel biology-backed targets that disrupt these multi-dimensional tumor sustaining dynamics
- Inform the design and testing of more effective combinatorial approaches in preclinical platforms and near future clinical trials
- Use PDAC (and the PSRC program) as a model system to stimulate further studies of the TME as a co-organizer in other cancers

The PSRC program intends to further cultivate and support tumor cell intrinsic and immuno-oncology studies, but they must also triangulate with the key basic and translational goals highlighted above. This consortium consists of one resource center U24 grant and six U01 research projects (**Table 22**):

[13] Vayrynen, S., et al., Composition, Spatial Characteristics, and Prognostic Significance of Myeloid Cell Infiltration in Pancreatic Cancer. *Clinical Cancer Res*. Feb;27(4):1069-1081 (2021).
[14] Huang, L., et al., Commitment and oncogene-induced plasticity of human stem cell-derived pancreatic acinar and ductal organoids. *Cell Stem Cell*. Jun 3;28(6):1090-1104 (2021).
[15] Kemp, S., et al., Apolipoprotein E Promotes Immune Suppression in Pancreatic Cancer through NF-κB-Mediated Production of CXCL1. *Cancer Res*. Aug 15;81(16):4305-4318 (2021).
[16] Rojas, L., et al., Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer. *Nature*. Jun;618(7963):144-150 (2023).

| Activity Code | PI(s) | Grant Title | Lead Institution |
|---|---|---|---|
| U01 | William Hahn, Andrew Aguirre, Stephanie Dougan | Stromal modulation of pancreatic cancer malignant cell state and therapeutic sensitivity | Dana-Farber Cancer Institute |
| U01 | Marina Pasca di Magliano, Howard Crawford, Timothy Frankel, Costas Lyssiotis | Fibroblast orchestration of the immune response in pancreatic cancer | University of Michigan |
| U01 | Bumsoo Han, Melissa Fishel, Matthew Flick | Systematic Interrogation of the Pancreatic Cancer Microenvironment in Patient-Derived Specimens | School of Mechanical Engineering Purdue |
| U01 | Michael Karin, Andrew Lowy, Robert Schwabe | Regulation of PDAC metabolism and immunity by collagen and its cleavage products | University of California San Diego |
| U01 | Kenneth Olive | Elucidation and targeting of paracrine cascades in PDAC | Columbia University |
| U01 | Jen Jen Yeh | Integrating tumor and stroma to understand and predict treatment response | University of North Carolina |
| U24 | Anirban Maitra, Subrata Sen | PASSCODE (Pancreatic Adenocarcinoma Stromal Reprograming ConSortium COordination, Data Management and Education) | University of Texas MD Anderson Cancer Center |

TABLE 22: SEVEN PSRC CONSORTIUM MEMBERS.

The Division of Cancer Biology and the DCTD Cancer Diagnosis Program collaborated to conceptualize, create, and manage the consortia.

## RESOURCES FOR THE SCIENTIFIC COMMUNIITY

### NCI Experimental Therapeutics (NExT) Program

#### Overview

NCI is working on multiple fronts to develop more patient-specific and effective therapies for cancer. One initiative, the NExT Program, combines DCTD's extensive expertise in cancer treatment with the dynamic intramural research resources of the NCI Center for Cancer Research (CCR) and the NIH Clinical Center to assist projects focused on developing therapies for unmet medical needs in oncology that are not typically addressed by the private sector.

In 2009, NCI created the NExT Program to consolidate existing translational programs across NCI into a single discovery-development pipeline analogous to the multidisciplinary best practices model used successfully in the pharmaceutical industry. As part of the newly developed NExT Program, NCI established a collaborative network, the Chemical Biology Consortium (CBC), composed of Dedicated and Specialized Centers, with broad capabilities - including high-throughput screening (HTS), bioinformatics, medicinal chemistry, and structural biology - to support early-stage drug discovery.

The CBC is the main resource for early discovery activities, while DCTD's Developmental Therapeutics Program supports late discovery/preclinical development/IND-enabling activities. DTP has successfully brought new small molecules and biologic anti-cancer agents into the clinic over the last several decades. The NExT Program also develops molecular imaging agents with support from DCTD's Cancer Imaging Program (CIP), and proof-of-mechanism pharmacodynamic (PD) assays through the efforts of the PD Assay Development and Implementation Section of the Frederick National Laboratory for Cancer Research (FNLCR) for application in preclinical animal studies and/or NCI-supported early phase clinical trials. Finally, early phase clinical trials are performed in the NCI Developmental Therapeutics Clinic (DTC) or the NCI Experimental Therapeutics Clinical Trials Network. These coordinated activities, described in greater detail below, incorporate cutting-edge technologies into every step of the NExT drug discovery and development continuum, increasing the potential for successful clinical evaluation of new target- and mechanism-based therapies.

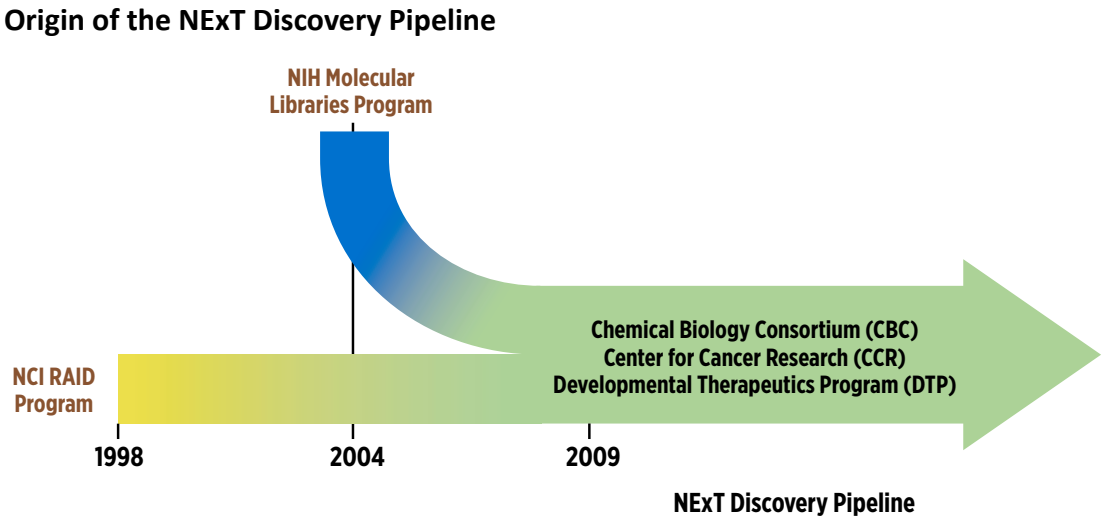



FIGURE 26: THE ORIGIN OF THE DISCOVERY PORTION OF THE NExT PIPELINE.

The NCI Rapid Access to Intervention Development (RAID) Program initiated in 1998 (**Figure 26**) was a vehicle to provide researchers with access to IND-enabling resources leading to investigator-driven clinical trials; the NCI provided translational expertise and preclinical service contracts at no cost to the researcher. Until incorporation into the NExT Program in 2009, the RAID Program pursued 139 projects. IND-enabling studies were done for 30 small molecules and 33 biological agents, of which 15 and 24, respectively, entered clinical trials. The efforts behind two small molecules culminated in FDA approval (Pralatrexate, 2009; Omacetaxine, 2012). CIP managed a similar program for imaging agents called Development of Clinical Imaging Drugs and Enhancers (DCIDE), that started in 2002. Of the ten formal applications, five reached clinical trials with IND-directed toxicology studies supported by RAID/NExT: $^{18}$F FACBC, Cu-64-ATSM, In-111 Annexin, $^{18}$F Fluorocholine, and $^{18}$F DCFBC. One of these, $^{18}$F FACBC, received FDA approval for prostate cancer (Axumin®) in 2016.

### Chemical Biology Consortium (CBC)

The CBC, created to fill the early drug discovery void at the NCI, was modeled after and capitalized on the significant NIH Common Fund investment in the Molecular Libraries Program and the Molecular Libraries Probe Production Centers Network. The CBC discovery module of NExT differs from the Molecular Libraries Program in that it maintains confidentiality of the findings until appropriate patents are filed. This is critical to the success of the projects in that it allows NExT applicants and/or the NCI to develop an Intellectual Property (IP) space that encourages downstream investment in the technologies developed through the consortium and most critically helps commercialize any eventual investigational agents or FDA-approved drugs.

Probing cancer's complex network of signaling pathways requires cutting-edge chemical tools, the discovery of which often exceeds the capabilities of an individual laboratory or an individual research university. NCI's CBC is designed to be a flexible network of scientists working to increase the flow of early-stage drug candidates into the development pipeline. This network, which includes participants from government, academia, and industry, focuses on the identification and synthetic optimization of novel chemical leads for drug discovery. The foundation of the consortium is based on applying a task-oriented approach to address challenging projects with clear objectives, deadlines, and milestones. By adopting pharma's multidisciplinary drug discovery best practices, the CBC empowers academic and biotech investigators with the required capabilities and resources to drive their agents toward clinical development.

With funds from the America Recovery and Reinvestment Act of 2009, NCI rapidly assembled the infrastructure to support the CBC, including acquisition of a secure central

database, mobilization of a small molecule repository at Evotec, and subsequent procurement of a diverse collection of commercial compounds to support HTS/High Content Screening. Collaborating under a Master Service Agreement mechanism, the centers receive base funding sufficient for maintaining the infrastructure and staff necessary to provide constant support for CBC projects, ultimately reducing administrative costs and ensuring greater continuity in participation.

CBC discovery projects are composed of multidisciplinary teams with the required breadth of expertise to tackle difficult targets. Project team members, including scientists from participating CBC centers, the Applicant Principal Investigator (PI), an NCI Project Leader, and a Scientific Project Manager from Leidos Biomed, are solely responsible for the scientific direction of the project, defining clear objectives and milestones throughout the life cycle of the project. Regularly, the applicant PI assumes the role of project champion given their broad knowledge of the target biology and pathway under investigation for pharmacological intervention. The composition of the team may change as the project advances through the discovery stages of the NExT pipeline and different expertise is required. Contract research organizations (CROs), such as Pharmaron, Reaction Biology, IRBM, and Curia support consortium-wide activities. Centers and/or CROs are brought into project teams when incorporation of their expertise is needed to advance the science and decision-making process.

In 2022, an external panel of chemical biologists, molecular oncologists, and clinicians favorably reviewed the CBC program, resulting in the re-issuance of the CBC RFP. The third iteration/phase of the program now comprises 19 centers (**Figure 27**) with 6 new centers joining the consortium (highlighted in red).

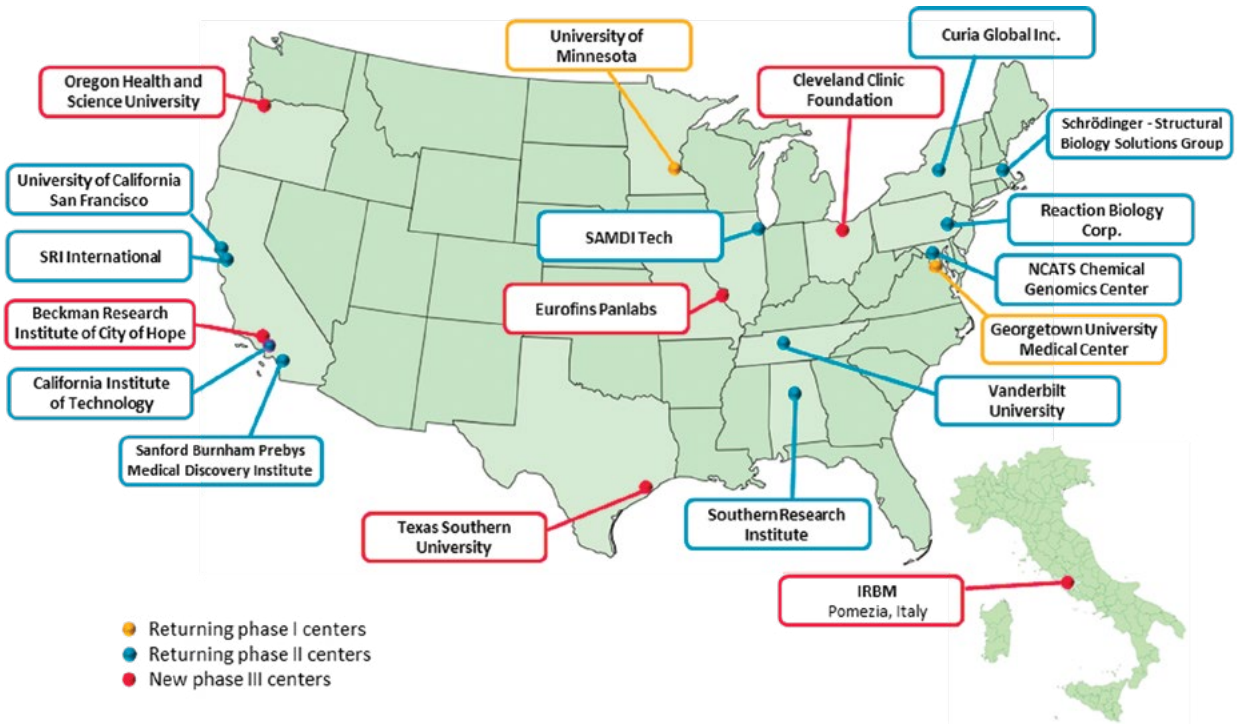



FIGURE 27: CBC NETWORK.

## NExT Applications

Drug discovery and development projects enter the NExT pipeline on a competitive basis and are focused on unmet therapeutic needs in cancer treatment that are not adequately addressed by the private sector. Of vital importance to the success of this initiative is the careful selection of projects and rigorous evaluation of the portfolio to progress the most promising concepts toward the clinic. A Special Emphasis Panel, composed of outside experts who evaluate all incoming NExT applications, is also charged with assisting the NCI in a yearly strategic portfolio evaluation and prioritization process. This periodic external assessment of a project's relevance, performance, and impact in relation to stated goals and objectives ensures that resources are used effectively.

Since its inception in late 2009, the NExT Program has received more than 1,000 applications (more than 200 during this reporting period) and has an overall acceptance rate of nearly 15%. The distribution of projects entering the pipeline by agent class and category of submitting institution is highlighted in **Figure 28**. The pie charts include early (CBC) and late stage (IND-enabling) discovery as well as development (early clinical evaluation) projects accepted into the program.

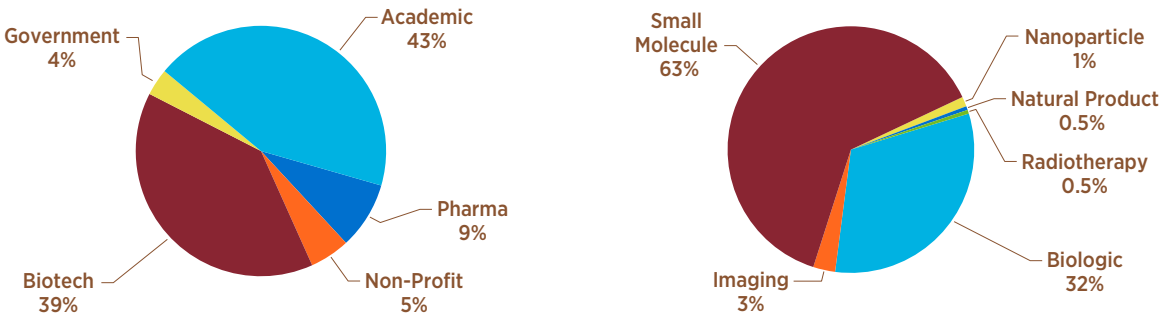



FIGURE 28: NExT PORTFOLIO STRATIFIED BY AGENT CLASSIFICATION (RIGHT) AND CATEGORY OF SUBMITTING INSTITUTION (LEFT).

## CBC Accomplishments

Several first, high-resolution structures of CBC targets have been solved (**Table 23**).

| Structure | Investigators | Publication |
|---|---|---|
| Artemis endonuclease | Fazlul Karim, Shanshan Liu, Adrian R. Laciak, Leah Volk, Mary Rosenblum, Michael R. Lieber, Mousheng Wu, Rory Curtis, Nian Huang, Grant Carr and Guangyu Zhu. | Structural analysis of the catalytic domain of Artemis endonuclease/ SNM1C reveals distinct structural features. *Journal of Biological Chemistry.* 295:35, 12368 -12377 (2020). |
| Taspase1 | Nirupa Nagaratnam, Silvia L Delker, Rebecca Jernigan, Thomas E EdwardsJaney Snider, Darren Thifault, Dewight Williams, Brent L Nannenga, Mary Stofega, Lidia Sambucetti, James J Hsieh, Andrew J Flint, Petra Fromme, Jose M Martin-Garcia. | Structural insights into the function of the catalytically active human Taspase1. *Structure.* 29(8):873-885 (2021). |
| p97 ATPase | Soojay Banerjee, Alberto Bartesaghi, Alan Merk, Prashant Rao, Stacie L Bulfer, Yongzhao Yan, Neal Green, Barbara Mroczkowski, R Jeffrey Neitz, Peter Wipf, Veronica Falconieri, Raymond J Deshaies, Jacqueline L S Milne, Donna Huryn, Michelle Arkin, Sriram Subramaniam. | 2.3 Å resolution cryo-EM structure of human p97 and mechanism of allosteric inhibition *Science.* 351(6275):871-875 (2016). |
| Beta-catenin | | Unpublished data<br>Structural knowledge enabled by the first known X-ray structures of small molecules bound to this historically difficult target is facilitating elaboration of the hits into heterobifunctional degraders. |

TABLE 23: SELECTED CBC TARGETED STRUCTURES.

The NExT Program supports development projects within the NCI DTC. First-in-human studies are underway for two DNA (cytosine-5-)-methyltransferase 1 (DNMT1) inhibitors discovered by Southern Research Institute and brought into the NExT Program for the additional resources essential to advance into human clinical trials - 4'-thio-2'-deoxycytidine (T-dCyd) and 5-aza-4'-thio-2'-deoxycytidine (5-aza-T-dCyd). These two deoxycytidine analogues displayed pre-clinical efficacy in distinct tumor types, implying that their mechanisms of action are not identical.

The National Center for Advancing Translational Sciences (NCATS) Chemical Genomics Center discovered a novel class of compounds targeting mutant isocitrate dehydrogenase 1 (IDH-1). NExT-supported studies demonstrated that these compounds are just as efficacious in preclinical studies as another small molecule that Agios, Inc. discovered, and which the FDA approved in 2018 for the treatment of relapsed or refractory acute myeloid leukemia with IDH1 mutation. NCATS is assessing out-licensing opportunities for this agent.

The NExT Program expanded its biologics footprint into the immune cell therapy field with the establishment of cGMP capabilities for CAR T-cell, lentivirus, and gamma-retrovirus products at the Biopharmaceutical Development Program (BDP) within the FNLCR. NCI commissioned four additional GMP suites and expanded QC lab space at the BDP facility to accommodate recently approved NExT cell therapy projects:

- Gamma-retrovirus for producing a GPC2-targeted CAR T-cells for pediatric neuroblastoma and medulloblastoma (PI: Crystal Mackall, Stanford University)
- Lentivirus for producing a BCMA-targeted metabolically enhanced CAR T-cells for multiple myeloma (PI: Sidi Chen, Yale University)
- Gamma-retrovirus for manufacturing an autologous CD22-targeted TCR-T cells for B-cell malignancies (PI: Kazusa Ishii, NCI CCR)
- Autologous patient CAR T-cells (including the lentivirus vector) that target the six-transmembrane epithelial antigen of prostate (STEAP) 1 in prostate cancer patients (PI: John Lee, Fred Hutchinson Cancer Research Center)

The BDP has also generated two antibody products for first-in-human imaging studies. The anti-human Annexin-A1 antibody targets a unique epitope of annexin-A1 expressed in caveolae of tumor endothelial cells and will be studied in patients with solid tumors at the University of Alabama with sponsorship from the Proteogenomics Research Institute for Systems Medicine (PRISM). The anti-TF-Ag antibody (hJAA-F11) targets the α-linked isoform of the disaccharide tumor marker Thomsen-Friedenreich glycoantigen (TF-Ag) and will be studied in breast cancer patients in an imaging trial at Roswell Park. This agent was discovered by For-Robin, Inc. (NExT applicant), and has recently been licensed to Intellective Biologics - Suzhou Regen-Pharma Tech Ltd for commercial development.

The CBC is investigating inhibitors of additional cancer therapeutic targets, including β-catenin, a central nexus for the Wnt signaling pathway, and a target historically considered to be undruggable. Another project, brought into the program by Pengbo Zhou at Weill Cornell Medicine, focuses on the identification of CUL4 inhibitors as dual precision oncology and immune-oncology drugs. Another submission by Samantha Pattenden and Ian Davis at the University of North Carolina at Chapel Hill (UNC), seeks to target Ewing sarcoma tumor-specific chromatin accessibility using a unique screening platform pioneered by the PIs. This assay is being miniaturized and optimized for HTS at NCATS with HTS to be performed at UNC. A small number of projects are using targeted protein degradation as a therapeutic modality to tackle tough targets by hijacking a cells natural process for disposing of misfolded proteins.

In addition, the NExT Program supported studies of the following first-in-class agents:

- Small molecule inhibitor of WDR5, which has progressed from the early hit-2-lead to the late preclinical development stage
- Inhibitor of the metabolic enzymes lactate dehydrogenase-A and B (LDHA/B) for the treatment of primary and idiopathic hyperoxalurias, which came into NExT at the HTS stage and is currently in a phase 1 clinical trial

A list of current projects in the pipeline is publicly available.

## Other DCTD Efforts Supporting NExT

*Investigative Toxicology Laboratory (ITL)*

The objectives of the ITL at FNLCR, overseen by DTP's Toxicology and Pharmacology Branch, are to identify and advance mechanistic understanding of potential toxicity of therapeutic agents that come into the NExT pipeline. The program provides investigative toxicology deliverables to the extramural scientific community by serving the immediate needs of the NExT portfolio (**Figure 29**).

The laboratory's services include:

- Developing *in vitro* models and assays to generate deeper insight about cellular toxicity of therapeutic agents
- Profiling early adverse effects for high-priority organ systems using both *in vitro* and *in vivo* assays
- Applying mechanism-based approaches to characterize and aid in selection of drug candidates
- Generating data to describe biologically qualified pathways that are mediating mechanisms of toxicity for classes of approved agents
- Detecting target modulation and off-target effects to inform and manage potential safety liabilities

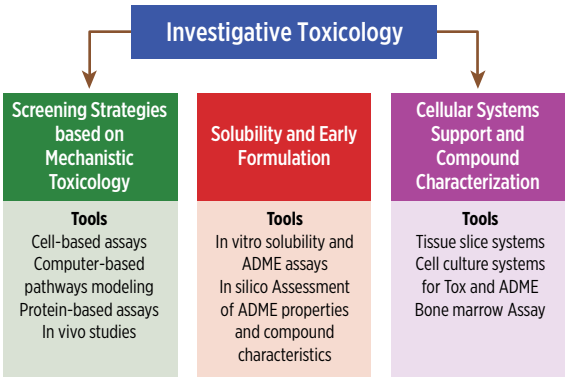



FIGURE 29: THE INVESTIGATIVE TOXICOLOGY PROGRAM'S ACTIVITIES IN SUPPORT OF NEXT PROJECTS.

*Pharmacokinetic (PK) Laboratory*

The PK Laboratory at FNLCR analyzes samples from preclinical and clinical trials. Samples from patients enrolled on protocols in the DTC, as well as at approved extramural sites, are sent to the PK Laboratory for analysis of systemic exposure to the drug and its metabolites. For earlier-stage projects, the PK Laboratory investigates the metabolism of compounds in vitro, including the development of methods for measuring incorporation of bases into DNA. The laboratory then works closely with DTP's Biological Testing Branch to conduct PK and metabolic studies in mice to provide information about the feasibility of achieving concentrations relevant to activity in cell culture, as well as the potential roles for active or toxic metabolites.

*Radioactive Drug and Small Animal Imaging Programs*

Molecular imaging has an enormous impact on the spectrum of clinical cancer management and cancer research. Almost every NCI strategic priority will depend on the information and knowledge gained from imaging, whether it is from the use of molecular imaging as a surrogate marker, assay, or therapeutic effectiveness metric or from a greater understanding of tumor biology and molecularly targeted therapeutic interventions. The great promise of image-guided therapeutic interventions is just beginning to be realized.

However, the ability to provide this information requires significant innovations in imaging probes and systems, especially for molecular imaging agents, where the greatest opportunities and the strongest challenges lie. The DCIDE program was an important contributor of molecular imaging drugs for the strategic priorities in early detection, prevention, and prediction; integrative cancer biology; strategic development of cancer interventions; and integrated clinical trials. In 2007, the Imaging Drug Group integrated the activities of several trans-NCI imaging drug activities into one decision-making committee, incorporating the DCIDE program and bridging to other important programs, such as CCR's Molecular Imaging Program and the Nanotechnology Characterization Laboratory (**Figure 30**).

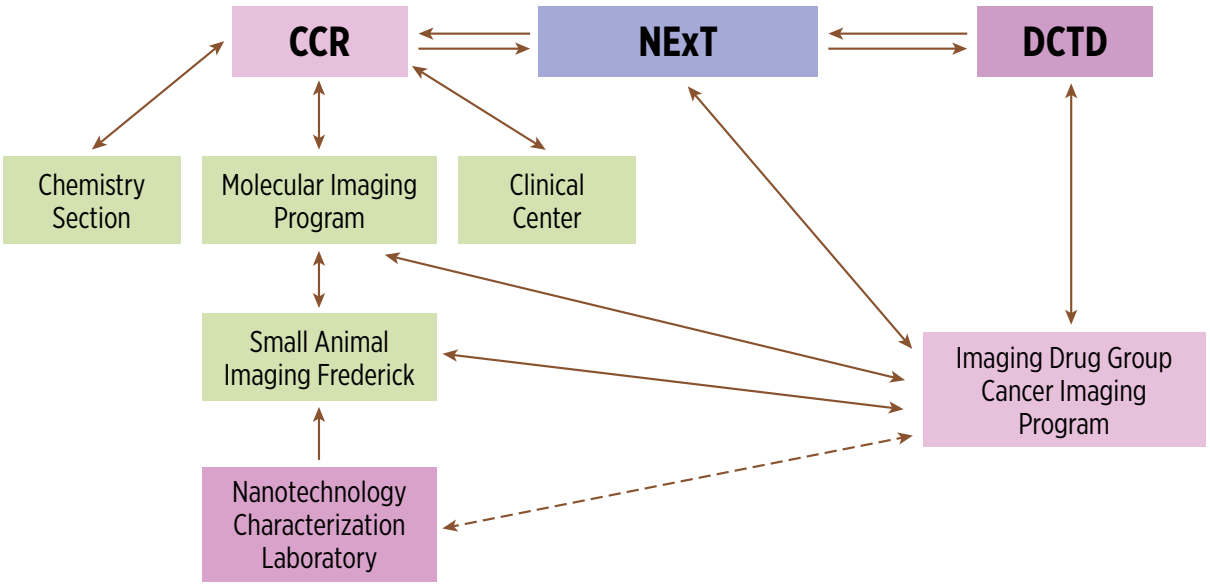



FIGURE 30: IMAGING DRUG DEVELOPMENT AT NCI.

The NExT Program assumed the responsibilities and resources of the Imaging Drug Group and provides an excellent mechanism to bridge the gap between new discovery in imaging drugs and delivery of new agents to people with cancer. As well as evaluating imaging agents that are accepted into NExT, the NCI Laboratory Animal Sciences Program (LASP) Small Animal Imaging Program has assisted in NExT projects by using molecular imaging to confirm therapeutic drug targeting with labeled drugs and animal models with the appropriate target. Independent confirmation of critical targeting is essential prior to a commitment for development.

## Complex Spheroids

The development of model systems to test new single-agent and combination cancer therapies, allow for rapid throughput screening, and produce results that accurately predict patient response is a challenge. The NCI Patient-Derived Models Repository (PDMR)'s rich resource of diverse, genetically well-characterized patient-derived tumor cell lines spurred the development of a cell-based assay that rapidly identifies new agents and combinations to be tested in patient-derived xenograft (PDX) models. In collaboration with scientists in the Frederick Laboratory for Cancer Research (FNLCR), research involving several hundred patient-derived cell lines covering diverse solid tumors as well as rare and recalcitrant tumors formed the basis for model development.

To mimic the complexity of a tumor, tumor cells are grown in 3D with a stromal component including endothelial cells and mesenchymal stem cells, providing the complex spheroids with cell-cell interactions resembling tumors *in vivo*. Human mesenchymal stem cells are highly plastic and adapt rapidly to growth factors, cytokines, and cell surface adhesion molecules in the microenvironment. The mesenchymal stem cells bring the tumor cells and endothelial cells together in a tight cluster resembling a tissue. For experiments, 20-30 patient-derived cell lines with documented genetic alterations are grown as complex spheroids for 3 days and are exposed to about 20 single agents and combinations for 7 days. The experiment is terminated using CellTiterGlo 3D to measure the ATP content of each well, which correlates with the number of viable cells, and comparison is made between the treated and untreated wells. Each screen requires approximately one thousand 384-well plates.

As of December 2023, more than 12 complex spheroid single-agent and combination screens have been performed.

- Inhibitors of DNA repair pathways including ATR, ATM, DNAPK, and DNA polymerase θ inhibitors were screened

in combination with DNA damaging agents and targeted agents.

- RAS pathway inhibitors directed toward KRAS G12C, KRAS G12D, SHP2, and SOS1 were screened in combination with agents targeting downstream components of the RAS-RAF-MEK pathway and components of parallel pathways.
- Apoptosis targeting agents, RNA splicing inhibitors, and epigenetic target inhibitors including lysine demethylase (LSD1) inhibitors, histone deacetylase (HDAC) inhibitors, and DNA methyltransferase 1 (DNMT1) inhibitors were screened in combination with approved and investigational agents.
- Isoform-specific and pan-PI3K kinase inhibitors were screened in combination with targeted agents.
- The combination of cediranib, a VEGFR inhibitor, and erlotinib, an EGFR inhibitor, were screened in detail in complex spheroids, endothelial cell spheroids, and mesenchymal stem cell spheroids, and the drug activity was compared to other VEGFR and EGFR inhibitors.
- The aryl hydrocarbon receptor (AhR) is involved in detoxification of xenobiotic small molecules; therefore, AhR inhibitors were screened in combination with a wide spectrum of approved and investigational agents with very interesting results.

Future research includes screening new investigational agents directed toward molecular targets of interest and incorporating a normal tissue component into the screen to provide guidance on the potential of potent combinations poised for clinical benefit.

## NCI Patient-Derived Models Repository (PDMR) Program

In 2013, NCI began developing a national PDMR to serve as a resource for public-private partnerships and for academic drug discovery efforts. Patient-derived models (PDMs), such as patient-derived xenografts (PDXs) and cell lines (PDCs), are thought to reflect human tumor biology more closely than established cell lines due to their low passage number, and thus are potentially more predictive models than traditional cancer cell lines which have been passaged *in vitro* for decades. The Developmental Therapeutics Program's (DTP) Biological Testing Branch (BTB) is developing PDMs for the repository that are derived from tumor tissue from patients with cancer and are propagated both *in vitro* using 2D or 3D cell culture systems and *in vivo* via passaging in host mice as PDXs. The PDMR distributes:

- Viable PDX tumor fragments for implantation in mice
- Cellular fractions such as DNA and RNA
- Tumor fragments that can be used for protein extraction
- 3D *in vitro* organoid models (PDOrgs)
- 2D *in vitro* cell cultures (early-passage tumor cell lines [PDCs] and/or cancer associated fibroblasts [CAFs])

The publicly available PDMR database provides access to extensive molecular characterization information and clinical and social history for all models. A key goal of the PDMR effort is to establish and make publicly available a set of SOPs for all aspects of PDM creation, propagation, and quality control.

Specimens for model development are collected from consenting people with cancer at clinical sites including, but not limited to, the NCI Clinical Center, NCI-designated Cancer Centers, the NCI Experimental Therapeutics Clinical Trials Network (ETCTN), and the NCI Community Oncology Research Program through two NCI-sponsored tissue procurement research protocols allowing the patient biomaterial to be used for the generation of PDMs. In addition, NCI is working with external groups through several NCI funding opportunities who have:

- Access to patient cohorts with rare histologies and pediatric populations
- Access to rapid-autopsy tumor material
- Their own previously established early-passage PDX models
- Viably cryopreserved patient material collected under Institutional Review Board-approved protocols, that with the proper material transfer agreements, could be released to the PDMR for further propagation and distribution to the scientific community

The PDMR is an active member in the PDX Development and Trial Centers Research Network (PDXNet). The goal of this consortium is to perform multi-center collaborative preclinical studies and work with ETCTN clinicians to leverage

their expertise for preclinical study design. Successful studies will be prioritized to target early phase clinical trials within the NCI ETCTN or ComboMATCH setting.

The targeted goal of the PDMR is to develop and make available more than 1,500 unique, quality-controlled, early-passage, molecularly characterized PDXs that can serve as standardized reagents, enabling comparison of research results across laboratories. Ideally, the PDMR will have 50 unique PDX models for each common tumor type to capture the disease heterogeneity present in the population, provide a representative molecular landscape, and allow in-depth preclinical trial efforts by the research community. In addition to common cancers, the PDMR is also focusing on the creation of models for less prevalent cancer types that are under-represented in the research model space, such as prostate cancer, small cell lung cancer, sarcomas, and other rare histologies (such as malignant peripheral nerve sheath tumor, Hürthle cell carcinoma, adrenocortical carcinoma, and cholangiocarcinoma) as well as representation from racial and ethnic minorities. Another unique feature of the PDMR is that it has over 250 model sets where a PDX, PDOrg, and PDC have been created from the same originating patient material. This provides a unique opportunity for researchers to do a full translational study from the *in vitro* to the *in vivo* setting with genetically matched patient-derived models. In the past 10 years, the NCI has received and processed more than 11,900 tumor and blood specimens (**Table 24**) from more than 6,800 patients covering a variety of malignancies (**Figure 31**). As of December 2023, 865 PDXs, 376 PDOrgs, 429 PDCs, and 392 CAFs are publicly available for distribution, and more than 2,900 vials of material have been distributed to academic and commercial institutions for research purposes. In addition, multiple new data types are available in the PDMR data set including HLA characterization for all PDX models, gene fusion calls, and CMS categorization for colorectal carcinoma models to help investigators select the best models for their research. In January 2023 the PDMR was opened to international requests.

PDMR models are being used in preclinical drug studies within the BTB. One study involving the administration of five standard-of-care agents against more than 76 PDX models has already demonstrated responses to agents in the appropriate histology and at a similar percentage as that seen in the clinical setting. Another large preclinical trial evaluating 56 novel therapeutic combinations tested against 39 PDXs of rare cancers (e.g., mesothelioma, osteosarcoma, Hürthle cell cancer) – more than 2,000 independent experiments – is ongoing to identify new therapeutic approaches for treating people with these tumors. Combinations demonstrating tumor growth inhibition are followed up with additional studies to determine if the observed activity is due to the drug combination or one of the single agents. While not yet complete, some of the results have already resulted in phase 1 clinical studies for rare cancers at NCI's Developmental Therapeutics Clinic.

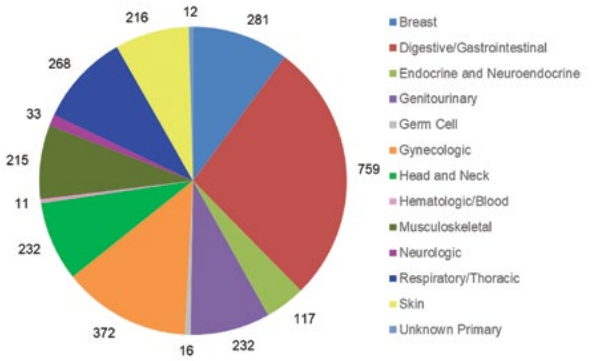



**FIGURE 31: PDMR MODEL DEVELOPMENT.**

PDMR Models in Development, by Disease Location. Number of tumor specimens by disease location that, at the time of publication, are undergoing model development or had successfully developed as a model for the NCI PDMR. PDX models are discontinued if no tumor growth is seen in Passage 0 (P0) after 300 days.

| | |
|---|---|
| Total Specimens Received | 11909 |
| Total Number of Unique Patients | 6918 |
| Total Specimens with PDXs at ≥P0 or with Confirmed Growth: | 2740 |
| Tumor (pie chart) | 2732 |
| CTCs (confirmed PDX out of >2800 implants) | 8 |
| Unique Patients with PDXs at ≥P0 or with Confirmed Growth: | 2557 |
| Total discontinued specimens: | 9352 |

**TABLE 24: PDMR MODEL INVENTORY.**

## NCI Program For Natural Products Discovery (NPNPD)

Natural products (NP) or chemical entities derived from nature have been and continue to be a major source of new drugs and drug leads. This is particularly important in cancer therapy since NP pharmacophores represent greater than 40% of all approved small molecule anticancer drugs. The NCI's Natural Products Repository is one of the largest and

most diverse collections of plant, marine invertebrate, and microbial biota used for NP-based research. However, in its crude form, these extracts are very difficult to screen in a high-throughput manner and require long and labor-intensive purification steps to identify a single active ingredient.

To fully use this unique collection of chemical diversity, the Natural Products Branch (NPB) within DCTD's Developmental Therapeutics Program (DTP), together with the NCI Center for Cancer Research, established the NPNPD, which has created an enhanced pre-fractionated library suitable for high-throughput targeted screens.[17] This resource also enhances the efficiency of subsequent NP chemistry efforts to discover new molecules that specifically modulate targets within biological pathways central to human disease. The goal of the NPNPD is to implement new technologies towards increasing the scope and efficiency of NP drug discovery. This program, launched through the Cancer Moonshot℠ and funded by the 21st Century Cures Act, is an exceptional opportunity for NCI to facilitate discovery not only for cancer, but across all disease states. It will also promote multi-disciplinary, intramural-extramural collaborations and uncover new biological frontiers.

NPB has thus far released 500,000 fractions available in 384-well plates that are publicly accessible, free of charge, and open to screening against any disease target. Operations are in a purpose-built automation laboratory at Frederick National Laboratory for Cancer Research (FNLCR), which houses state-of-the art liquid handling, automation, microbial fermentation, and analytical chemistry equipment. The NPNPD fraction library workflow (**Figure 32**) required extensive customization of commercially available instrumentation; it encompasses solid phase extraction chromatography, drying, plate generation, and storage, and can produce up to 16,000 NP fractions per month. Previous NP fractionated sample production throughput at this scale and scope has never been demonstrated.

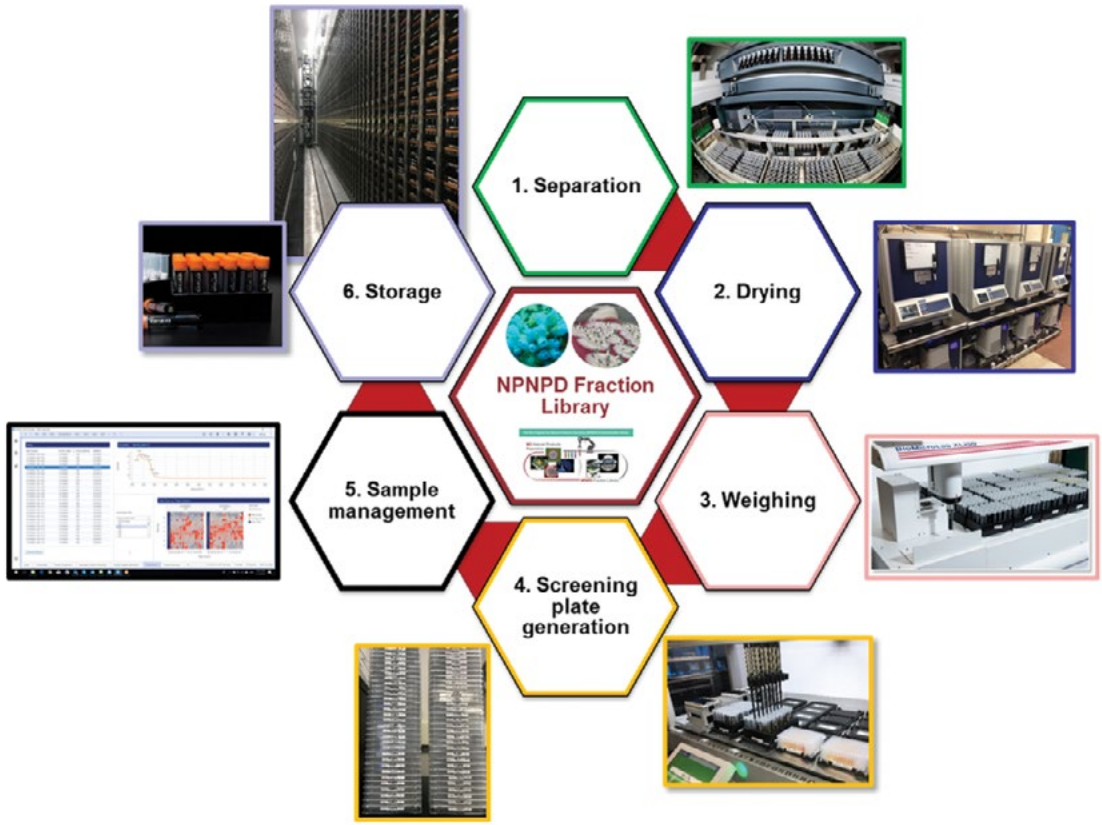



FIGURE 32: NPNPD FRACTION LIBRARY WORKFLOW.

[17] Thornburg, C. C., et al., NCI Program for Natural Product Discovery: A Publicly Accessible Library of Natural Product Fractions for High-Throughput Screening. *ACS Chemical Biology*. 13 (9), 2484-2497 (2018).

NPB also developed and validated methodologies for rapid second-stage active compound purification and identification to further support the use of NP samples in high throughput-screening (HTS) (Grkovic, 2020). Traditionally, in NP-based HTS campaigns, this step is material- and time-consuming as it requires multiple fractionation and screening steps before the identification of the active components. Here, by utilizing multiple high-throughput and high-capacity parallel HPLC systems, the fully automated NPNPD workflow can process 500 primary hit fractions in a two-week period (**Figure 33**). Overall, the rapid second-stage purification conserves extract mass, requires much less chemist time, and introduces knowledge of structure early in the isolation workflow, enabling faster turnaround times in NP-based HTS.

The program has developed bioinformatic resources for better integration of NPs with HTS. With the aim of establishing a bioinformatics platform capable of integrating biological activity, source organism taxonomy, and chemical structure, a proof-of-concept study was published using an artificial neural network of the NCI-60 human tumor cell anticancer drug screen data (Evans, 2023).

## NCI Formulary

The NCI Formulary is a public-private partnership whose purpose is to provide academic investigators with rapid access to agents for cancer clinical trial use or preclinical research, particularly for combination trials involving agents from multiple collaborating pharmaceutical companies. To date, the NCI Formulary pharmaceutical collaborators approved 14 of the 31 preclinical research proposals and 10 of the 20 clinical proposals that were received. As the use of genomic sequencing data becomes mainstream in cancer therapy, requests for, and access to, multiple targeted agents for the conduct of clinical research studies are becoming more common.

To develop the Formulary, DCTD negotiated with 12 companies to supply 36 agents using specific NCI Formulary Clinical Cooperative Research and Development Agreements (CRADAs). Negotiations for additional agents continue. These CRADAs provide academic investigators access to the collaborators' proprietary agents, thus eliminating the often-lengthy negotiation process that occurs between individual

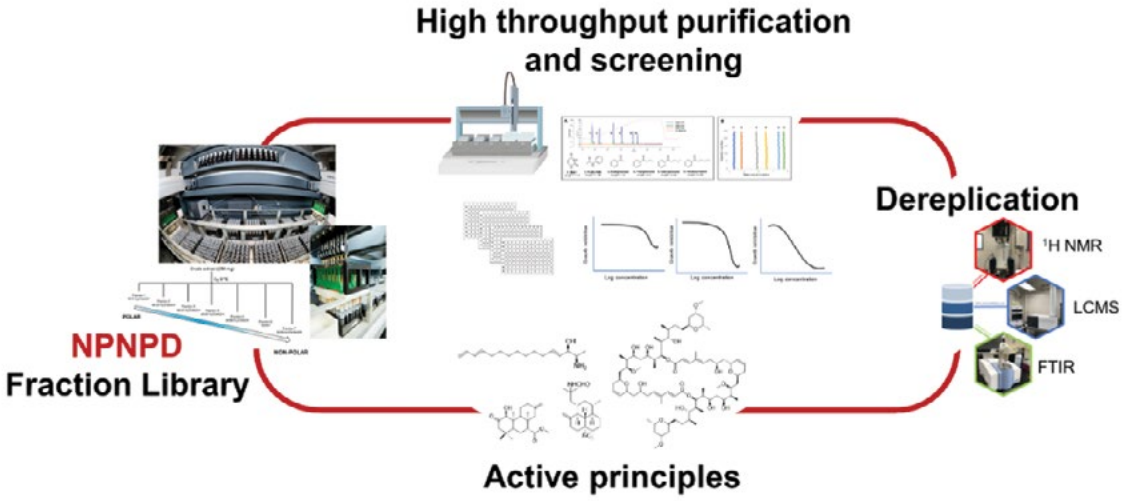



**FIGURE 33: FULLY AUTOMATED NPNPD WORKFLOW.**
Multiple high-throughput and high-capacity parallel HPLC systems

investigators and pharmaceutical collaborators. Agents within the NCI Formulary are accessible to NCI main-member Experimental Therapeutics Clinical Trials Network (ETCTN) and NCI National Clinical Trials Network (NCTN) institutions and their investigators in the United States, with a clinical Material Transfer Agreement used to formalize the expectations of each party. The NCI clinical trial infrastructure facilitates conduct of the trials, from proposal submission and timely review by the collaborating pharmaceutical companies, to agent distribution, serious adverse event submission, and clinical data reporting.

## Clinical Pharmacodynamics Program (CPP)

DCTD established the CPP in 2005 at the Frederick National Laboratory for Cancer Research (FNLCR). The CCP ensures that the assay and assay reagent principles and practices of the clinical diagnostics industry are applied to pharmacodynamics (PD) to enable the reliable measure of molecular drug activity in patient samples and validate that an investigational drug's mechanism of action could be confirmed at an early stage of clinical drug development. Assays are nominated for development based on compounds in the NCI Experimental Therapeutics (NExT) Program. The CPP consists of three laboratories:

- Pharmacodynamics Assay Development and Implementation Section (PADIS; see below) – assay development and analytical validation to ensure it is accurate within specified parameters and for the expected type of clinical trial specimen, and the results are reproducible over time and at different locations
- Internal Quality Control Laboratory - comprehensive support for reagent quality control
- National Cancer Target Validation Laboratory (NCTVL) – performs assays developed and validated on clinical samples in PADIS using the accompanying Standard Operating Procedures (SOPs) in support of clinical trials conducted in the Developmental Therapeutics Clinic (DTC) and allied medical centers, and as part of the National Clinical Laboratory Network (NCLN) laboratory supporting Experimental Therapeutics Clinical Trials Network (ETCTN) investigator-led clinical trials

The guiding principle of the PADIS laboratory is that the methods used by the clinical diagnostics industry for blood analysis can be applied to measuring drug activity in tissue biopsies from patients with cancer. The first assay developed, an immunoassay performed on tumor biopsy extracts to measure inhibition of PARP1/2 by ABT-888[18], was widely adapted in support of clinical trials in the U.S. and licensed by NIH to a small business for commercial development and marketing. SOPs associated with each clinical assay are publicly available and FNLCR provides training classes to interested investigators. For certain assays, calibrators and test reagents may also be available to investigators supporting NCI-sponsored trials. This approach is applied to preclinical and clinical tissue and blood specimens for both extraction and image-based assays.

To enable discrete quantitative measurement of patient specimens, PADIS is constantly evaluating, applying and adapting new technologies with modifications to specific tests/kits, software script development, and custom instrumentation. PADIS is developing multiplex assays capable of simultaneously measuring several analytes in the same tumor biopsy or circulating tumor cell samples, for example, to quantify DNA Damage Repair pathway activation and differentiate cell death pathways. A 5-channel multiplex assay for monitoring T-cell activation in the tumor microenvironment was deployed to understand why the immune checkpoint inhibitor atezolizumab is active in alveolar soft-part sarcoma, the DCTD trial that led to the 2022 FDA approval of the drug for this indication.

### Molecular Characterization Laboratory (MoCha)

MoCha is a DCTD-supported laboratory at FNLCR that facilitates early phases of assay development and transition to clinical laboratory readiness. MoCha's clinical laboratory is Clinical Laboratory Improvement Amendment (CLIA)-certified, performing multiple analytically validated next-generation sequencing (NGS) assays in support of DCTD clinical studies and precision medicine initiatives. To support the clinical trials, MoCha built a strong group consisting of histotechnologists, molecular biologists, quality assurance specialists, bioinformaticians, scientific project/program managers, scientists, and molecular pathologists. MoCha aims to improve clinical outcomes by providing a comprehensive assessment of key cancer-related genes in people's tumors and blood.

[18] Ji, J., et al., Modeling pharmacodynamic response to the poly(ADP-Ribose) polymerase inhibitor ABT-888 in human peripheral blood mononuclear cells. *PLoS One*. 6(10):e26152 (2011).

MoCha collaborates with NCI to manage the Molecular Diagnostic Network (MDN) that includes external subcontractors (MD Anderson Cancer Center, Brigham and Women's Hospital, Fred Hutchinson Cancer Center, Children's Hospital Los Angeles, and Nationwide Children's Hospital), and MoCha's CLIA laboratory. MDN has supported the NGS activities for the NCI Molecular Analysis for Therapy Choice (NCI-MATCH) Clinical Trial (CTEP-EAY131), the NCI-Children's Oncology Group (COG) Pediatric MATCH Clinical Trial (APEC1621SC), and other precision medicine initiatives. After the conclusion of NCI-MATCH in December 2022, MoCha and the NGS Laboratory Network began to support the NCI-MATCH Archival Initiative, a correlative research proposal under NCI-MATCH. This study aims to determine whether fresh biopsies are required for precision medicine studies by assessing the concordance between treatment assignments based on molecular data using fresh biopsies (baseline specimens) compared to archival specimens.

Pediatric MATCH screened more than 1,300 patients and planned to screen about 1,000 pediatric and adolescent patients for somatic and germline mutations. As part of this support effort, MoCha contracted with Nationwide Children's Hospital as the biorepository and preanalytical laboratory. Additional contracts were established with Children's Hospital Los Angeles and Baylor College of Medicine for germline reporting. A germline validation study was completed to enable germline testing. Dartmouth and MD Anderson Cancer Center were subcontracted to support NGS for Pediatric MATCH alongside MoCha. Enrollment in the screening portion of the study, which involved MoCha, ended on Dec 31, 2021. The trial is open with one treatment arm and will close completely at the end of 2024.

MoCha plays a central role in reviewing applications for membership in NCI's Designated Laboratory Network, as well as in the administration of a qualification study given to all laboratories as part of the laboratory application process. To date, the Designated Laboratory Network has contributed nearly 700 patients to NCI precision medicine clinical trials and demonstrated the feasibility of enrolling patients to rare cancer arms.

Given its extensive experience in the precision medicine arena, MoCha was delegated to support the development of three NCI precision medicine trials. The three initiatives (ComboMATCH, iMATCH, myeloMATCH) have each required extensive development of genomic assays that require customization due to the broad variation in disease types and molecular targets. The MoCha laboratory validated several genomics assays designed for each initiative. These assays have been instrumental in the regulatory aspects of the Investigational Device Exemption for myeloMATCH, which will enroll newly diagnosed leukemia patients on trials of novel therapies in 2024. The MoCha clinical laboratory also supported NCI's Molecular Profiling-Based Assignment of Cancer Therapy (MPACT) for Patients with Advanced Solid Tumors Clinical Trial (CTEP Protocol #9149). The trial screened 193 biopsies between January 2014 to April 2018, an actionable mutation of interest was detected in 108 biopsies. The study was completed in 2021 (Chen, 2021).

The MoCha CLIA laboratory supports the NCORP Tissue Procurement Protocol (CTEP Protocol #10231). The protocol aims for 150 people with paired biopsies before and after treatment, with each person receiving an Oncomine™ clinical report. This study is a project of the Cancer Moonshot℠ Biobank, which aims to recruit approximately 1,000 pre/post biopsy specimens from patients on standard-of-care therapy. The specimens from patients on this study are being tested with the Oncomine™ panel producing a clinical report of their genes with careful annotation that the treating physician can choose to use for clinical care. The MoCha laboratory jointly manages all aspects of this project with DCTD's Cancer Diagnosis Program.

The MoCha CLIA NGS and Histology laboratories have developed assays for MGMT (O-6-Meth-ylguanine-DNA Methyltransferase) immunohistochemistry screening and a methylation assay based on reverse-transcription polymerase chain reaction in support of DTC studies. In addition, the MoCha CLIA NGS laboratory has provided support for the myeloMATCH trial with the Oncomine™ Myeloid Assays that provide NGS results from patients with AML to allow for protocol selection.

*Research and Development Activities*

MoCha's Research and Development (R&D) group is involved with developing new technologies and has established robust research assays to support genomic characterization in blood and several tumor tissue types. MoCha's R&D group is directly involved in NCI's Patient-Derived Models Repository project.

The goal is to establish approximately 1,000 patient-derived models and make tumor material and associated genomic data from these models freely available to the research community for preclinical and other studies. In support of the project, MoCha generates all RNA sequencing and whole-exome sequencing data. The MoCha histopathology group confirms the histopathology of all models and performs an immunohistochemical characterization of selected models of interest. Additional efforts include the genomic characterization of models derived from rare and recalcitrant tumor types.

MoCha also evaluates and optimizes cutting-edge assays, sequencing platforms, and data analysis methods. The 10x Genomics Single Cell Sequencing platform and an assay to identify RNA fusions were developed and are being applied to elucidate tumor biology in depth. MoCha laboratory staff and bioinformaticians collaborate to evaluate genomic characteristics, such as tumor mutational burden (TMB), microsatellite instability, copy-number variants, single-nucleotide variants, and insertions/deletions, using minimal amounts of starting material, including plasma-derived circulating DNA. Other activities include implementation of novel technologies, such as R&D sequencing assays from the Illumina® HiSeq 2500 sequencing platform to the newest Illumina sequencing instrument, the NovaSeq™ 6000. This activity required substantial testing and optimization but is an important step to increase both data output and sample throughput while decreasing sequencing times and overall cost.

MoCha has collaborated with two groups to evaluate and characterize NGS quality control standards. These materials will prove invaluable by providing universal materials and guidelines that can be used to accurately determine assay performance. A partnership with the Foundation for the National Institutes of Health focuses on circulating tumor DNA (ctDNA) reference standards. Projects with Friends of Cancer Research evaluate TMB reference standards and homologous recombination deficiency in tissue samples.

The advantage of MoCha having both a CLIA-accredited clinical laboratory and an R&D laboratory is the ability to easily convert research-grade assays into clinical assays for care of people with cancer. The groups have collaborated on several projects aimed at identifying predictive biomarkers and understanding treatment response and resistance in tumors. The MoCha R&D and CLIA laboratories have collaborated to develop a clinical grade ctDNA assay, the Illumina TruSight Oncology 500. The assay will be used to support DTC studies, as well as ComboMATCH, to examine serial plasma samples to detect genes that may allow an 'early read' on whether a patient is responding to therapy. MoCha has also received more than 4,000 NCI-MATCH plasma samples as part of a correlative proposal to characterize ctDNA.

MoCha is also part of the NCLN and provides genomic support for ETCTN trials, performs whole-exome and RNA sequencing, and recently added ctDNA to their list of services. This takes advantage of MoCha's extensive experience in harmonization and validation experiments for whole-exome, RNA and ctDNA sequencing workflows. As part of the NCLN, MoCha has subcontracted with Nationwide Children's Hospital as the biorepository and preanalytical laboratory for the ETCTN.

## The Cancer Imaging Archive (TCIA)

Cancer imaging research requires access to large, standardized, purpose-built imaging collections. In 2010, the Cancer Imaging Program (CIP) leveraged its long-term investment in the development of imaging curation and archiving technology to initiate a funded service hosted at the University of Arkansas for Medical Sciences that would fill the unmet needs of cross-disciplinary image researchers for open access to clinical images. Each month, more than 20,000 unique users visit TCIA to find more than 200 datasets of computed tomography, magnetic resonance imaging, positron emission imaging, x-ray mammography, digitized histopathology slides, and radiation therapy planning imaging studies. At least 1,800 peer-reviewed publications are based upon these TCIA-hosted data, and more are likely as most of the collections are available for public use (**Figure 34**). In addition to supporting the imaging components of major NCI data collection initiatives, CIP leads an advisory group that prioritizes the curation and publishing of researcher-initiated proposals based on how well the data sets fill gaps to support critical research for a clinical need, novel/unique datasets, research reproducibility, and investigation of biological hypotheses or other discoveries about the pathophysiological basis of cancer.

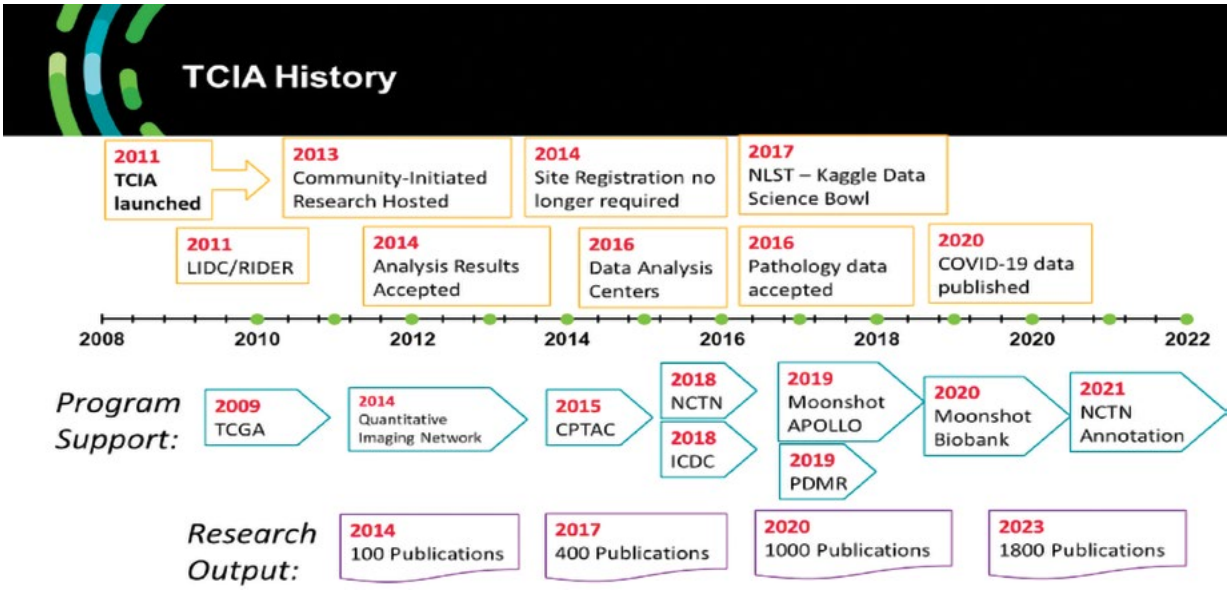



FIGURE 34: TCIA MILESTONES SINCE INCEPTION IN 2011.

More than three-quarters of the datasets also have associated supporting data, such as demographics, outcomes, therapy, image analyses, pathology images, genomic and proteomic data, and imaging labels and segmentations. TCIA maintains the documentation and meta-data for each of its collections and provides help desk staff to assist with questions about the data from the research community. The archive has data from more than 73,304 patients and includes more than 79 million individual images.

**A Resource for the Global Cancer Imaging Community**

TCIA has become a vital resource known throughout the global cancer imaging community. It has collected data from more than 112 institutions and has served more than 1.1 million users from 224 countries and regions (based on Google Analytics "New Users") (**Figure 35**). On average, 20,000 users access TCIA each month, and users download more than 2.5 petabytes of data annually. TCIA is a data publisher and recommended repository for *Nature*, *PLOS One*, *Medical Physics*, *Elsevier,* and other leading journals. More than 1,900 peer-reviewed publications that leverage TCIA data have been indexed. TCIA provides regular updates on social networks and hosts a variety of TCIA-centric sessions during annual meetings of the Radiological Society of North America to stimulate interest and cross-fertilize ideas. CIP publishes a TCIA newsletter distributed to 8,000 recipients each month.

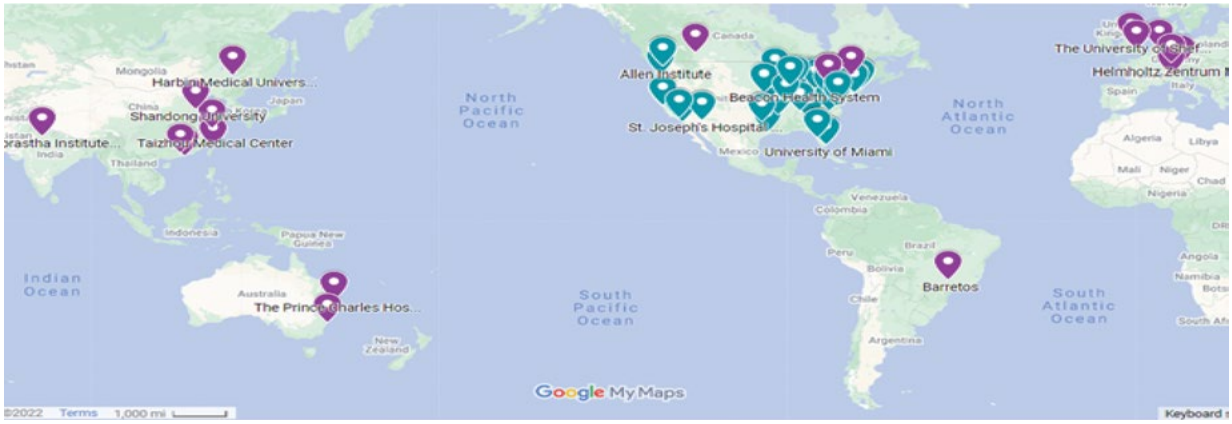



FIGURE 35: 112 INSTITUTIONS HAVE CONTRIBUTED DATA TO TCIA.

**Submission and De-identification**

Since TCIA contains a large repository of open-access clinical imaging data, protection of Private Health Information while preserving the scientific utility of the data is critical. TCIA has developed robust tools and extensive procedures to transmit, de-identify, and quality assess the medical images submitted to the archive and is staffed with curation experts who review and publish the submitted images. Further refinement and testing of advanced, standards-based tools are routinely performed to enable more efficient de-identification of medical image data for public consumption. TCIA provides full research-focused de-identification services and makes its tools and knowledge base available to the scientific community.

**Crediting Data Generators for Data and for Data Reuse**

To enhance research reproducibility and validation and to encourage data submissions from academic researchers, TCIA freely provides standards-based Digital Object Identifiers (DOIs) for each of its data collections and to researchers using customized data cohorts. The DOIs are frequently used to reference data in peer-reviewed publications, support data-use tracking, and provide authorship citations for use in academic CVs.

**Imaging-Proteogenomics Research Support**

TCIA supports a research community that seeks to connect cancer phenotypes to genotypes. To accomplish this, TCIA hosts data sets that connect clinical images with patient genomic and proteomic data. For example, TCIA collected and hosts radiological imaging from The Cancer Genome Atlas (TCGA), along with the results of characterization and analysis work done by TCIA-TCGA imaging phenotype research groups. TCIA is also part of three major NCI programs that collect medical and pathological images matched to proteomic, as well as genomic, clinical, and pathological data.

- The National Cancer Institute's Clinical Proteomic Tumor Analysis Consortium (CPTAC) is a national effort to accelerate the understanding of the molecular basis of cancer through the application of large-scale proteome and genome analysis, or proteogenomics. TCIA has partnered with CPTAC to collect and host more than 1,600 patients' histopathology images, 500 patients' radiology images, and coordinate a special interest group to support cross-disciplinary research across imaging and omic data. In addition, four CPTAC collections have been annotated and segmented through CIP's annotation initiative (see Annotated Data for AI/ML, below).
- A trilateral collaboration with the VA, DOD, and NCI called the Applied Proteogenomics OrganizationaL Learning and Outcomes (APOLLO) network provides genomic and proteomic screening to targeted therapies for up to 8,000 active service members and veterans. TCIA's data curation and collection capacity have been extended to the VA's research Precision Oncology Data Repository and to the DOD Defense Health Agency data cloud (in progress). TCIA has supported multiple pilot data collection activities, is the imaging data collection and characterization portal for the APOLLO 5 prospective data collection and is establishing a first-of-its kind enterprise clinical imaging de-identification application and sharing system among VA, DOD, and NCI. Imaging from DOD, VA, and participating civilian sites is posted on TCIA (hosting data from more than 260 APOLLO-enrolled patients) and will be mined for clinically relevant information in combination with APOLLO proteogenomic findings.
- The Cancer Moonshot℠ Biobank collects biospecimens (blood and tissue removed during medical procedures) and associated data from at least 1,000 patients (across at least 10 cancer types), who represent the demographics of the U.S. and received standard of care cancer treatment at multiple NCI Community Oncology Research Program (NCORP) sites. De-identified radiology and histopathology images collected from Biobank patients are available in TCIA, and associated genomic, phenotypic, and clinical data will be hosted by the database of Genotypes and Phenotypes (dbGaP) and other NCI databases.

**Quantitative Imaging Network (QIN) Support**

TCIA hosts 11 QIN collections, several of which are accessed by members for cross-institutional algorithm validation or as part of pilot challenges. See the QIN section in the Major Initiatives chapter of this book.

**National Lung Screening Trial (NLST) Data Portal**

TCIA has absorbed and joined images from both arms of the NLST trial from the American College of Radiology Imaging Network (ACRIN) and the Lung Screening Study group. TCIA hosts the full NLST image set with clinical metadata and pathology images, along with a specially developed query tool that supports filtering on associated clinical data parameters.

**Preclinical Imaging Support**

TCIA hosts high-value preclinical image collections. These include studies of specialized phantoms, devices that permit standardization of quantitative imaging parameters across instruments and sites, as well as imaging studies of patient-derived xenograft models from the NCI Patient-Derived Models Repository and canine clinical trial data from the Canine Immunotherapy Trials Network.

**NCI National Clinical Trials Network (NCTN) Support**

NCTN clinical trials help to establish new standards of care, set the stage for approval of new therapies by the Food and Drug Administration, test new treatment approaches, and validate new biomarkers. TCIA has published 24 datasets from NCTN clinical trials, most with links to extensive clinical data. Half of those trials were funded through an NCI initiative begun in 2019 to expand its data collection services to support the NCTN. Imaging data associated with NCTN trials were centralized and de-identified under a subcontract with the Imaging Radiation Oncology Core (IROC). The TCIA team documented its curation procedures and trained IROC staff to apply them. Trial image datasets are hosted on TCIA for final review and linked with clinical data hosted in the NCTN/NCORP Data Archive.

**Annotated Data for AI/ML**

NCI recently launched an initiative to annotate NCI trials with tumor segmentation labels and seed points to stimulate development of artificial intelligence (AI) segmentation models. Supervised machine learning (ML) algorithms require labeled data for algorithm training and validation. CIP continues to improve its support for AI and ML-based research by prioritizing new TCIA data collections that provide annotations and labels that can be leveraged for algorithm development and funding the expert annotation of existing TCIA data. Sixty-nine TCIA data collections include detailed segmentations, of which seventeen were generated through CIP annotation funding.

**Childhood Cancer Data Initiative (CCDI)**

TCIA has taken proactive steps to support CCDI's goal to "build a community of pediatric cancer researchers, advocates, families, hospitals, and networks committed to sharing data to improve treatments, quality of life, and survivorship of every child with cancer." TCIA hosts seven clinical trial datasets from the NCTN Children's Oncology Group, and tumor annotations for each trial are being generated and published. TCIA is engaged with the CCDI Data Catalog team to ensure TCIA datasets are discoverable as they are added.

**COVID-19**

To support the urgent public health need to have COVID-19 image data for all disease stages freely available for caregivers and the research community, CIP provided TCIA as a resource for making image sets available to the public since it was uniquely ready to carry out a short-term effort to collect, curate, and host COVID-19 patient images for immediate reference by the community. TCIA hosts six comprehensive COVID-19 datasets in its public archive.

## Responses to Oncology Agents and Dosing in Models to Aid Preclinical Studies (ROADMAPS)

The Cancer Chemotherapy National Service Center (CCNSC) was created in 1955 via a $5 million Congressional investment aimed at providing standardized procedures for testing potential anticancer compounds. This effort resulted in the screening of thousands of candidate compounds primarily using rodent tumor models. In 1976, the CCNSC was relocated within the Developmental Therapeutics Program (DTP) and continued to operate a large-scale rodent anti-tumor screening effort until the mid-1980s. At that time, the focus for anticancer drug development moved toward

cell-based methods with the capacity for a greater number of compounds being screened annually; however rodent tumor studies were still crucial to translate the *in vitro* findings into potential new therapies.

Concerns related to the relevance of mouse tumors in human drug development led to the creation of a panel of human tumor xenografts in immunologically compromised mice. Compounds with activity in *in vitro* tumor lines could be assessed against the same tumor cells that were grown in the mouse microenvironment. These models largely involved subcutaneously implanted tumors that are amenable to continuous monitoring of the tumor volume to effectively record growth delays and tumor regressions. These efforts led to the development of a large anticancer drug database containing more than 3,000 unique combinations of tumor model, drug, and dosing regimen together with the tumor-model response, vehicle formulation, and overall tolerability of the agents in treated xenograft models. Since most of the studies did not result in detectable antitumor activity, the information was not publicly disseminated, and as such research groups interested in preclinical drug studies were unaware these data existed.

This was addressed through publication of the ROADMAPS describing the technical underpinnings of how the data are presented and made available to the scientific community (Hollingshead, 2022). The ROADMAPS resource provides access to drug activity information on 70 FDA-approved anticancer drugs in one or more tumor models including 121 human cell line derived tumor xenografts and 19 patient derived xenografts.

### The Integrated Canine Data Commons (ICDC)

The ICDC is a node in the larger NCI human Cancer Research Data Commons (CRDC) and was developed by DCTD to advance research on human cancers by enabling comparative analysis with tumors that arise spontaneously in pet dogs. The dog is an excellent model for human cancer, especially since it is immunocompetent and shares many aspects of the disease with humans, including its response to treatment. The types of canine cancer information contained within the ICDC include genomic, proteomic, methylomic, imaging, clinical trial, biomarker, population studies, and immuno-oncology data. The data model for the ICDC is flexible to allow for ingestion of additional types of data in the future. Submitted data are harmonized to maintain data and metadata consistency, integrity, and availability to the ICDC users and compatibility with other components of the CRDC, allowing investigators to query across canine and human data sets in the web-based interface and to perform analytical operations using NCI cloud-based resources and tools.

The ICDC is now fully operational and contains greater than 35 TBs of data including 678 cases, 937 samples, and 1953 case files. The ICDC functions are guided by a Steering Committee consisting of subject matter experts from the extramural and intramural veterinary and human cancer research communities, as well NCI and FNLCR staff. A Data Governance Advisory Board was established to define the processes for accepting new data submissions, evaluating proposals, and providing the NCI a recommended prioritization for inclusion in the ICDC. A Best Practices Subcommittee and its specific working groups have also been established to recommend clinical, pathological, immunological, imaging, and sequencing data standards for the ICDC. The group has also worked with a semantics team to ensure the application of standard definitions/language throughout the harmonization and coding processes. The ICDC will continue in the future to serve as a resource to submit and access data related to cancer and empower the cancer research community to generate new hypotheses that can be tested by comparative analysis of dog and human data.

## ADDITIONAL ASSISTANCE TO THE CANCER RESEARCH COMMUNITY

### Stepping Stones Program

The Developmental Therapeutics Program (DTP) launched the Stepping Stones Program in 2019 as a complementary mechanism to the NCI Experimental Therapeutics NExT (NExT) Program, to assist NCI-funded investigators who are developing small molecule anti-cancer therapeutics or small molecules to mitigate cancer treatment-associated toxicities. Grant funding alone typically does not provide adequate support to allow the iterative studies needed to develop lead drug candidates, and many institutions do not have the deep resources to help their investigators fill some of these critical areas of need. Stepping Stones provides access to drug development expertise and resources such as chemical syn-

thesis (non-GMP) and route optimization, in vitro ADMET, exploratory pharmacokinetics, and formulation studies. The intent is to maximize grant-funded research by assisting the investigator with addressing preclinical data gaps that could advance their innovative therapeutic candidates. Furnished with data provided via Stepping Stones, investigators can be better positioned to successfully apply for development support through the NExT Program or other mechanisms.

Key eligibility criteria for support through Stepping Stones:

- The therapeutic candidate must
  - be a small molecule
  - exhibit evidence of preclinical efficacy
- Presence of a well-characterized intervention target/mode of action
- Current NCI grant funding support
- No other financial support for activities under consideration for Stepping Stones

DTP program staff and the program officer associated with the grant evaluate NCI-funded research projects, and those deemed in scope for Stepping Stones may be invited to consult with DTP staff to identify potential opportunities and prioritize discrete studies to address the most critical gaps. DTP prioritizes those programs that target cancer indications representing the most critical unmet need for new therapeutic strategies (e.g. pancreatic cancer, glioblastoma, ocular melanoma). Since its inception, Stepping Stones has supported 12 preclinical development projects arising from the DTP grants portfolio (**Figure 36**). This valuable support has led to advances in therapeutic strategies, including towards IND filings, or in some cases, to the identification of early challenges that enabled swift termination or re-evaluation (**Figure 37**).

| Round 1 | Round 2 | Round 3 | Round 4* | Round 5 |
|---|---|---|---|---|
| 3 | 4 | 2 | 3 | 2 |

**Variety of Malignancies and Conditions:**

- Uveal Melanoma
- Pancreatic Cancer
- K-Ras Mutant Cancers
- GBM
- Melanoma
- Prostate Cancer
- AML
- TNBC
- CIIPN
- Neuroblastoma

* One project not started due to change in institution

| Institutions |
|---|
| Washington University (2) |
| Emory University |
| University of Nebraska |
| University of Maryland |
| University of Virginia |
| Albert Einstein |
| University of Tennessee |
| University of Michigan |
| UC Davis |
| Virginia Commonwealth |
| Auburn University |
| Childrens Hospital of Philadelphia |

FIGURE 36: SUMMARY OF SUPPORTED PROJECTS.

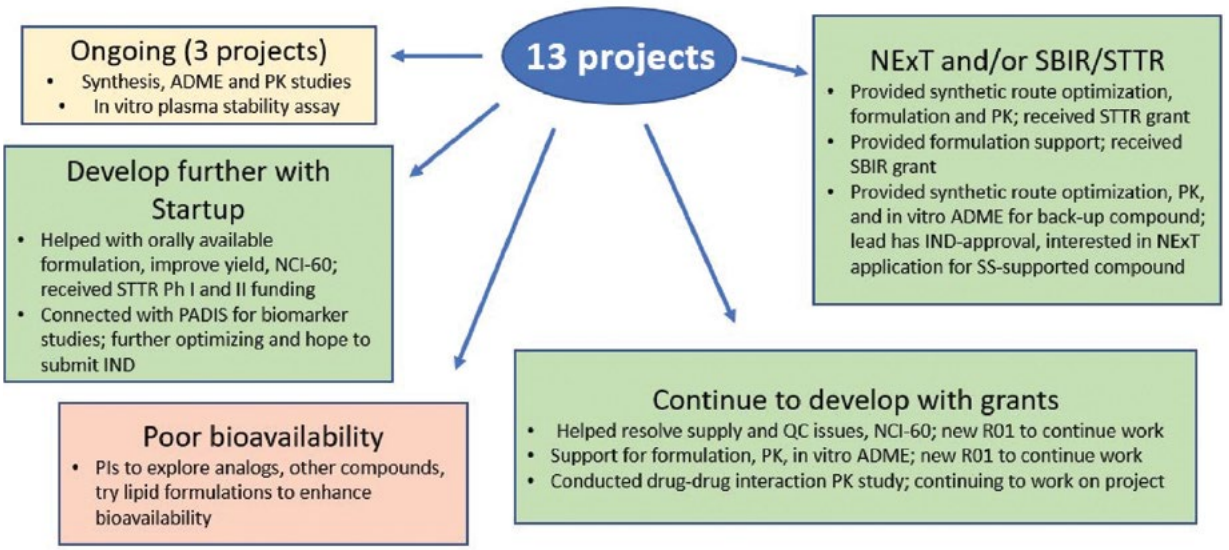



FIGURE 37: OVERVIEW OF PROJECT OUTCOMES.

### NCI Clinical and Translational Exploratory/ Developmental Studies (R21 Clinical Trials Optional)

This funding opportunity supports preclinical and early phase clinical research, as well as correlative studies, directly related to advancements in cancer treatment, diagnosis, prevention, comparative oncology, symptom management, and/or reduction of cancer disparities. This includes (but is not limited to):

- Development and testing of new molecular agents or biologics for cancer treatment (including radiotherapies)
- Management strategies for cancer-related symptoms or treatment-related toxicity
- Cancer screening or diagnostic tools, such as imaging techniques
- Cancer preventive agents or approaches
- Predictive and prognostic biomarkers for patient selection or stratification
- Clinically relevant *in vivo* or *in vitro* tumor models (including genetically engineered mouse models, patient-derived xenograft models, organoids, and cell lines)
- Strategies to address therapeutic outcome disparities among underserved populations.

In addition to novel agents, new treatment and prevention strategies may involve repurposed agents or novel combinations of interventions (including radiation), based on established mechanisms of action. Comparative correlative studies in patients with age, gender, racial/ethnic, or health disparities are encouraged to explore mechanisms underlying their differential responses (efficacy and toxicity) and resistance to therapeutic interventions. Comparative oncology studies in dogs investigating strategies for treatment and diagnosis of human disease are supported as well.

This trans-divisional exploratory grant mechanism, suitable for high risk, high reward projects as well as developmental research projects, involves DCTD, the Division of Cancer Prevention, and the Center to Reduce Cancer Health Disparities.

The scope of work appropriate for this funding opportunity is listed below:

- Early-phase clinical studies
- Correlative studies and clinical biomarker development
- Target and agent discovery and development
- Model development and analysis
- Studies to reduce the unequal burden of cancer in diverse populations

Response to the initial issuance in 2019 as PAR 19-356 (updated as PAR-20-292) was remarkable, with nearly 2,600 applications submitted (**Table 25**). Many studies performed in these R21 grants led to high quality peer-reviewed publications and provided the preliminary studies necessary for R01 grant applications. The popularity within the extramural community led to its reissuance in 2022. The first receipt date for PAR 22-216 was in October 2022.

| PAR 19-353/PAR 20-292 R21 Grants (7 rounds of submission) | |
|---|---|
| Total Grants Submitted | 2,598 |
| Total Grants Funded | 299 |
| Grants Funded within the Payline | 295 |
| Grants Funded beyond the Payline (by exception) | 4 |
| Success rate | 11.5% |

TABLE 25: PAR 20-292/PAR 19-356 R21 GRANTS.

## Cancer Grand Challenges

The Cancer Grand Challenges program was launched in 2020 by Cancer Research UK and NCI to advance bold cancer research and improve outcomes for people affected by cancer. The initiative inspires innovative ideas by supporting interdisciplinary global research teams with multiple rounds of funding to take on some of cancer's toughest challenges. Every two years, the most complex problems in cancer research and treatment are identified after convening workshops, open online calls, and consultation with cancer research leaders, clinicians, people affected by cancer, and patient advocates.

For the 2021 challenges, NCI and Cancer Research UK received expressions of interest submissions from 169 diverse research teams from more than 60 countries for the 9 open challenges. The Cancer Grand Challenges Scientific Committee narrowed the innovative ideas to 11 teams that received seed funding to develop their ideas into full proposals. The Cancer Grand Challenges program (jointly funded by Cancer Research UK and NCI) is awarding up to $5 million per year for 5 years to each of the four selected interdisciplinary teams (**Table 26**).

| Team | Challenge Focus |
|---|---|
| CANCAN | Understand and reverse cachexia and declining performance status in cancer patients |
| eDyNAmiC | Understand the biology of extrachromosomal DNA generation and action and develop approaches to target these mechanisms in cancer |
| NexTGen | Develop novel therapies to target unique features in solid tumors in children |
| PROMINENT | Understand how cells and tissues maintain "normal" phenotypes while also harboring oncogenic mutations and how they transition to become a tumor |

TABLE 26: FOUR CGC-FUNDED TEAMS IN 2021.

This trans-NCI initiative, managed by the Center for Strategic Scientific Initiatives, works closely with relevant subject matter experts within the NCI for each funded Team. DCTD provides subject matter expertise for the NexTGen team, who are focused on developing novel immunotherapies for pediatric solid tumors. This team aims to overcome the many barriers to developing effective treatments for children with solid tumors by creating and optimizing novel chimeric antigen receptor (CAR) T-cell therapies. To change the treatment paradigm for children with solid tumors, the NexTGen team is focusing on the following five integrated aims:

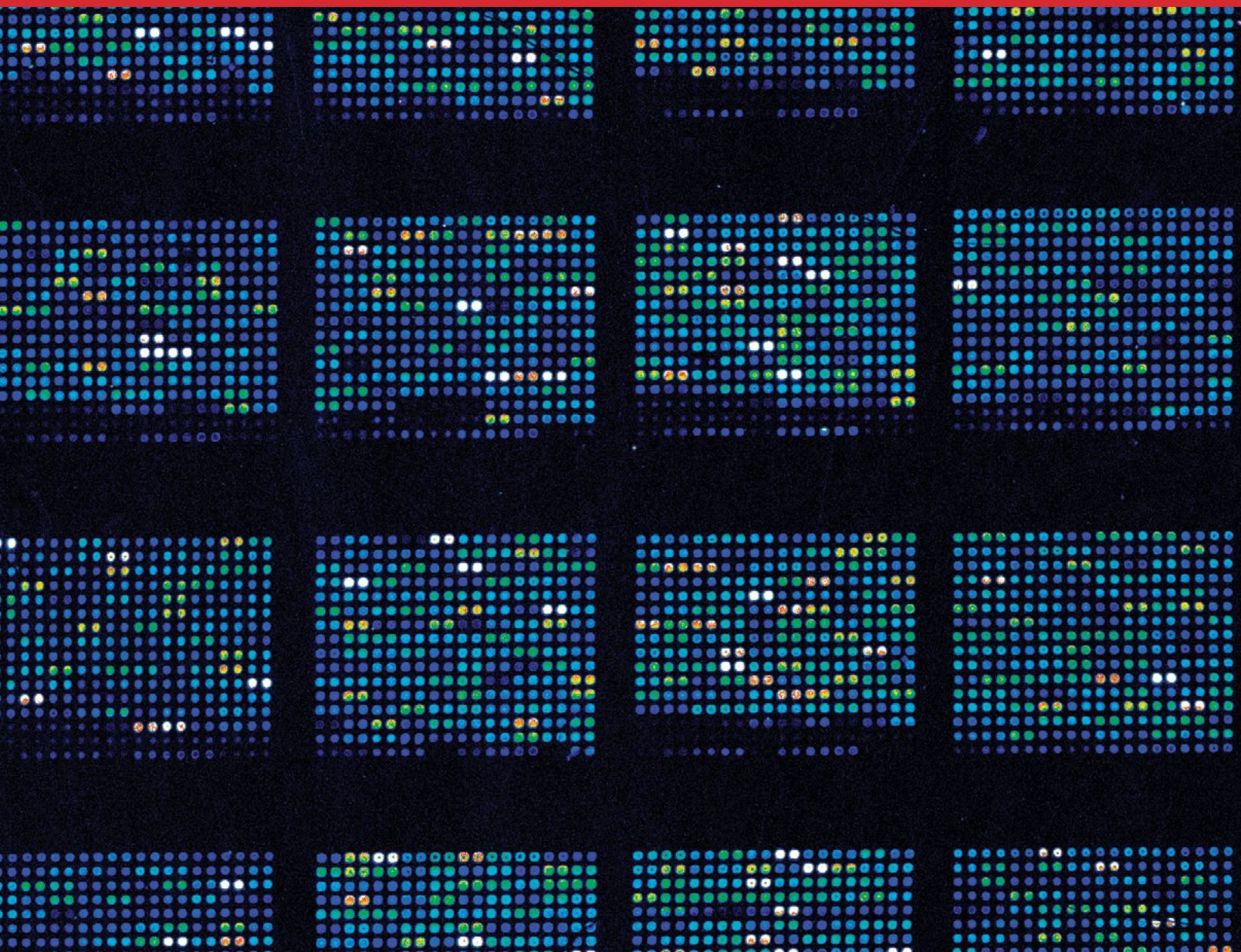
- Identifying new targets
- Modulating the tumor microenvironment
- CAR T-cell component engineering
- Preclinical models to test immunotherapies
- Conducting innovative phase 1 clinical trials

Catherine Bollard, MD, Children's National Hospital, Washington, DC, and Martin Pule, University College London, lead the NexTGen Team, which spans nine institutions across three countries. In addition to CRUK and NCI, The Mark Foundation for Cancer Research also funds the NexTGen team.

In March 2023, the Cancer Grand Challenges Scientific Committee announced nine new challenges, including one focused on pediatric cancers, which were chosen from 300 ideas. In September 2023, the Scientific Committee chose 12 teams from 176 global teams to develop their ideas into full proposals. Each team could receive up to $25 million, and winners will be announced in March 2024.

PROGRAMS AND INITIATIVES (2020-2023)

# BIOMETRIC RESEARCH PROGRAM



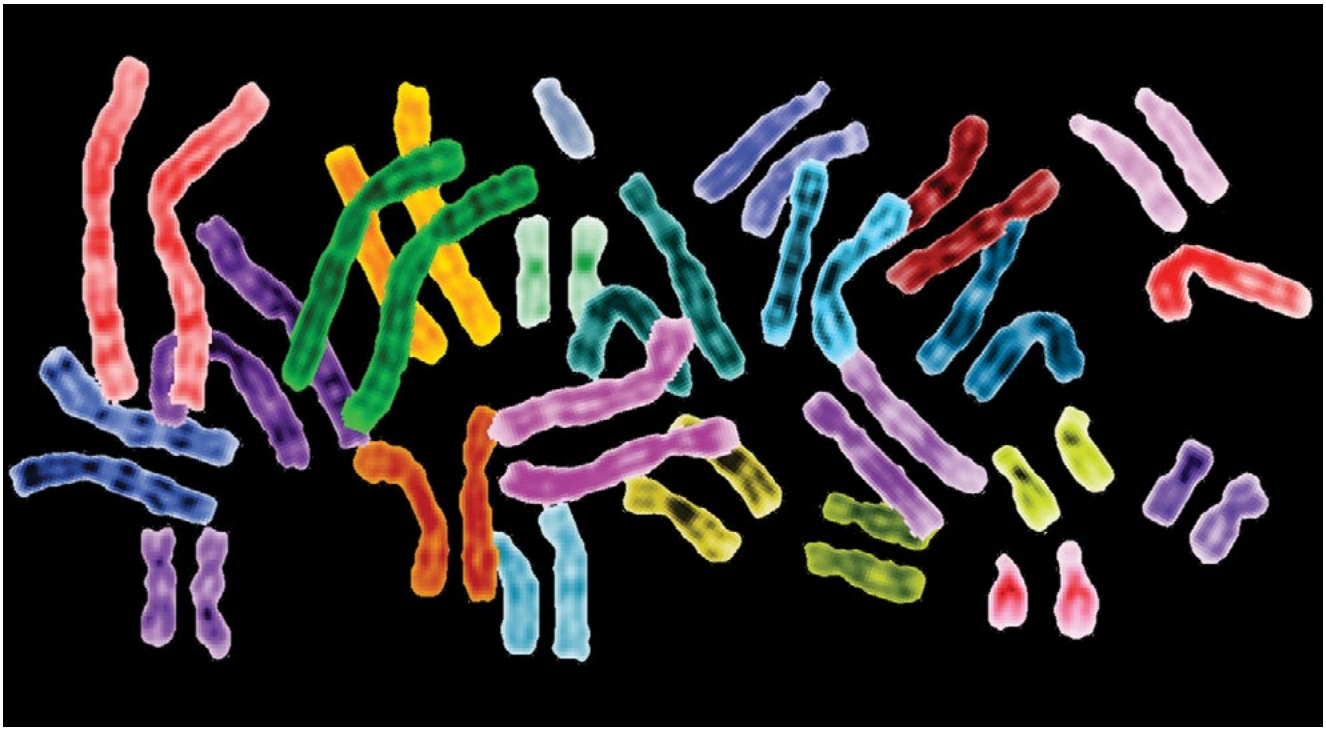
# OVERVIEW

The Biometric Research Program (BRP) is the statistical and computational biology component of DCTD. It provides leadership for DCTD programs in these areas, and conducts research in clinical trials methodology, biostatistics, computational biology, and bioinformatics.

In addition to collaborating and consulting with DCTD and the Center for Cancer Research (CCR) investigators, BRP investigators conduct self-initiated research. This enables BRP to recruit and retain a world-class research staff, provide high-quality collaboration and consultation with DCTD and NCI scientists, and make major research contributions motivated by important problems in cancer research. BRP does not have a grant, cooperative agreement, or contract portfolio and does not sponsor or fund extramural research.

The major areas of BRP research encompass:

- Developing efficient/adaptive clinical trial designs
- Integrating imaging, genomics, and molecular profiling into clinical trials
- Biomarker-driven clinical trial designs for precision medicine
- Computational and systems biology of cancer
- Bioinformatics resources for the research community



# LISA MEIER MCSHANE
## ASSOCIATE DIRECTOR

Lisa McShane, PhD, is Associate Director of BRP. Dr. McShane holds a doctoral degree in statistics from Cornell University in Ithaca, New York. She is internationally recognized for her expertise in cancer biomarkers and precision medicine cancer clinical trials. In 2013, she was elected Fellow of the American Statistical Association for her outstanding statistical contributions to the development of clinical tests for personalized medicine, international efforts to improve the quality and reproducibility of tumor marker research, exceptional ability to communicate statistical principles to cancer researchers, and distinguished service to the statistics profession. She is a coauthor of more than 150 statistical and biomedical papers, a dozen book chapters, and the book "Statistical Design and Analysis of DNA Microarray Investigations." Her statistical research interests include biomarker-driven clinical trial design, analysis methods for high-dimensional omics data, development of predictive signatures for precision medicine, multiple comparisons methods, surrogate endpoints, and biomarker assay analytical performance assessment. She co-led efforts to develop "REporting guidelines for tumor MARKer prognostic studies (REMARK)" and "Criteria for the use of omics-based predictors in clinical trials." Additionally, Dr. McShane co-leads an international working group addressing statistical challenges and opportunities for the analysis of studies involving high-dimensional data as part of the STRATOS (STRengthening Analytical Thinking for Observational Studies) Initiative.

Dr. McShane joined the NCI in 1995 after spending a few years as a mathematical statistician at the National Institute of Neurological Disorders and Stroke. Since joining NCI, she has specialized in cancer biomarker and omics research. She was appointed Chief of the Biostatistics Branch of BRP in 2015, Acting Associate Director of BRP in July 2017 with full appointment as Associate Director in September 2019. Dr. McShane has served on multiple journal scientific advisory and editorial boards, Institute of Medicine committees, FDA panels and working groups, and American Society of Clinical Oncology panels and committees that developed guidelines for HER2 and hormone receptor testing in breast cancer, EGFR mutation testing in lung cancer, and use of tumor biomarkers in early-stage breast cancer. In January 2022, she was appointed co-Editor-in-Chief of the journal *Statistics in Medicine*. Her scientific contributions have had a major impact on the design, conduct, analysis, and reporting of cancer biomarker studies and precision medicine clinical trials and have helped to bring high quality biomarker and omics tests into the clinic to improve care and outcomes for people with cancer.

# STRUCTURE AND FUNCTION

## BIOSTATISTICS BRANCH

Statisticians in the Biostatistics Branch are each designated to collaborate with specific colleagues in other DCTD programs to assist with all major DCTD activities, including clinical trials, drug discovery, molecular diagnostics, and biomedical imaging. It is the philosophy of BRP that statisticians must be deeply involved in a clinical or preclinical research area to make important scientific contributions in that area and to provide appropriate statistical guidance and oversight for DCTD and NCI activities. In addition to their statistical expertise, BRP statisticians are knowledgeable in cancer biology and therapeutics, and many of their major duties are assigned by cancer type so that they develop a fundamental understanding of clinical issues relevant to their areas of responsibility.

BRP statisticians have advisory and oversight responsibilities through their interactions with other NCI programs, including:

- Reviewing concepts and protocols for all DCTD-sponsored clinical trials
- Serving as liaison to NCI clinical trial network group statistical centers
- Participating with NCI and extramural scientists in drug development strategy groups
- Providing statistical leadership for CTEP Project Team drug development efforts
- Serving on data monitoring committees and assuring adherence to procedures established for the NCI-sponsored clinical trials networks (NCI National Clinical Trials Network (NCTN) and Experimental Therapeutics Clinical Trials Network (ETCTN))
- Serving on Intergroup Clinical and Correlative Science Committees
- Reviewing correlative science and cancer imaging protocols submitted by the NCI clinical trial network groups

BRP statisticians collaborate with other DCTD programs on initiatives and research projects, including:

- Design and implementation of the Myeloid Malignancies Precision Medicine Initiative platform trial (MyeloMATCH)
- Design and development of the Combination Therapy Platform Trial with Molecular Analysis for Therapy Choice (ComboMATCH) and ImmunoMATCH (iMATCH) basket trials
- Design, interim monitoring, and analysis of the phase 2 NCI Developmental Therapeutics Clinic (DTC) trial ML39345 (CTEP 10005; NCT03141684) evaluating atezolizumab monotherapy in advanced alveolar soft part sarcoma (ASPS) that led to the first ever FDA approval of a treatment for advanced ASPS in 2022
- Design and conduct of the NCI Exceptional Responders Initiative
- Design, implementation, and analysis of data for the NCI COVID-19 in Cancer Patients Study (NCCAPS), including clinical and biomarker analyses and in collaboration with extramural researchers and the BRP Computational and Systems Biology Branch (CSBB)
- Establishment and implementation of the ETCTN Data Safety Monitoring Board (DSMB), including development of the DSMB charter and standard operating procedure
- Participation in the development of molecular and imaging biomarkers to aid in clinical decision making
- Collaboration on the planning and conduct of extramural programs to develop and apply molecular and imaging diagnostics technologies
- Engagement in the design, conduct, and data analysis for NCI program-sponsored projects that aim to address research questions of broad interest to the scientific community, such as systematic reviews of clinical trials in a particular disease area, inter-laboratory assay comparability studies, or systematic reviews of technical performance of imaging procedures
- Oversight of the development and operation of the Web-based NCTN/NCORP Data Archive to store and enable appropriate sharing of data generated in completed NCI-sponsored clinical trials for which primary analyses have been published
- Collaboration with CCR intramural clinical branches (Radiation Oncology Branch, Lymphoid Malignancies Branch, Urologic Oncology Branch and Molecular Imaging Program), the DTC, and other NCI divisions

- Serve as principal statisticians for multiple NCI intramural early-phase clinical studies and provide expertise for clinical, laboratory, and imaging study design and analysis, including analysis of data generated by novel and state-of-the-art imaging modalities, genomic, transcriptomic, proteomic, and other omics technologies, and patient-derived xenograft (PDX) mouse models
- Collaboration with investigators in the CCR Pediatric Oncology Branch (POB) and NCI Division of Cancer Epidemiology and Genetics (DCEG) Clinical Genetics Branch (CGB) on a variety of projects, including studies of imaging-based surveillance strategies for individuals with Li-Fraumeni syndrome, and treatment and natural history studies for individuals with germline neurofibromatosis type 1 (NF-1) mutations and symptomatic plexiform neurofibromas to evaluate how therapeutic interventions (especially MEK inhibitor versus non-MEK therapy) and other factors relate to the likelihood of developing malignant peripheral nerve sheath tumors

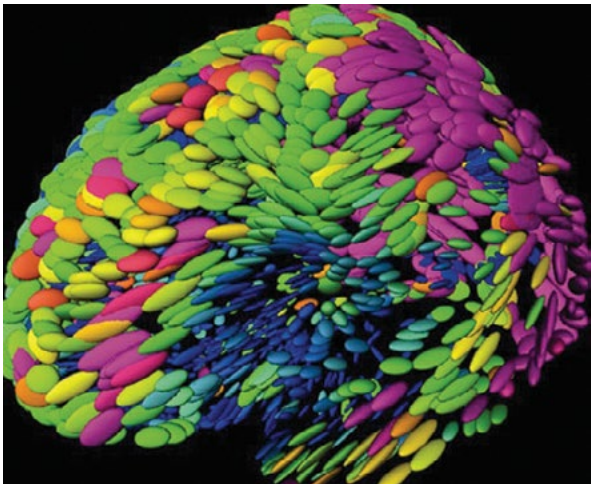
Collaborations and contributions of BRP statisticians extend beyond NCI to activities arising from NCI partnerships with other stakeholders, including external research groups, advocacy and professional organizations, journals, other NIH institutes, and government agencies.

Examples of such activities include:

- Serving as
  - Members of committees convened by professional and scientific societies and charged with the development of clinical practice and molecular testing guidelines, and standards for the design, analysis, reporting, and ethical conduct of biomedical research
  - Study statisticians for national precision medicine trials such as NCI-MATCH and MyeloMATCH, which are conducted through a partnership between NCI and the NCTN
- Providing statistical leadership and analyses for
  - Establishment of the NCI-MATCH and Combo-MATCH outside assay network and credentialing of new laboratory participants
  - Friends of Cancer Research (FOCR) tumor mutation burden (TMB) assay harmonization project
  - FOCR homologous recombination deficiency assay harmonization project
  - Blood Profiling Atlas in Cancer (BloodPAC) and Foundation for the National Institutes of Health ctDNA initiatives
- Participating in
  - Initiatives conducted collaboratively across government agencies, such as NIH, Centers for Disease Control and Prevention, Food and Drug Administration (FDA), and the National Institute of Standards and Technology, to promote best practices for drug, diagnostics, biomarker, and imaging modality development
  - International working groups to standardize or harmonize methods for measurement of laboratory and imaging biomarkers and clinical endpoints
  - Multi-institutional efforts to standardize and harmonize statistical methodology for the development and validation of tests based on laboratory and imaging biomarkers
- Leading statistical and bioinformatic analyses to investigate differences in molecular profiles of tumors from adolescent and young adults compared to those from older adults

BRP statisticians have participated in the Response and Evaluation Criteria in Solid Tumors (RECIST) committee working groups to update RECIST 1.1 to incorporate advances in treatment, such as immunotherapy, targeted agents, and imaging technologies (iRECIST, FDG-PET RECIST, modified RECIST for brain metastasis and RECIST for targeted agents). BRP staff have been the lead statisticians in a multi-year, international working group effort to standardize the measurement of Ki67 proliferation index in breast cancer.

BRP statisticians also maintain active research programs for the development of new biostatistical methodology for clinical trials, preclinical drug development, and development and evaluation of molecular diagnostics and cancer imaging. The wealth of statistical issues that BRP statisticians encounter in their collaborations with other NCI programs informs and motivates these statistical research programs.



BRP statisticians are internationally recognized for their expertise, which covers a broad range of topics encompassing statistical design and analysis of clinical trials, including

- Biomarker-driven and adaptive clinical trials
- Statistical approaches for assessment of surrogate endpoints; methods for development and evaluation of prediction models
- Statistical techniques for analysis of high-dimensional omics data; analysis of analytical and technical performance for laboratory assays and imaging devices

Examples of ongoing statistical methodology research programs are listed in **Table 27**.

| | |
|---|---|
| **Improvement** | Clinical trial designs to evaluate treatments in the presence of delayed treatment effect, as typically found for immunotherapies |
| | Designs for non-inferiority clinical trials and methodology for detection and risk-stratification of prostate cancer |
| **Development** | New approaches to evaluate clinical utility of molecular signatures |
| | Methods to enhance therapy predictive signatures by incorporating biological pathway information |
| | New designs for quantitative assessment of the prognostic and predictive capabilities of biomarker panels |
| | Evidentiary standards for assessment of treatment effect in biomarker-defined subgroups |
| | New methodology and statistical software for evaluation of inter-observer agreement and diagnostic accuracy in human reader-based imaging studies |
| | Methods for causal inference in personalized medicine |
| | New analysis strategies for competing risks survival data |
| **Assessments** | Efficiency, potential bias, and ethics of certain types of adaptive clinical trial designs |
| | The impact that outcome adaptive randomization could have on subsequent biomarker studies using clinical trial specimens, and development of methods to correct for design-induced bias |
| **Evaluations** | Statistical methods to augment randomized clinical trials with historical controls |
| **Modeling** | Efficacy of drug monotherapy, as well as combination therapy synergism and antagonism, observed in preclinical drug screening studies, particularly those utilizing PDXs |

TABLE 27: EXAMPLES OF ONGOING STATISTICAL METHODOLOGY RESEARCH PROGRAMS.

## COMPUTATIONAL AND SYSTEMS BIOLOGY BRANCH (CSBB)

The objective of the CSBB is to provide DCTD and NCI with a tightly integrated group of scientists knowledgeable in cancer biology, drug pharmacology, genomics, computational and systems biology, and bioinformatics, and to train investigators to do research that spans cancer biology and computational biology. The CSBB investigators have backgrounds and expertise in computational biology, cancer biology, structural chemistry, genetics, bioinformatics, pharmacology, biostatistics, and computer science. They also have expertise in the management and analysis of genome-wide tumor characterization data of all types. They use this knowledge to provide biologically and medically meaningful interpretations of genomic alteration data, for using transcriptional pharmacodynamics data to understand resistance mechanisms, and for identifying biomarker candidates. The branch also designs and develops large-scale bioinformatics systems that empower the community of cancer biologists worldwide to effectively use genome-wide tumor characterization data and to perform genomics driven clinical trials.

CSBB members play a crucial role in providing comprehensive computational and bioinformatics support and oversight through their interactions with preclinical and clinical programs within DCTD, including:

- Study of nilotinib/paclitaxel combination mechanism of action in collaboration with DCTD preclinical programs
- Collaboration with the NCI Pharmacodynamic Assay Development and Implementation Section (PADIS) Lab to identify molecular markers of activity and mechanism of action of TdCyd and AzaTdCyd, other than DNMT1 inhibition
- Analyzing responses of rare tumor PDX models to novel drug combinations to identify signals of activity and potential genomic predictors of response
- Examining the association of molecular genomic features with chemosensitivity of cancer cell lines to WDR5 inhibitors and drug combinations for the NCI Experimental Therapeutics (NExT) Program
- Assisting with PDX proteomic data preprocessing and quality evaluation for an NCI Patient-Derived Models Repository (PDMR) project
- Providing database support and system maintenance for sample registration and delinking for an NCI nationwide tumor procurement project

CSBB members are deeply involved in the development of bioinformatics tools and systems that empower cancer biologists and pharmacologists to harness the potential of whole-genome tumor characterization data. These tools facilitate the identification of resistance mechanisms, predictive biomarkers, and innovative combinations to advance cancer research. A few notable examples are:

- TMB Calibration Tool "tmbLab" for phase 2 of the FOCR TMB harmonization project
- Interactive TPWShiny tool for the NCI Transcriptional Pharmacodynamic (TP) Workbench to visualize NCI60 pre-and post-treatment gene expression profiles
- MutSpliceDB database of splice site mutation effects in cancer, now linked to via ClinVar/ClinGen
- Probabilistic classification tool for genetic subtypes of Diffuse Large B Cell Lymphoma with therapeutic implications

CSBB members actively engage in cutting-edge methodology research in the fields of computational biology and data science. Their expertise and dedication have led to notable advancements in the following projects:

- Methods to develop predictive signatures for therapy selection
- Comparative study of quantification measures for the analysis of RNA-seq data from the NCI PDMR
- Review of machine learning-based algorithms for predicting protein stability changes upon mutation
- Evaluation of:
  - Pathway score and development of LASSO-based protein signatures for survival prediction in human cancer cohorts
  - Multiple and single sample Gene Set Enrichment Analysis (GSEA) algorithms using TCGA data
  - Machine learning approaches for prediction of cancer cell line response to drug combinations using features of the tumor cells and drugs
  - Deconvolution methods for tumor purity estimation
  - Data imbalance bias in the prediction of protein stability change upon mutation

CSBB members have contributed significantly to advancing knowledge and discoveries in oncology research through their active collaborations with investigators from the NIH/NCI as well as esteemed national and international oncologists.

Examples of recent collaborations (2020-2023) are listed in **Table 28**.

| | |
|---|---|
| **Analysis** | Tumor genomic features of AYA vs non-AYA patients in the NCI-MATCH trial |
| | FOCR homologous recombination deficiency assay harmonization project, providing statistical and bioinformatic leadership |
| | Longitudinal tumor mutation profiles in archival specimens from patients enrolled on treatment arms of the NCI-MATCH trial |
| | Genomic and response data on cell lines treated with natural products |
| | HDAC and SIRT genes using the NCI TP Workbench data |
| | TP53 isoform junction reads in malignant and normal contexts |
| | Proteomic profiles in patients with glioblastoma (GBM) to identify potential prognostic and predictive candidate biomarkers for treatment response |
| | Association of gene imprinting with drug sensitivity in cancer cell lines |
| | Biological insights from single cell RNA-seq data for neuroblastoma and on EMT using UCS PDX data |
| | Prediction models of gemcitabine response in pancreatic adenocarcinoma PDXs |
| | Effect of ibrutinib with R-CHOP chemotherapy in DLBCL genetic subtypes |
| | Epstein-Barr virus peptide sequences associated with differential IgG antibody response |
| | Olink proteomics and CyTOF immune profiling for NCI COVID-19 in Cancer Patients Study (NCCAPS) |
| **Development** | Recommendations for standards to classify the pathogenicity of somatic variants in cancer (oncogenicity) with the Clinical Genome Resource (ClinGen), Cancer Genomics Consortium (CGC), and Variant Interpretation for Cancer Consortium (VICC) |
| | International collaboration on developing a harmonized meta-knowledgebase of clinical interpretations of somatic genomic variants in cancer |
| | Nanostring based gene expression diagnostic test that can classify an FFPE T-cell lymphoma sample into subtypes |
| | Analysis pipeline to monitor viral integration events around whole genome in pre-infusion CAR T-cell products with NIH/CC/DTM |
| | Diagnostic model for differentiation status of early gastric cancer using microRNA profiles |
| | Understanding whether and how microbial antigens may contribute to immune reactivity against glioblastoma with international collaborators |

TABLE 28: CSBB EXAMPLE COLLABORATIONS.

## FUTURE DIRECTIONS

In upcoming years, BRP plans to focus on the following:

- Development and application of statistical, computational, and systems biology approaches to:
  - Facilitate and accelerate the development and clinical evaluation of effective molecularly targeted therapeutics for people with cancer along with companion diagnostics to guide their use
  - Derive molecular signatures to enhance precision medicine approaches
  - Enhance understanding of oncogenesis through examination of data generated from a variety of comprehensive molecular characterization technologies, including massively parallel sequencing, transcriptomics, methylomics, and proteomics
  - Analyze genomic data to elucidate the early steps of tumor pathogenesis and to identify key molecular targets for cancer prevention, early detection, and therapy
- Development of novel statistical designs and analytical methods to enhance the efficiency of cancer clinical trials and expedite the development of technology of potential importance for biomedical investigation
- Development of bioinformatic tools to empower cancer biologists and pharmacologists using whole genome tumor characterization data in the identification of resistance mechanisms, predictive biomarkers, and innovative combination therapies

PROGRAMS AND INITIATIVES (2020-2023)

# CANCER DIAGNOSIS PROGRAM

# OVERVIEW

Established as a DCTD program in 1996, the Cancer Diagnosis Program (CDP) strives to improve outcomes for people with cancer by effectively moving molecular diagnostics from research into clinical practice. CDP's primary mission is to stimulate, coordinate, and fund research for the development of diagnostic and therapeutic biomarkers, novel technologies and biospecimen resources, and biospecimen science.

CDP's activities fall into three major categories:

1. Developing, validating, and evaluating assays for clinical decision making and precision medicine clinical trials.
2. Discovering biomarkers and developing enabling technologies for their detection and measurement.
3. Providing the resources, particularly human specimens and other infrastructure, to ensure that discovery and development can proceed.

CDP collaborates with programs in the NCI Office of the Director, the NIH Common Fund, the All of Us Research Program, the National Institute of Biomedical Imaging and Bioengineering, the National Center for Advancing Translational Sciences (NCATS), and many DCTD programs including but not limited to the Cancer Therapy Evaluation Program (CTEP), the Cancer Imaging Program (CIP), and the Biometric Research Program (BRP).

A significant challenge is the large amount of information that can now be generated by various omics technologies. CDP works to validate such technologies for clinical use and collaborates to solve the challenging bioinformatics problems associated with these technologies and their use in patients with cancer.

Part of CDP's mission is to enable and promote precision cancer medicine by improving the diagnostics for, and thereby the treatment of, cancer. CDP accomplishes this by effectively moving new scientific knowledge about biomarkers into clinical practice. This national program stimulates, coordinates, and funds resources and research on diagnostics and improved technologies to better characterize cancers, to guide the choice of treatment, and to define new technologies that best predict response to treatment. The overarching goals of CDP are to:

- Support development of the most effective in vitro diagnostic tools to ensure precise diagnosis and optimize treatment decision making
- Encourage research on the clinical utility of biomarkers to guide clinical practice
- Facilitate translational research by supporting the collection of research biospecimens and sharing of previously collected biospecimens for research
- Develop best practices and tools to improve the quality of biospecimen collection

CDP has been instrumental in the implementation of several of NCI's precision medicine trials: NCI-MATCH (Molecular Analysis for Therapy Choice), NCI-COG Pediatric MATCH, and ComboMATCH, by creating a network of laboratories that identifies potentially eligible cases for the NCI-MATCH and ComboMATCH trials using centrally vetted next-generation DNA sequencing (NGS) assays being conducted in the context of clinical care. The Designated Laboratory Network consists of laboratories that are evaluated and selected by a precision medicine leadership committee for quality standards, and all laboratories operate under the Clinical Laboratory Improvement Amendments (CLIA) standards to molecularly profile tumors in the clinical setting.

CDP collaborates closely with CTEP to promote the effective integration of biomarker studies and well validated biomarker assays into CTEP-sponsored clinical trials and to implement recommendations of the Clinical Trials Working Group (CTWG), especially through the NCI Biomarker, Imaging, and Quality of Life Studies Funding Program and the DCTD Biomarker Review Committee. These reviews are focused on the development of a fit-for-purpose reliable assay for the intended clinical trial. CDP strongly encourages clinical investigators to collaborate closely with laboratorians, molecular and clinical pathologists, statisticians, and others to bring biomarker guided clinical trials to reality. CDP also manages the National Clinical Laboratory Network (NCLN) that serves the research community by providing access to validated assays to support early-stage clinical trials and teaches other groups how to perform these assays in a rigorous fashion. It also supports the Molecular Diagnostic Network (MDNet) that provides assay support to DCTD's precision medicine trials.

CDP supports earlier stages of biomarker discovery research and clinical assay development through an actively managed portfolio of investigator-initiated research project grants. Nearly half of its grant portfolio has been developed via targeted initiatives designed to provide grant mechanisms, such as exploratory grants, that sustain each part of the assay development process.

# LYNDSAY N. HARRIS
## ASSOCIATE DIRECTOR

Lyndsay Harris, MD, is Associate Director of CDP. Prior to coming to NCI, she was Professor of Medicine at Case Western University and Director of the University Hospital's Seidman Breast Cancer Program. She was on faculty at Yale University where she led the Breast Cancer Program, and Dana-Farber Cancer Center where she directed the Tissue, Pathology and Clinical Data Core for the Dana-Farber/Harvard Cancer Center SPORE in Breast Cancer. Her research in the last 30 years has focused on the development of biomarkers and targeted therapeutics to improve outcome for people with breast cancer. Her laboratory focused on the use of genomic technologies to develop breast cancer signatures for optimizing therapy selection. Her experience as a clinician, clinical-trialist and translational researcher brings an important skill set to the program, publishing more than 170 scientific research articles, and contributing to the understanding of molecular subtypes of breast cancer and the implication of gene, gene expression, and protein expression profiles on treatment response and resistance. She has held a variety of national and international leadership positions related to cancer clinical trials and translational studies, including co-leader of American Society of Clinical Oncology (ASCO) Breast Cancer Biomarker Guidelines, co-leader of Translational Studies for Breast Committee in Cancer and Leukemia B (CALGB), Breast Committee Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN), Leader of Audit committee for Pan American Cancer Trials Network and Member of the (Neo) ALTTO International Adjuvant Breast Cancer Clinical Trial Steering committee. As the Associate Director, Dr. Harris directs her team in the development of robust, prognostic, and therapeutic biomarkers through the study of biospecimen science, innovation and technology, pathology evaluation, and clinical application of biomarkers.

CDP is actively engaged in the ethical, legal, and social issues (ELSI) of clinical molecular profiling in tumors and how these new technologies can be expected to affect a person's perception of their treatment options, or the impact on families/relatives of having molecular information about oneself. CDP informs and participates in discussions of ethical issues surrounding biospecimen procurement, storage, and use, as well as ELSI surrounding the generation and public availability of omics data. CDP sponsors community and patient engagement research related to biobanking and operates biospecimen collection programs that return clinical results to patients and their providers to help guide treatment decisions.

CDP-supported research extends to the development of new technologies: the instruments and analytical methods that provide the technical platforms for innovative diagnostics. CDP scientists keep abreast of emerging technologies and their intersection with cancer molecular science. These development efforts encompass:

- Genomics and next-generation sequencing (NGS)
- RNA and microRNA expression and sequencing
- DNA methylation and epigenetic regulation
- Proteomics and immunoassays
- Metabolomics and glycomics
- Circulating tumor cells, nucleic acids, and other analytes
- Assays that demonstrate target engagement by a cancer drug
- Collaboration with experts and programs in functional imaging
- New engineering techniques (e.g., molecular machines, nanotechnology)
- New techniques and access to informatics technology
- Point of care devices for molecular diagnostics
- Diagnostics that are appropriate and effective for use in low- and middle-income countries

Biospecimens of sufficient quality are essential to the biomarker research and assay development that leads to diagnostic tests. CDP is a critical component of NCI's efforts to provide cancer biospecimens for research and to develop the biospecimen resources of the future. CDP provides support for three major sources of biospecimens:

- The Cooperative Human Tissue Network (CHTN), the National Clinical Trials Network (NCTN) Biospecimen Banks, and the Early-Phase and Experimental Clinical Trials Bank (EET) each year provide thousands of biospecimens with appropriate pathologic and clinical data to researchers across the country.
- Specialized biospecimen collections for research include the GTEx Biobank, the Biospecimen Preanalytical Variables (BPV) Biobank, and the Cancer Moonshot℠ Biobank.
- CDP's Specimen Resource Locator (SRL) enables researchers to quickly and efficiently access existing biospecimen resources housed in pathology archives within and outside NCI or NIH-funded resources.

CDP also generates standards for biorepository infrastructure through publication of the NCI Best Practices for Biospecimen Resources. CDP has developed resources to assist patients with cancer and members of the public to understand how tissue specimens are used in research and the importance of tissue donation. As part of efforts to improve research reproducibility, CDP conducts and supports research on the effects of biospecimen pre-analytical variation on molecular testing results. A primary focus is the development of evidence-based procedures for biospecimen collection and utilization, to support assessment of biospecimens for fit-for-purpose use in assays that will be intended for prognosis and prediction.

## STRUCTURE AND FUNCTION

CDP's primary mission is to stimulate, coordinate, and fund research for the development of diagnostic and therapeutic biomarkers, novel technologies and biospecimen resources, and biospecimen science. None of this work would be possible without the strong contributions of each CDP branch:

- Biorepositories and Biospecimen Research Branch (BBRB)
- Diagnostic Biomarkers and Technology Branch (DBTB)
- Diagnostics Evaluation Branch (DEB)
- Pathology Investigations Research Branch (PIRB)

### BIOREPOSITORIES AND BIOSPECIMEN RESEARCH BRANCH (BBRB)

Researchers' access to biospecimens of known quality, together with associated clinical data, is essential for the progress of all cancer research and critical for molecular diagnostics. Biospecimen science, best practices, and biobanking are the basis of the work of BBRB.

BBRB provides leadership, tools, resources, and policies in biobanking for the global biomedical research community, to enable translational research and precision medicine. BBRB's goal is to increase the reproducibility of cancer research involving the use of biospecimens. BBRB develops biorepository standards and conducts and sponsors biospecimen science studies that form the basis of evidence-based practices to guide clinical cancer research and other biomedical studies (**Figure 38**). BBRB also develops and coordinates high quality biospecimen and associated data collection programs for major NCI and NIH research initiatives including the Cancer Moonshot℠.

BBRB activities include:

- Development and dissemination of the NCI Best Practices for Biospecimen Resources, a foundational document for biobanking that is used internationally. The Best Practices represent operational standards for all aspects of biobanking, including quality management, governance, legacy planning, and data management, along with ethical, legal, and policy best practices.
- Development of the Biospecimen Evidence-Based Practices (BEBPs), a series of literature-annotated procedural documents that are intended to optimize investigators' biospecimen procedures to support high quality molecular analysis.
- Ongoing development and support of the Biospecimen Research Database, a curated resource for biospecimen-related literature and Standard Operating Procedures (SOPs).
- Biospecimen science research to better understand and mitigate the effects of different collection, processing, and storage procedures on the outcome of molecular analysis conducted for basic research and clinical diagnostics, including the U01 program, Integrating Biospecimen Science Approaches into Clinical Assay Development.
- Programs to better understand and improve public engagement in biobanking, including development and dissemination of patient brochures, sponsored research in patient engagement and the ethical, legal, and social issues (ELSI) of biobanking, and incorporation of evolving ELSI approaches and policies into Best Practices documents.
- Development and operational management of robust biospecimen collection infrastructures to facilitate major team science initiatives in genomics and biospecimen science, including GTEx, BPV, and the Cancer Moonshot℠ Biobank.
- International collaborations to coordinate biospecimen science with standards initiatives and to harmonize biobanking policies and procedures.
- Participation in and contribution to NCI research programs including Informatics Technology for Cancer Research, Innovative Molecular Analysis Technologies (IMAT), Affordable Cancer Technologies, Exploratory/Developmental Bioengineering Research Grants (EBRG) (R21), and Academic-Industrial Partnerships for Translation of Technologies for Diagnosis and Treatment (R01).

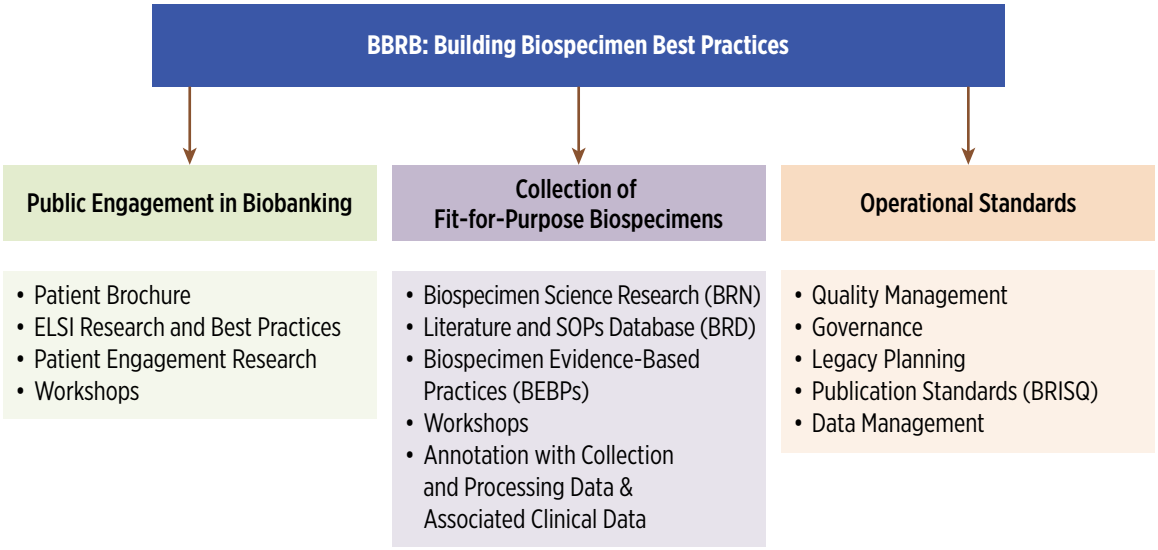



FIGURE 38: BBRB ACTIVITIES DESIGNED TO IMPROVE THE QUALITY OF BIOSPECIMENS AND BIOSPECIMEN RESEARCH.

## DIAGNOSTIC BIOMARKERS AND TECHNOLOGY BRANCH (DBTB)

DBTB stimulates and supports research to develop new biomarkers, diagnostic strategies, models, innovative technologies, improved devices, and molecular assay platforms that will lead to better research tools and assist in clinical decision-making. This branch maintains information on novel technologies that may prove useful for precision diagnostics. Significant input from DBTB staff into NCI's Innovative Molecular Analysis Technologies (IMAT) program, the Small Business Innovation Research (SBIR) program, Bioengineering Research Grants, and the Academic Industrial Partnership Initiative allow CDP and NCI to support important research in the development and application of new technologies to improve cancer diagnostics. Other specific activities of the branch include:

- Stimulating research that applies new knowledge from cancer biology and tumor-host interactions to facilitate cancer diagnostics research
- Supporting research focused on the development of innovative technologies and devices to use for cancer diagnosis, prognosis, and prediction
- Supporting research to apply results from biomarker research and technology development into novel platforms for cancer diagnosis, including diagnostics suitable for low- and middle-income countries and other point-of-care diagnostics
- Stimulating research focused on the development and implementation of algorithms for analysis of high-dimensional data applied to cancer diagnostics, prognosis, and prediction
- Stimulating novel interdisciplinary technological research for use in precision cancer medicine, bridge the gap between innovative ideas and technologies applicable to cancer diagnosis and treatment, and their practical clinical application
- Facilitating the movement of novel technologies toward product development

These efforts are critical to further the development and deployment of novel technologies and methodologies to the practice of biomarker research and clinical translation. DBTB also garners input from industry, academia, and government to further the branch mission. For example, DBTB organized a workshop in 2017 to understand and promote translation of circulating tumor DNA (ctDNA) assays to clinical research with potential to advance their use in clinical practice. In 2023, DBTB organized a follow-up ctDNA workshop to examine the state of the field and elucidate ctDNA's potential to affect decision-making in the treatment of patients with solid tumors.

## DIAGNOSTICS EVALUATION BRANCH (DEB)

DEB focuses on the development of predictive and prognostic diagnostic assays from the translational research stage through assessment of their clinical utility (**Figure 39**). DEB collaborates with CTEP to promote the effective integration of biomarker studies into DCTD's cancer therapy trials as well as to develop appropriate clinical trials that can be used for patients whose tumors have or will be molecularly profiled. Barriers impeding progress in the field of biomarker and assay development include the absence of a well-defined pathway for the development and evaluation of clinical biomarkers, and a lack of standards that assays must meet before being incorporated into trials or clinical practice.

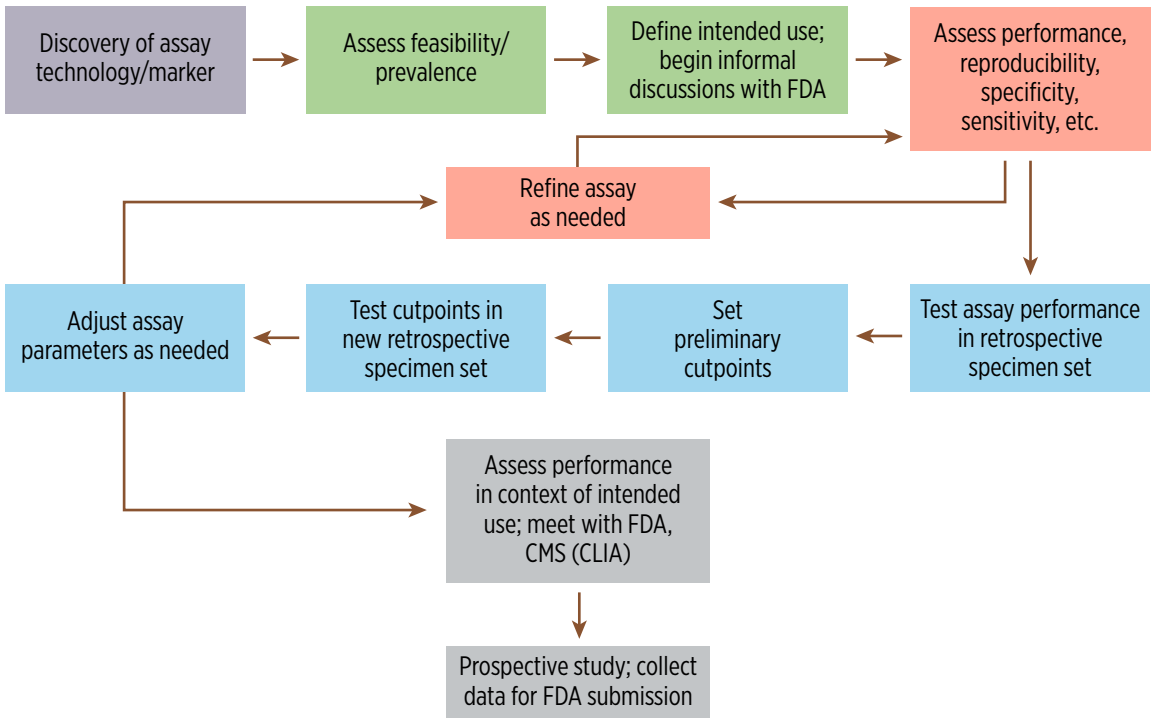



FIGURE 39: THE MARKER DEVELOPMENT PROCESS.

DEB also keeps abreast of molecular diagnostics and precision oncology needs in the cancer community and supports collaborative research involving the expertise of clinicians and laboratorians from different universities to develop appropriate molecular assays that can further guide precision medicine.

DEB activities include:

- Stimulating research to use *in vitro* diagnostics as prognostic markers to improve tumor classification, and predictive markers to improve response to therapy
- Collaborating with other researchers and government agencies to validate *in vitro* diagnostics analytically and clinically, establishing their clinical utility
- Stimulating interdisciplinary research to develop novel assays or novel uses of existing assays to inform about the behavior or the response of cancers to treatment regimens

- Interacting with other agencies such as the Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS) to understand problems in the development of promising assays, particularly those that can be used to identify people for whom certain treatments could be beneficial

These efforts are critical to facilitating the development of high-quality biomarker assays applied in the clinical setting to ensure optimal care for patients with cancer.

## THE PATHOLOGY INVESTIGATION AND RESOURCES BRANCH (PIRB)

PIRB supports the collection and distribution of human biospecimens, pathology investigation to facilitate the discovery of novel molecular features of cancers, and translational cancer research that requires patient biospecimens.

Biomarker discovery research, assay development, and evaluation of the clinical utility of assays depend on the availability of human tumor (or associated) specimens for which there are also associated demographic and clinical data. PIRB has a long history of creative approaches to addressing these needs, including managing the CHTN, NCTN Banks, and NCI Early Phase and Experimental Clinical Trials Biospecimen Bank (EET Bank). In the past, PIRB supported the Cooperative Breast Cancer Tissue Resource, Cooperative Prostate Cancer Tissue Resource and ETCTN biobanking infrastructure.

PIRB activities include the following:

- Development and support of human biospecimen resources listed above that procure, store, and distribute a variety of clinical biospecimens for research
- Assistance for investigators in locating and acquiring human cancer specimens needed for their research
- Development and administration of the SRL, a searchable website that maintains information about existing biospecimen resources
- Support for the NCI Tissue Expediter, an individual who assists investigators in locating appropriate resources as well as identifying potential collaborations
- Provision of pathology expertise on human tissue specimen resources, sample preparation for researchers, and pathology assessment and QA/QC for CDP/DCTD/NCI scientific initiatives
- Collaboration with investigators to optimize biospecimen quality, identify the best molecular QA/QC methods, and overcome challenges in molecular analysis of human samples
- Participation in NCI's IMAT program, particularly in the biospecimen research arm of the initiative
- Support and development of informatics tools to improve access to human biospecimens and associated clinical data found in NCI-funded biospecimen resources
- Contribution to the Cancer Moonshot℠ that provides 'legacy' specimens to investigators that compete successfully for the Moonshot grant award
- Development of optimal biomarker collection processes for the Cancer Immune Monitoring Analysis Centers and Cancer Immune Data Commons (CIMAC-CIDC) clinical trials

These contributions are essential to NCI's scientific mission to support the research community by providing access to cancer samples that are optimally collected, clinically annotated, and easily accessible.

## CDP GRANTS OVERVIEW

The CDP research portfolio included 307 funded grants during fiscal year 2023. The grant award mechanisms used by CDP and their distribution in terms of research support in 2023 are shown in **Figure 40** and **Figure 41**.

The predominant mechanism is the individual research project grant (R01), followed by cooperative agreements that support both targeted research and research resources such as tissue banks.

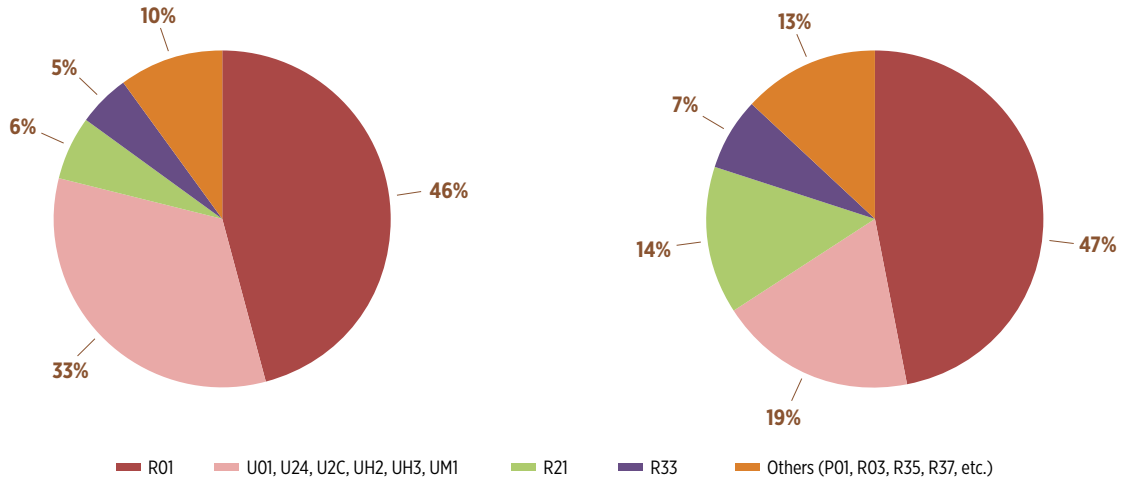



FIGURE 40: DISTRIBUTION OF CDP 2023 GRANT FUNDS (LEFT) AND NUMBERS OF GRANTS (RIGHT) BY MECHANISM.

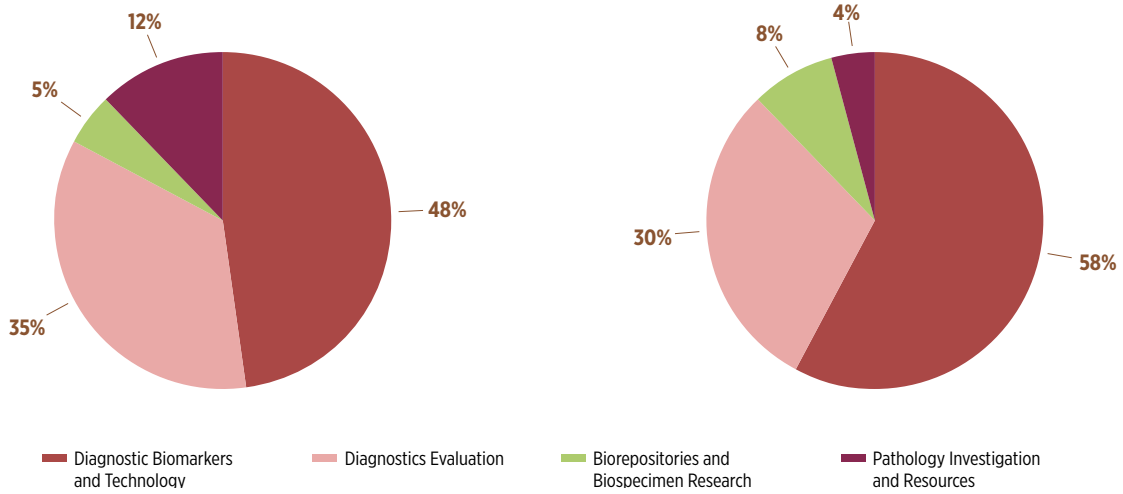
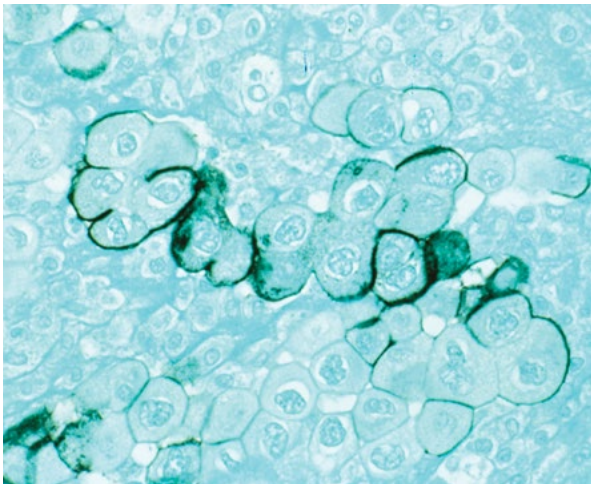



FIGURE 41: DISTRIBUTION OF CDP 2023 GRANT FUNDS (LEFT) AND NUMBERS OF GRANTS (RIGHT) BY RESEARCH AREA.





# ASSISTANCE TO THE CANCER RESEARCH COMMUNITY

## MOLECULAR CHARACTERIZATION LABORATORY (MOCHA)

CDP oversees the activities of MoCha at the Frederick National Laboratory for Cancer Research (FNLCR) in its instrumental support to many DCTD initiatives. MoCha provides genomic characterization of biospecimens obtained from patients with cancer in DCTD-supported clinical trials, for example, the NCI-MATCH study, NCI-COG Pediatric MATCH, ComboMATCH, MyeloMATCH, the Cancer Moonshot Biobank, and ETCTN trials through the National Clinical Laboratory Network (NCLN), as well as the Patient-Derived Models Repository (PDMR). In addition, MoCha has provided invaluable support and advice to the CIMAC-CIDC investigators by working with the team on assay harmonization, an area with which it has extensive experience. Furthermore, MoCha is closely involved with the development of the Molecular Diagnostics Network that supports three large NCI-supported precision medicine clinical trials.

## THE TAILORX TRIAL

TAILORx, a trial concept originally developed by CDP, tested whether a set of genes whose expression has been shown to be associated with the risk of recurrence in women with node-negative, hormone receptor-positive breast cancer, can be used to assign women to the most appropriate and effective treatment. The signature tested is the 21-gene Oncotype DX™ panel, developed by Genomic Health, Inc. in collaboration with the National Surgical Adjuvant Breast and Bowel Project, an NCI cooperative group. U.S. Postal Service sales of breast cancer stamps played a critical role in making possible a groundbreaking treatment trial by providing a portion of the funding for TAILORx. Without this support, the trial would not have been possible.

TAILORx has been carried out as a collaboration between CDP, CTEP, and all NCTN Groups that perform breast cancer studies. The trial was launched in the spring of 2006 and completed its testing and accrual of more than 11,000 patients in the summer of 2010. The first major result was published in the *New England Journal of Medicine* in 2015, which indicated that women meeting the trial's entry criteria whose tumors had a low-risk score on the 21-gene panel could safely be treated with hormonal therapy alone.

Analysis of the randomized arm of the trial was reported in 2018 and clearly showed that chemotherapy was not beneficial for most women in the intermediate risk group although a subgroup analysis suggested benefit for women under 50.[20] Together with the results reported in 2015, the outcomes in the two arms of TAILORx provided definitive evidence that as many as 70% of women with early-stage breast cancer can safely avoid treatment with, and therefore avoid the side effects of, chemotherapy. In 2023, a meta-analysis including longer follow-up reported that the score is prognostic for long-term risk of distant recurrence and overall survival.[21] This trial has had a major impact on the treatment of women with breast cancer.

## BIOMARKER EVALUATION IN NCI CANCER THERAPY TRIALS

CDP staff review biomarker studies proposed for inclusion in concepts and protocols for CTEP trials, considering both the analytic validity and the clinical utility of novel assays, to provide recommendations at all stages of trial design. This effort improves the quality of clinical studies and serves CDP's planning processes by enabling staff to identify obstacles to progress in the field. Clinical trials that include investigational biomarker assays, particularly where assays are integral to the trials (i.e., necessary for the trial to be performed, such as to choose patients based on a molecular profile or to stratify patients by a molecular characteristic) require time and effort for adequate analytical and/or clinical validation of the assays. Considering that these trials pose special challenges to the timely activation of trials, CDP staff engage with CTEP and the investigators of its clinical trials consortia to improve both the efficiency and the scientific output of DCTD trials. CDP and CTEP collaborate to foster research on biomarkers of response to new and novel immune therapies, other targeted therapies, and combinations of different therapies. CDP staff also serve as reviewers on the NCTN Central Correlative Science Committee for applications to use specimens from the NCTN biospecimen repositories. CDP provides critical biomarker expertise at clinical trials planning meetings and serves on intergroup task forces.

## EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC)-NCI CANCER MOLECULAR MARKERS COLLABORATIONS

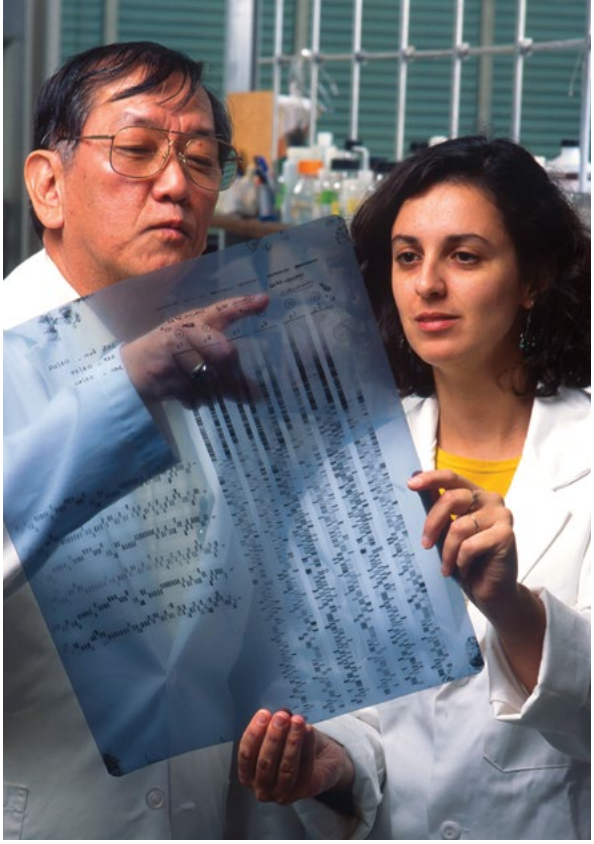
CDP has led an NCI collaboration with the EORTC to convene a series of meetings on molecular diagnostics. Partners have included the American Society of Clinical Oncology (ASCO), the American Association for Cancer Research (AACR), and regulatory agencies in each continent (European Medicines Agency or the U.S. FDA). These meetings occur on a biannual basis in Europe and are usually held in conjunction with the AACR/ASCO/NCI Molecular Targets meeting that year.

## CLINICAL ASSAY STANDARDIZATION

Members of CDP are acknowledged experts in the fields of clinical cancer research, engineering, biology of cancer, and assay methodology as well as anatomic, surgical, and molecular pathology. As members of major professional societies, they contribute to the establishment of nationwide practice guidelines for cancer pathology and tumor staging. CDP has initiated proactive efforts to improve the standardization and reliability of newer assays entering clinical practice. Recent projects led by the MoCha Lab focused on how to evaluate the clinical utility of predictive and prognostic assays and to ensure that assays being evaluated in clinical trials or used in clinical practice can be performed with sufficient reproducibility and minimal laboratory-to-laboratory variation. This is critical for dissemination of clinical laboratory tests into community practice.

As part of a consortium, the MoCha Lab contributed to the analysis and interpretation of data in the Tumor Mutational Burden (TMB) Harmonization Project organized by the Friends of Cancer Research. TMB is a measure of the number of somatic mutations in a tumor and was approved as a predictive biomarker for the immune checkpoint inhibitor pembrolizumab. Phase 1 of the TMB Harmonization project focused on identifying sources of variability between TMB estimates by comparing estimates derived from panels of X

[20] Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. *N Engl J Med*. 2018 Jul 12;379(2):111-121.
[21] Sparano JA, Crager M, Gray RJ, et al. Clinical and Genomic Risk for Late Breast Cancer Recurrence and Survival. *NEJM Evid*. 2024 Aug;3(8):EVIDoa2300267





to Y genes to calculations based on whole exome sequencing (WES). This analysis led to the development and publication of guidelines for TMB reporting and the conditions of analytical validation (Merino, 2020). A second publication reported results comparing TMB analysis of 10 control and 29 clinical tumor samples performed in 16 clinical laboratories to a WES "gold standard" performed in the MoCha Lab (Vega, 2021).

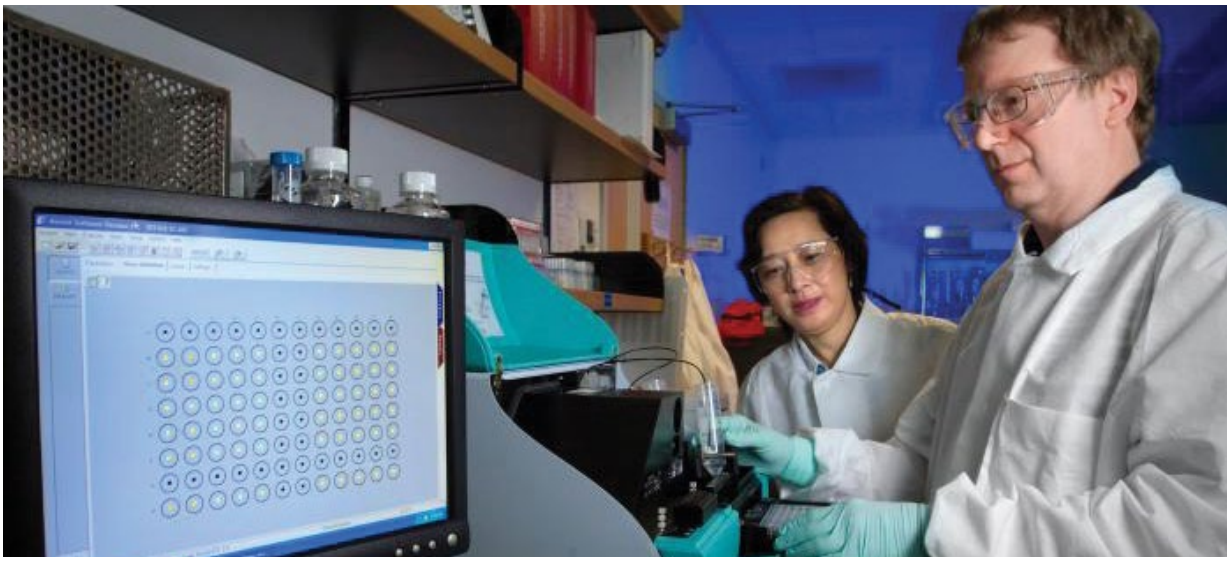
The MoCha Lab has been instrumental in leading phase 1 of the ctDNA Quality Control Materials (QCM) project sponsored by the Foundation for NIH, which is an evaluation of the performance of the QCM in four core laboratories. The goal of the QCM project is to enhance confidence in ctDNA biomarker assay results, enabling better clinical applications, informed decisions on appropriate therapy, and improved regulatory evaluation, thereby facilitating the production of QCM that could be candidates for FDA clearance. The results and relevance of phase 1, supporting the utility of the QCM in testing ctDNA assay analytical performance, have been published (Williams, 2021).

The MoCha Lab also participates in the International Liquid Biopsy Standardization Alliance (ISLA) Collaborative Community (Connors, 2020), a collection of organizations that exchange information to further their common goal of harmonization in the broader adoption of liquid biopsy and use of shared reference standards in oncology.

## ASSAY VALIDATION OF HIGH-QUALITY MARKERS FOR CLINICAL STUDIES IN CANCER

Since 2015, CDP's Diagnostics Evaluation Branch has led DCTD's participation in this NCI program. Sponsored jointly by DCTD, the Division of Cancer Prevention, and the Division of Cancer Control and Population Sciences, this program has issued a series of Notices of Funding Opportunity to support the analytic and clinical validation of laboratory biomarkers for use in cancer diagnosis, screening, and epidemiology. Most of the grants have used the phased (UH2/UH3) award mechanism to provide support for analytic validation of an assay followed by expedited transition to a clinical validation study after the benchmarks for adequate analytic performance have been achieved. These awards have supported development of assays for a range of analytic platforms and clinical applications:

- Targeted sequencing assays to detect kinase gene fusions and microsatellite instability
- Detection of a prognostic mRNA immune signature in melanoma
- Molecular subtyping of colorectal cancer
- Multi-gene expression assay for activation of the immune system in breast cancer
- Urine-based assay to monitor for the recurrence of bladder cancer
- Detection of deficiency in DNA repair to identify pancreatic cancers sensitive to DNA-damaging drugs
- APC and TP53 proteins as biomarkers of cetuximab response in colorectal cancer



## BIOSPECIMEN ACCESS FOR THE CANCER RESEARCH COMMUNITY

CDP funds several biospecimen banks, each with a different focus.

### Cooperative Human Tissue Network (CHTN)

The CHTN provides access to human tissues for basic and translational research scientists with the goal of accelerating discoveries in cancer diagnosis and treatment. CHTN offers prospective procurement of malignant, benign, and uninvolved (normal adjacent) tissues upon request by an investigator. CHTN routinely procures biofluids and formalin-fixed, paraffin-embedded tissue from all organ sites, but fresh and fresh-frozen tissue can also be obtained if needed, a unique strength of the CHTN resource. Network academic institutions, organized into six divisions, coordinate the collection and distribution of tissues across the United States and Canada. Trained personnel at member institutions conduct the retrieval, preservation, and delivery of specimens obtained from surgical resections and autopsies according to protocols defined by the investigator. Board-certified anatomic pathologists conduct quality assurance review on all biospecimens. From 2020-2023 the CHTN has provided nearly 140,000 specimens to more than 1,300 investigators. More than 200 peer-reviewed scientific publications (~50% with Impact Factor > 5) and 39 patents have resulted from the use of CHTN resources (2020-2023), reflecting relatively easy access to tissue specimens by many investigators. CHTN also produces and distributes tissue containing multiple tissue types collected from a series of patients, as well as several disease-specific configurations.

The CHTN is accessible to any academic or industry investigator via submission of a project summary for which the biospecimens are requested and a signed tissue and data use agreements. Priority is given to requests from investigators with peer-reviewed, funded research projects and to new investigators at academic or nonprofit research institutions. As such, about 80% of the investigators using CHTN samples are academic researchers, and most use the samples for their R01 grant funded projects.

### NCI National Clinical Trials Network Biospecimen Banks

The NCTN Biospecimen Banks, formerly the Cooperative Oncology Group Banks, collect and store high-quality human specimens from patients enrolled in NCI-funded phase 3 and large phase 2 clinical treatment trials and other NCTN trials. These banked specimens are well-annotated with clinical information and are most useful for clinical correlative studies or clinical assay validation studies on uniformly treated populations of patients with cancer. PIRB has supported these banks since 2005 through U24 cooperative agreement grant awards and

ensured that the banks implement best practices such as common data structures and standardized collection and storage practices. The NCTN Group Banking Steering Committee was established with representatives from all the NCTN banks/groups and NCI to lead the implementation of SOP harmonization and a process for access to specimens.

NCTN biospecimens are initially available only to the NCTN investigators conducting the trials from which they are collected for research use as part of the approved NCTN clinical trial-specific protocol. Investigators in the research community, not only members of the NCTN Groups, can submit requests for NCTN legacy biospecimens and data from completed NCTN clinical trials either via NCTN Navigator or direct communication with the NCTN Group that conducted the trial. In both instances, investigators receive an assessment of whether there is sufficient material available to meet their request. NCTN biospecimens are available to investigators from the cancer research community based on a review and approval by the NCTN Core Correlative Sciences Committee.

## Early Phase and Experimental Trials (EET) Biobank

The NCI funds a clinical trials infrastructure to facilitate the early stages of development and evaluation of anti-cancer therapeutic agents. The EET Biobank was established in 2020 to promote the collection of standardized biospecimens by procuring, processing, banking, and distributing high-quality human biospecimens from patients with cancer who participate in ETCTN phase 0, 1, and 2 trials. These biospecimens contain associated information from surgical, pathological, and radiological reports, as well as comprehensive clinical data, including detailed drug information, treatment histories/outcomes, and cancer recurrence data making them a highly valued resource. The EET Biobank works closely with study teams and investigators to ensure that biospecimens are handled appropriately for planned and future research. In these efforts, the EET Biobank also supports the processing, banking, and distribution of biospecimens to the CIMACs. Similar to the NCTN Banks, biospecimens are first distributed to investigators for planned research designed to meet the objectives included in the clinical trial, after which they are made broadly available through a review process conducted by CTEP. In 2020-2023, 16,181 biospecimen kits were distributed (NCI COVID-19 in Cancer Patients Study (NCCAPS): 10,778); 179,237 specimens were received from 3,996 patients from 94 studies; 20,101 specimens were distributed (NCCAPS): 13,885; NCLN: 542; CIMAC: 4,173.

## The Cancer Moonshot Biobank

The Cancer Moonshot℠ Biobank aims to accelerate and advance our understanding of cancer and better understand how to intervene in cancer initiation and progression. The Biobank asks patients with cancer across the United States, who are receiving standard of care cancer treatment, to donate biospecimens and associated health information during cancer treatment. The biospecimens and associated deidentified health information will be made available to qualified cancer scientists to help those researchers learn how cancer grows and changes in people, and to find new cancer treatments. To ensure that patients from all population groups can potentially benefit from the research, people from diverse racial, cultural, ethnic, and socioeconomic groups are asked to participate in the Biobank.

The Moonshot Biobank works in collaboration with community hospitals and other medical institutions who are part of the NCI Community Oncology Research Program (NCORP) and NCTN to engage eligible patients and collect biospecimens along with clinical data. Samples are stored at a central biorepository that performs pathology quality control and distributes biospecimens. NCI's MoCha performs cancer biomarker assays on tumor tissue and returns results to research participants and their healthcare providers. The biomarker test results may provide more information for cancer treatment decisions and will help researchers better understand how genetic changes within a tumor cell can affect cancer progression and treatment. Participant and provider engagement strategies include an External Scientific Panel that provides input to the program, a secure website in English and Spanish for the return of results and other information to participants and providers, electronic consent available in English and Spanish, and funding of local, investigator-initiated engagement projects.

### NIH Genotype Tissue Expression (GTEx) Program

BBRB coordinated tissue acquisition for the GTEx Program, which has studied human gene expression and regulation in multiple normal tissues with a focus on the expression of quantitative trait loci and their potential disease associations. BBRB staff worked in partnership with the FNLCR to develop the infrastructure capable of delivering large quantities of high-quality annotated tissues from postmortem donors for genomic analysis. The same infrastructure was customized for collection of tumor tissues for BBRB's Biospecimen Preanalytical Variables (BPV) program and is now being used for biospecimen collections to support the NCI Clinical Proteomic Tumor Analysis Consortium (CPTAC).

Biospecimen collections for GTEx were completed in late 2015, with biospecimens from almost 1,000 postmortem donors. The program went on to plan and implement a legacy plan for the remaining biospecimens and all associated biospecimen and clinical data. Similar to the NCTN and EET Biobanks, residual biospecimens are now available to researchers outside the GTEx program upon request via the GTEx Portal. An extensive set of GTEx public resources has been developed and released to the research community, including a full set of the SOPs guiding the project and an online library of histological images that correspond to the clinical, DNA and RNA sequencing, and expression quantitative trait loci data now available at the database of Genotypes and Phenotypes (dbGaP). The SOPs provide transparency about the details of this biospecimen collection, which has served as the basis for heavily utilized genomic data and could enable high quality postmortem biospecimen collection by others in the research community. The GTEx dataset has proven to be one of the most heavily used genomic resources to date, with thousands of scientific studies utilizing the genomic data.

### The Specimen Resource Locator (SRL)

Finding appropriate tissue resources for translational research can be very difficult for an investigator. The SRL database was designed to assist with this process. This publicly accessible database searches across non-commercial, either NCI- or non-NCI-funded, biospecimen banks and sample procurement services, thereby providing investigators information on thousands of available biospecimens of various tumor, organ, and preservation methods.

In the event a researcher is unsuccessful in finding the appropriate specimen resource through the SRL, they may contact the NCI Tissue Expediter and speak directly with a scientist who can further assist them. The NCI Tissue Expediter can also assist researchers to identify potential collaborators.

## BIOSPECIMEN SCIENCE RESEARCH

Differences in biospecimen pre-analytic procedures (e.g., procurement, preservation, processing, shipping, storage) can influence the results of molecular analysis and impact the reproducibility of biomarker findings. BBRB funds and collaborates on biospecimen science studies to assess the effects of pre-analytical factors on the outcome of genomic and proteomic studies conducted for clinical diagnosis and cancer research purposes. By making the results of such research available to the scientific community and incorporating the data into biospecimen evidence-based, BBRB aims to significantly improve the quality and reproducibility of NCI-funded research.

Current NCI biospecimen science activities (BRN) include the 2022 re-issuance of the funding announcement for Integrating Biospecimen Science Approaches into Clinical Assay Development, and the Biospecimen Research Database (BRD) for biospecimen science literature and SOPs. Results from these research activities have been published and provided significant data to support optimal procedures for controlling key pre-analytical factors when possible and understanding their effects.

## TOOLS AND GUIDANCE FOR BIOBANKING

### NCI Best Practices for Biospecimen Resources

After an extensive due diligence process, BBRB published the First-Generation Guidelines for NCI-Supported Biorepositories in the Federal Register (71FR 25184), where public comments were requested. The Guidelines were subsequently revised based on public comment and input from content experts and issued in 2007 as the NCI Best Practices for Biospecimen Resources.

The NCI Best Practices do not comprise detailed laboratory procedures, but rather represent salient guiding principles that define state-of-the-science biospecimen resource practices, promote biospecimen and data quality, and support adherence to ethical and legal requirements. The recommendations are intended to be adapted, as appropriate, based on the mission and scientific needs of individual biospecimen resources. Although adoption of the NCI Best Practices is voluntary, the outlined principles support the goal of optimizing biospecimens for cancer research. Notably, the College of American Pathologists has developed a Biorepository Accreditation Program based on the NCI Best Practices.

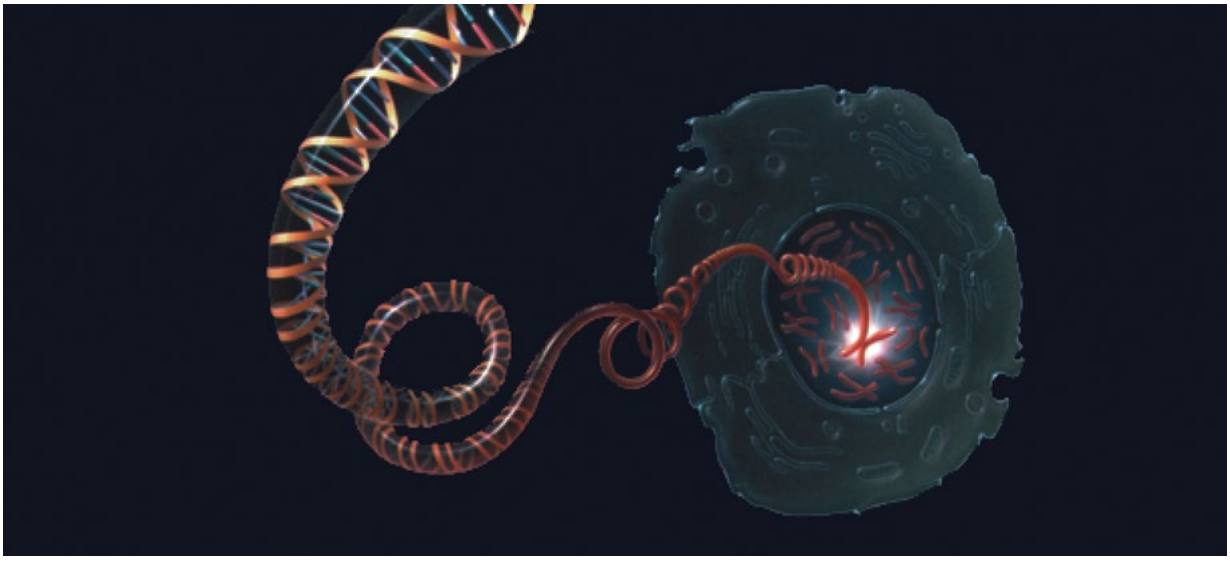
The most recent revised edition included recommendations based on the most recent research, guidance, and standards for collecting, processing, and storing specimens, along with informatics practices updates including removal of legacy IT infrastructure references. The Ethical, Legal and Policy Best Practices was also updated based on more recent guidance concerning informed consent for genomics research, the return of research results and incidental findings, genomic data sharing, and community engagement.

Updates to the Ethical, Legal and Policy Best Practices and expanded legacy planning recommendations are in progress. In conjunction with BBRB's work in developing the biospecimen collection program for GTEx, BBRB also published a Best Practices document for post-mortem biospecimen collection: Best Practices for Postmortem Recovery of Normal Human Tissue for Research.

### Biospecimen Evidence-Based Practices (BEBPs)

The NCI BEBP series is an expanding collection of procedural guidelines that provides evidence-based and practical information for researchers collecting and utilizing human biospecimens for research. Each document contains:

- Step-by-step procedural guidelines
- Supportive annotated summaries of literature evidence
- Optimal procedures
- Acceptable alternatives when the evidence allows, should key reagents be unavailable



The detailed, yet adaptable format, is intended to facilitate the creation of fit-for-purpose SOPs by researchers. Experts from the research community are engaged in review and modification of draft BEBPs so that real world experience is incorporated along with published literature. BEBPs published to date include the following: Cell-free miRNA: Blood Collection and Processing; Cell-free DNA: Biospecimen Collection and Processing; Nucleic Acid Extraction from FFPE Tissue; Snap-Freezing of Post-Surgical Tissue Biospecimens.

### Open-Source Versions of Biobanking Software and Vocabulary Used in NCI Programs

NCI's Comprehensive Data Resource (CDR) is a distributed web-based system that manages and maintains multi-dimensional data models on biospecimens. CDR was developed for the NCI BPV and NIH GTEx programs to facilitate the collection of biospecimen and clinical data on biospecimens donated from patients with cancer and post-mortem donors. CDR is currently used to facilitate biospecimen management for DCTD's Clinical Proteomics Tumor Characterization Consortium (CPTAC). A simplified version of CDR known as "CDR Lite" was also released as open-source software.

To facilitate future research, the biobanking and clinical data terminology used in the GTEx and BPV programs was independently reviewed and released for public use in the NCI Cancer Data Standards Registry and Repository (caDSR) and the NIH Common Data Elements (CDE) Repository.

## FUTURE DIRECTIONS

### CIRCULATING TUMOR NUCLEIC ACIDS

Tumor cells can often be detected in the bloodstream, and diagnostic tests have been devised to enumerate and characterize these cells. More recent reports indicate that genetic material derived from tumor sites can also be identified in the blood of patients with cancer. These studies have demonstrated the potential of this genetic material to be used as a source of screening through so called "liquid biopsy" for actionable somatic mutations. This approach permits screening of virtually all patients, even those whose tumors cannot be biopsied. It has also been reported that serial assessment of circulating tumor DNA (ctDNA) is useful in determining treatment response and disease progression. Additional applications for circulating nucleic acid assays include monitoring of treatment effect or recurrence, monitoring for the development of actionable resistance mutations, and potential detection of target engagement by novel therapeutics.

CDP plans to approach this opportunity in two ways. First, it will pursue an ongoing research program at FNLCR to:

- Assess current methods available for collection, shipment, and purification of ctDNA from blood or urine
- Examine methods to identify many somatic mutations in ctDNA using NGS

- Develop a full clinical grade assay to identify and/or monitor actionable somatic mutations in patient body fluids. The MoCha laboratory has already developed a novel 500-gene ctDNA assay in collaboration with Illumina™ and is working on clinical validation.

Second, CDP will work with outside investigators and the FDA to develop strategies for demonstrating the clinical utility of ctDNA-based diagnostic tests in clinical decision-making for people with cancer. The first step was a workshop in October 2016. BBRB's best practice documents, 'Cell Free DNA: Biospecimen Collection and Processing and Cell-free miRNA: Blood Collection and Processing,' are step-by-step procedural guidelines supported by literature evidence to support optimal SOPs for liquid biopsy molecular diagnostics.

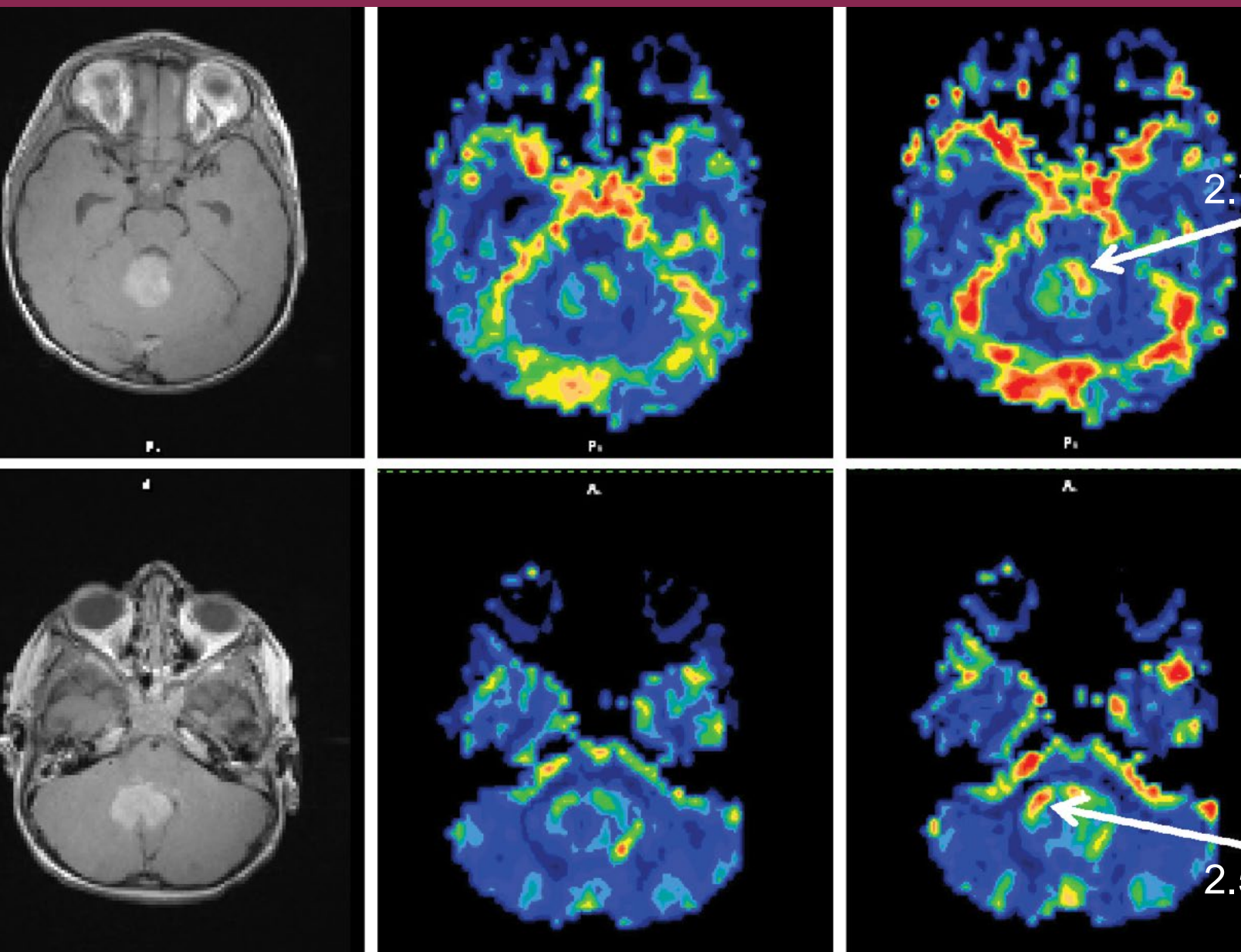
In 2023, DBTB organized a ctDNA workshop to examine the state of the field and elucidate ctDNA's potential to affect decision-making in the treatment of patients with solid tumors, with speakers recruited from academia, industry, and government. The presentations covered topics such as ctDNA for treatment management in the neoadjuvant and adjuvant settings, ctDNA for minimum residual disease surveillance, challenges of ctDNA as a biomarker, ctDNA analysis beyond DNA mutations, and ctDNA from samples other than blood.

## MULTICANCER DETECTION

Recent advances in cancer detection in earlier stages of cancer have begun to be developed and are the focus of an initiative run by the Division of Cancer Prevention (DCP). CDP is involved in a large study being run by DCP that will evaluate blood-based assays for early multicancer detection in healthy individuals in a randomized controlled trial. This trial is critical to establish the value of these assays at improving patient outcomes such as detection of cancer in earlier stages of disease where treatment tends to be more effective and improving overall survival. CDP provides expertise in evaluating multicancer detection assays (MCDs) for inclusion in the trial and developing a diagnostic pathway for patients that come in with a positive MCD result. This trial is anticipated to start in 2024 and involves several institutions across the country.

PROGRAMS AND INITIATIVES (2020-2023)

# CANCER IMAGING PROGRAM



## OVERVIEW

The Cancer Imaging Program (CIP) encourages coordination and collaboration among experts in basic, translational, and clinical research to advance the understanding of cancer through imaging and to create better diagnosis and treatment options for patients with cancer.

### THE CIP MISSION:
VISUALIZING THE PROBLEM AND DIRECTING THE SOLUTION:

- Enabling discovery
- Directing development
- Personalizing care

To advance this mission, CIP supports:

- Basic biological research
- Technological innovation to provide tools
- Early-phase clinical trials
- Integration of imaging into therapeutic drug development
- Imaging applications
- Imaging interventions in cancer

Imaging is a scientific discipline combining methods in advanced technology and complex analysis to provide the ability to extract spatial and temporal information from *in vivo* systems. Imaging enables interrogation of intact biologic systems across the spectrum from subcellular to macroscopic levels and from discovery research to clinical decision making. In the last decade, major advances have been made in our understanding of tumor systems, in large part due to advanced imaging capability.

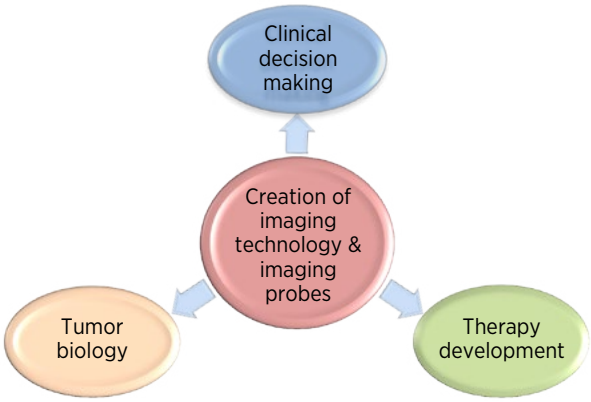



**FIGURE 42: ROLE OF IMAGING TECHNOLOGIES.**
Importance of imaging in understanding basic tumor biology, therapeutic development, and informing clinical decisions

Because of its successes, the role of imaging in cancer research is changing, and CIP continues to be a catalyst for this transformation. In the past, the focus of imaging research was on creating clearer and more detailed anatomic pictures of organs and tissues. Today, the primary thrust in imaging is functional or molecular imaging, to visualize and quantify the physiological, pharmacodynamics (PD), cellular, or molecular processes in living tissues. This is being aided by advances in artificial intelligence (AI), data extraction and processing for building and testing predictive models of cancer development, metastasis, and response to therapy. Connections to archives of clinical, genomic, and proteomic data are essential to this progress.

Advanced imaging is critical for fundamental improvements in the care of patients with cancer. As NCI continues to guide the discovery of new molecular signatures and cellular pathways of cancer, success can be achieved by understanding how these processes integrate into complex biological systems. With this information, we can contribute to effective therapy development. The challenge in medical imaging research is to continue to deliver sophisticated and integrated imaging methodologies to provide insight into the complex, heterogeneous, and dynamic biologic system that constitutes cancer. Even more challenging is integrating this wealth of information to better understand, manipulate, and defeat cancer through prevention and therapeutic intervention.

# LALITHA K. SHANKAR
## ACTING ASSOCIATE DIRECTOR

Lalitha K. Shankar, M.D., Ph.D., is the Acting Associate Director of the Cancer Imaging Program (CIP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), National Institutes of Health, in Bethesda, MD. Since joining NCI in 2003, she has served as an Advisor to the Associate Director of DCTD. She is the Chief of the Clinical Trials Branch, CIP. Her research interests have been both in the role of functional and molecular imaging in the diagnosis and treatment of cancer, as well as evaluating the performance characteristics of imaging modalities for optimal use in the management of the cancer patient. Her work involves establishment of and monitoring of clinical trials to evaluate imaging tracers and techniques, which aim to improve the prevention, diagnosis and treatment of cancer. She provides imaging expertise for trials of cancer diagnostics and therapeutics sponsored by NCI in the clinical trial networks such as NCTN and NCORP. She is the program lead for the Clinical Imaging Steering Committee and The Cancer Imaging Archive. She serves on the RECIST and RANO committees. She has served on FDA's Medical Imaging Drug Advisory Committee. She serves on the advisory committees of several trans-European biomarker initiatives. She is the recipient of several NIH and NCI Director Awards and is a Fellow of the Society of Nuclear Medicine and Molecular Imaging.

Dr. Shankar received her medical degree in Bangalore University, India and received her M.S. and Ph.D. in Radiation Sciences at Hahnemann University, Philadelphia. She then trained in clinical Nuclear Medicine and completed fellowships in Positron Emission Tomography and Theranostics at the University of Pennsylvania in Philadelphia. Prior to joining NCI, she was a faculty member in the Department of Radiology at Georgetown University and at the Lombardi Cancer Center and worked in the Division of Nuclear Medicine at Washington Hospital Center.

Imaging is essential to increasing our understanding of sub-cellular structural and molecular interactions executed by the proteome-to-cell microenvironment and cell-cell interactions through complex signaling and transfer processes. Imaging provides information across the genotype-to-phenotype continuum and is being applied to evaluate subcellular structure and biology, including protein-protein interactions and compartmentalization within unique intracellular microenvironments. Macro-level imaging is used clinically to evaluate cancer phenotype changes and characterize changes in the cancer microenvironment.

CIP-sponsored research continues to contribute to the basic understanding of cancer by:

- Creating novel methods to enhance the clinical role of imaging in noninvasive diagnosis
- Helping to identify disease subsets for effective treatment in patients with cancer
- Improving disease staging and treatment monitoring
- Playing a pivotal role for imaging in the development of new therapies
- Correlating medical images with genomic and proteomic data in precision medicine, particularly where obtaining tissue samples is difficult, such as in recurrent disease or multiple metastases

As part of its mission, CIP plays a critical role in NCI and NIH activities, contributing to the integration of imaging with emerging technologies, such as nanotechnology, cancer genomics, proteomics, high-throughput screening, and big data challenges. In addition to funding projects in key areas, CIP supports researchers by providing pooled resources and developing protocols that encourage the sharing of data, samples, and results.

CIP encourages coordination and collaboration among experts in basic, translational, and clinical research to advance the understanding of cancer through imaging and to create better diagnosis and treatment options for patients with cancer. Its mission is to visualize problems and direct


solutions by enabling discovery, directing development, and personalizing cancer care. This is done by supporting basic biological research and technological innovation to provide tools, early-phase clinical trials, and integration of imaging into therapeutic drug development.

Research in extracting information from imaging is a major CIP interest. Advanced imaging and quantitative and directed approaches are being developed through the funding of extramural research proposals that highlight extensive collaborations among biologists, systems modelers, bioinformaticists, physicists, and chemists. An emerging example is the application of imaging as part of hypothesis testing and hardening of network models that are derived from available deductive data, including the rapidly growing "omics" space. Medical images contain much more information than is obvious to the naked eye, and image data analytical approaches using structured computer-extracted features and AI are yielding increasing disease insights. Similar approaches employing complex cell systems have already revealed unanticipated cellular network connectivity when these systems are perturbed with drugs, thereby providing the potential to refine models for further drug development and for predicting target response and toxicity. Translation of these research results to clinical practice will likely depend heavily on collaboration with ongoing research in nanotechnology.

# CIP STRATEGIC GOALS

- Encourage investigators to design and apply imaging to better understand the tumor microenvironment and biochemistry
- Identify and promote the development of imaging techniques that are applicable to high-priority targets, where imaging could play a pivotal role
- Integrate imaging biomarker development with conventional biomarker development in the therapy development pipeline as they occur in parallel, providing a more robust biomarker platform for therapy translation
- Support development of clinically relevant imaging techniques
- Expand and improve integration of imaging data with clinical, genomic, and proteomic data to advance data science and artificial intelligence goals
- Translate imaging-derived knowledge and techniques to help realize the potential of precision medicine
- Support target identification, imaging agent development, and translation for radionuclide, and optical device-based therapy
- Support development and validation testing for new imaging technology and its applications

## STRUCTURE AND FUNCTION

CIP supports extramural investigators in academia and private industry as they create and apply the next generation of imaging technologies, including molecular probes, imaging devices, new contrast agents, and image-guided therapies to cancer problems.

CIP's five branches are responsible for activities in the following areas:

1. Molecular imaging
2. Clinical trials
3. Image-guided intervention
4. Imaging technology development
5. Nanotechnology

### MOLECULAR IMAGING BRANCH (MIB)

MIB supports *in vivo* cancer molecular imaging by providing a definitive, minimal, or noninvasive assay of the molecular status of cancer cells and their environment in preclinical models and clinical settings. The realization of that goal requires:

- *In vivo* molecular imaging agents that detect and report perturbations of genes, gene products, molecular pathways, PD, and physiological processes in cancer
- Imaging technologies capable of detecting rare events at the highest resolution *in vivo*
- Advanced image reconstruction and processing capabilities
- Highly multidisciplinary approaches

CIP supports these approaches primarily through its extramural grant program and by:

- Supporting state-of-the-science workshops and conversations across multi-disciplinary communities
- Collaborating with the Molecular Imaging Program in the NCI Center for Cancer Research and the Molecular Imaging Clinic in the NIH Clinical Center

## CLINICAL TRIALS BRANCH (CTB)

CTB supports clinical trials by:

- Awarding grants and contracts to extramural investigators for exploratory trials
- Advising and providing a strategic roadmap for imaging research in the extramural imaging community via a leadership role in the Clinical Imaging Steering Committee (CISC)
- Providing guidance for NCI-sponsored clinical trials through review of Cancer Therapy Evaluation Program (CTEP)-sponsored protocols that have imaging as a scientific objective
- Helping to promote standardization of imaging used in NCI-sponsored clinical trials by helping to establish and advise the Imaging and Radiation Oncology Core (IROC) as part of the National Clinical Trials Network (NCTN)
- Overseeing the development of imaging in trials conducted through NCI's Experimental Therapeutics Clinical Trials Network (ETCTN)
- Integrating quantitative imaging tool testing and validation in clinical trials
- Identifying and facilitating clinical trial imaging data incorporation into a publicly available archive to enable discovery research
- Developing trial-related informatics
- Promoting the development of radiomics-based clinical support tools
- Integrating imaging data into NCI efforts such as the Cancer Moonshot℠ Biobank, Clinical Proteomic Tumor Analysis Consortium (CPTAC) and Applied Proteogenomics Organizational Learning and Outcomes (APOLLO) network programs

CTB oversees and directs all aspects of clinical trials evaluating imaging and image-guided interventions in the phase 0 to phase 3 setting. CTB's overarching theme is to further evaluate imaging in cancer management. The branch serves as the primary CIP liaison with the NCI clinical trial system and ensures that the goals and priorities of both CIP and NCI for imaging are addressed in these activities.

## IMAGE-GUIDED INTERVENTION BRANCH (IGIB)

IGIB promotes the integration of imaging, informatics, and interventional methods to address diverse clinical challenges such as directed biopsy and surgical resection, image-guided tumor ablation, dimensionality of scale, and targeted drug delivery. IGIB is interested in image augmentation probe development, research in probes, tissue markers, and delivery vectors for applications where imaging plays a significant role in clinical decision making.

By its very nature, image-guided interventions (IGI) encompass all aspects of imaging, from disease detection and therapy planning to response assessment and disease recurrence monitoring. Central to the IGI mission is contributing to the therapy delivery process, which can be surgery, radiotherapy, cryotherapy, targeted drug therapy, or other relevant cancer treatments. Imaging approaches in this process may involve exogeneous agents or probes intended to augment the image. Combinations of imaging methods such as optical/MRI or ultrasound/MRI are often applied for image guidance during therapy.

## IMAGING TECHNOLOGY DEVELOPMENT BRANCH (ITDB)

ITDB supports the development and validation of biomedical imaging technology and methods to enable basic research and clinical investigations of cancer biology, diagnosis, and treatment to better understand disease onset, progression, and treatment response and to improve patient outcomes. Our strategy is characterized by a balanced emphasis on both the current-generation (commercially supported) and next generation imaging platforms. ITDB emphasizes multimodality imaging and methods of quantitative imaging on resolution scales from the molecular level to the organ level. An important branch interest area we support is new imaging informatics research, including the development and adoption of AI based tools and models, to enable the integration of cancer research across spatial and temporal scales.

## NANODELIVERY SYSTEMS AND DEVICES BRANCH (NSDB)

NSDB develops, funds, and administers initiatives aimed at solving contemporary cancer research and oncology problems with nanotechnology solutions. Nanotechnology has integrated well into the NCI funding portfolio and will continue to be supported through multiple NCI funding opportunities.

NSDB activities extend beyond nano-imaging and include novel *in vitro* diagnostics and therapeutics benefiting from the incorporation of nanotechnologies. NSDB serves as a focal point for nanotechnology-based grant and contract activities within DCTD and NCI. The NSDB also supports and oversees the Nanotechnology Characterization Laboratory (NCL) in the Frederick National Laboratory for Cancer Research (FNLCR). This laboratory group conducts comprehensive nanomaterials characterization with the aim of supporting translation.

## CIP RESEARCH GRANTS MANAGEMENT

The CIP research portfolio includes 487 funded grants during the fiscal year 2023, totaling $239 million. The predominant mechanism is the individual research project grant (R01), followed by exploratory/developmental research projects (R33). Because of the specialized nature of imaging research, CIP has developed several funding initiatives that encourage applications in specific areas. **Figure 43** shows the distribution of CIP's award mechanisms and research support in 2023.

## ASSISTANCE TO THE CANCER RESEARCH COMMUNITY

CIP collaborates with intramural NCI scientists to develop new imaging probes. A number of these probes are PET agents for molecular imaging directed at important targets such as prostate-specific membrane antigen (PMSA). This collaboration is bidirectional, forming a novel development pipeline with the extramural imaging community in infrastructure for early clinical trials of imaging probes, and DCTD, which provides expertise in drug development.

### SPECIALIZED INITIATIVES

Extramural imaging research funding at NCI includes traditional P01, R01, R21, and other investigator-initiated grants. Several specialized initiatives covering the spectrum of CIP's research efforts, from basic research to clinical trials, have been developed or reissued to address unmet needs in the field.

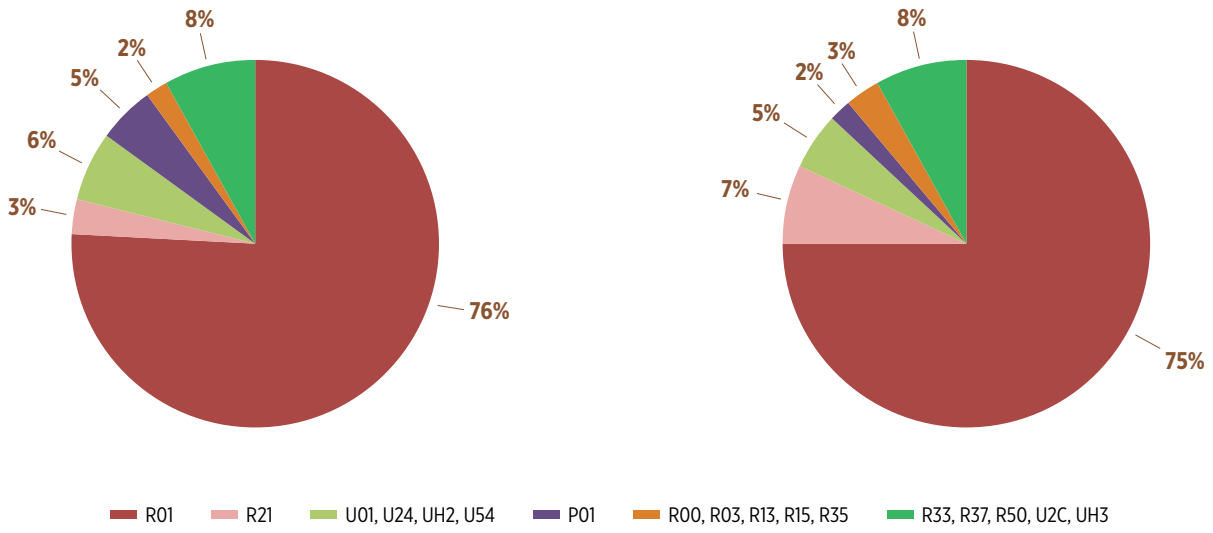



FIGURE 43: DISTRIBUTION OF CIP 2023 GRANTS BY MECHANISM (LEFT) AND BY FUNDS (RIGHT).

In addition to many investigator-initiated basic research efforts, several key program announcements use the R01 and R21 grant mechanisms to foster research in specific areas. Others use specialized grant mechanisms, such as U01, P50, and U24, suited for their positions in the research pipeline.

### Innovative Research in Cancer Nanotechnology – IRCN (R01).

PAR-20-284: This program enabled mechanistic research focused on understanding processes involved in the *in vivo* delivery of nanoscale systems to tumors, as well as nanomaterial properties that affect the detection of biomarkers using diagnostic devices. The goal was to gain further fundamental knowledge to help inform translation of nanotechnology to the clinical space.

### Toward Translation of Nanotechnology Cancer Interventions-TTNCI (R01).

PAR-22-071: The goal of this initiative is to translate nanotechnology-based cancer interventions that rely on nanoparticle formulations and/or nano-devices. Funding supports applications in clinical translational that focus on one or more of three areas: 1) Combination Therapy, 2) Immunotherapy, and 3) Imaging and Diagnostics.

### Academic–Industrial Partnerships (AIP) to Translate and Validate In Vivo Imaging Systems (R01).

PAR-20-155: In collaboration with the Radiation Research Program and the Cancer Diagnosis Program, this initiative encourages applications from academic and industrial research partners to accelerate translation of either preclinical or clinical *in vivo* imaging systems and methods that are designed to solve a cancer problem. The proposed imaging system or methods may include single or multi-modality *in vivo* imaging and spectroscopy systems, image-guided and drug delivery systems, image analysis, and related research resources.

### Notice of Special Interest (NOSI): Translation of Quantitative Imaging tools and Methods for the Academic Industrial Partnership (R01).

NOT-CA-21-032: The goal of this NOSI is to encourage applications that focus on the translation of mature, well-developed, and optimized quantitative imaging (QI) tools and methods to predict and/or measure response to cancer therapies, or for planning and translating radiation therapy (RT) treatment strategies in clinical trials and workflow. Funding supports collaborations between academia and industrial partnerships (AIP) with continual interplay between the AIP team and clinicians to produce high-quality QI tools through several rounds of iterative optimizations and validation.

### Integration of Imaging and Fluid-Based Tumor Monitoring in Cancer Therapy (R01 Clinical Trial Optional) (R01).

PAR-21-290: The long-term goal of this initiative is to determine the appropriate use of imaging and fluid-based tumor monitoring (liquid biopsy) assays to monitor therapy during the treatment of patients with cancer. The application of a combination of imaging and liquid biopsy assay should determine response or emergence of tumor treatment resistance at the earliest, unequivocal time point.

### Molecular Imaging of Inflammation in Cancer (R01).

PAR-21-294: The goal of this initiative is to leverage cutting-edge *in vivo* imaging technologies capable of monitoring specific cell populations or signal pathways to determine the relationship between inflammation and tumor biologic behavior. This initiative encourages applications that focus on developing integrated imaging approaches to understand the role of inflammation in cancer.

### Translation of Novel Cancer-Specific Imaging Agents and Techniques to Mediate Successful Image-Guided Cancer Interventions- for new business entities to engage in cancer imaging.

NIH/NCI 463: This is an opportunity for investigators with developed technologies to translate and commercialize their new technologies.

## IMAGING INFORMATICS

CIP's informatics activities address major challenges to the acceleration of cancer imaging research. CIP established and continues to support The Cancer Imaging Archive (TCIA) to provide readily accessible, large, curated clinical image collections and to overcome the barriers to interinstitutional sharing of image data. CIP is also involved with the design and building of the Imaging Data Commons, a new segment of the Cancer Research Data Commons. Program leaders within CIP have organized an internal oversight committee to integrate program input with the NCI's Center for Biomedical Informatics and Information Technology activities in building the data commons. CIP also provides significant support to other NCI data initiatives such as APOLLO, Cancer Moonshot™ tasks teams, Cancer Moonshot™ Biobank, as well as CTEP and IROC activities.

## MOLECULAR IMAGING RADIOPHARMACEUTICAL RESOURCES

CIP has filed INDs for imaging agent use including numerous molecular imaging radiopharmaceuticals for the imaging research community to perform multicenter clinical trials and to give access to the wider non-imaging research community:

- [$^{18}$F]Fluorothymidine (FLT), targeted to areas of increased proliferation
- [$^{18}$F]Fluoromisonidazole (FMISO), targeted to hypoxic tissues
- 16α-[$^{18}$F]Fluoro-17β-estradiol (FES), targeted to estrogen receptors
- [$^{18}$F]Sodium fluoride, accumulating in areas of increased osteogenic activity
- [$^{111}$In]Trastuzumab, targeted to HER2-expressing cancers
- [$^{89}$Zr]Panitumumab, targeted to cancers expressing epidermal growth factor receptor (HER1)
- Ferumoxytol, an iron oxide nanoparticle for magnetic resonance imaging (MRI)
- [$^{18}$F]Fluorodeoxycytidine, targeted to areas of increased DNA synthesis
- [$^{18}$F] dicarboxypropyl carbamoyl fluorobenzyl-L-cysteine (DCFBC), targeted to prostate specific membrane antigen
- Hyperpolarized [$^{13}$C]Pyruvate, targeted to areas of increased metabolism
- [$^{18}$F] 4-L-Glutamine (2S, 4R), targeted to areas of increased metabolism

NCI filed its first IND for an imaging agent, [$^{18}$F]fluorothymidine, in 2004, and acquired its most recent, C-13 hyperpolarized pyruvate, from General Electric in 2015. To further clinical research of these imaging drugs, NCI makes a subset of the documents filed in several of these INDs freely available for the research community to implement routine synthesis of tracers at their own facilities and to assist investigators with the filing of their own INDs, including a full set of manufacturing and quality control documents and an Investigator Drug Brochure. Extramural investigators can establish the synthesis at their sites and then file their own INDs with the U.S. FDA. CIP provides cross-reference letters for the NCI IND file at the FDA for pharmacology, toxicology, dosimetry, and previous human experience.

In addition, CIP has developed a process that authorizes qualified academic sites to manufacture and supply short-lived radiopharmaceuticals for NCI-sponsored clinical trials under the NCI-held IND. This effort has expanded the number of sites that can participate in the trials of advanced imaging agents while assuring that the drug is equivalent across sites, a serious concern with the necessary decentralized manufacturing.

## NANOTECHNOLOGY CHARACTERIZATION LABORATORY (NCL)

The NCL was founded in 2005 as part of the NCI Alliance for Nanotechnology in Cancer program to provide "pharmaceutical mentorship" to investigators working in cancer nanomedicine. Documented in a memorandum of understanding between the NCI, FDA, and the National Institute of Standards and Technology, NCL's mission was to develop an "Assay Cascade" of scientific tests that would help determine the reproducibility, safety, and efficacy of cancer drugs and diagnostics based on nanotechnology and provide investigators with additional tools and information required to meet regulatory requirements to move their technology towards the clinic. NCL's Assay Cascade evaluated nanomaterials submitted to NCL by extramural investigators with the aim of generating data to support future IND or Investigational Device Exemption (IDE) filings to the FDA.

The NCL has assisted more than 100 extramural investigators, tested close to 400 nano-formulations in its Assay Cascade, has 14 collaborators with nanomedicine products in clinical trials, and has published 200 plus scientific publications that describe important trends in nanomedicine development. The NCL has been developing new drug formulation capabilities designed to reduce drug toxicities and widen their therapeutic windows through nano-particle-based administration. Initial projects involved nanoparticle formulation of natural products from the NCI Natural Products Repository.

## CLINICAL TRIALS

Although phase 0 and imaging feasibility studies can be performed in the Molecular Imaging Clinic at the NIH Clinical Center, this venue has limitations. Certain studies are unachievable due to several factors, including an absence of PET radiochemistry capabilities and limited access to imaging time. CIP is working with academic centers and commercial vendors that have robust capabilities and patient populations complementary to those of the Clinical Center to support extramural efforts to develop imaging drugs.

Later-phase clinical trials, involving imaging drugs and imaging for the evaluation of therapy, are handled through ECOG-ACRIN, an imaging-focused group under the NCI NCTN structure. ECOG-ACRIN hosts quantitative imaging, clinical trials, and image sciences groups that are interdisciplinary within the overall organization to assess imaging issues in clinical trials and develop and implement new imaging clinical trials. Together with world renowned scientists and clinicians, an Imaging Science Advisory Committee, Early Diagnosis and Detection Science group, as well as cancer-specific disease committees were formulated. CTB staff participate on these committees and serve on ACRIN's Data Safety and Monitoring Board. Another mechanism to include imaging in therapy trials is via supplements to trials being funded through other NCTN Groups.

### COLLABORATION WITH CTEP

As a member of the CTEP Protocol Review Committee, CIP helps to identify opportunities to evaluate therapeutic response, such as demonstration projects evaluating functional imaging techniques in the assessment of response to therapy. CIP physicians are also primary reviewers and subsequent monitors for imaging-related concepts and clinical trials with molecular and functional imaging endpoints. CIP also ensures that NCI consensus guidelines for acquisition and interpretation of various imaging modalities are implemented.

### HIGHLIGHTS FROM ECOG-ACRIN IMAGING TRIALS - 2020-2023

#### EA8191, Phase III Study of Local or Systemic Therapy INtensification DIrected by PET in Prostate CAncer Patients with Post-ProstaTEctomy Biochemical Recurrence (INDICATE)

External beam RT to the prostate bed, with or without pelvic nodal RT, combined with short-term androgen deprivation therapy (STAD) is a standard-of-care treatment paradigm for patients with prostate cancer who present with evidence of biochemical recurrence (BCR) after radical prostatectomy (RP).

PET imaging with novel prostate-specific FDA approved agents demonstrates improved accuracy for detection of small volume metastatic disease compared to conventional imaging modalities (CIM) such as MRI, CT, and bone scan and are being performed worldwide in patients with post-RP BCR and negative CIM. The absence or presence of PET-positive extra-pelvic disease may help to identify potential candidates for local or systemic treatment intensification of the otherwise non-tailored approach of prostate bed/nodal RT and STAD. This PET-directed treatment intensification may in turn improve progression-free survival (PFS).

This trial involving 193 patients may help doctors determine if using PET results to deliver more tailored treatment (i.e., adding apalutamide, an androgen blocker, with or without targeted RT, to standard-of-care treatment) works better than standard-of-care treatment alone in patients with biochemical recurrence of prostate cancer.

### EA8171, Multiparametric MRI (mpMRI) for Preoperative Staging and Treatment Planning for Newly Diagnosed Prostate Cancer

Widely adopted diagnostics for identifying prostate cancer - Prostate-Specific Antigen (PSA) and transrectal ultrasound (TRUS)-guided biopsy - both lack specificity and sensitivity. The PSA is not specific to cancer, while the TRUS-guided biopsy may miss tumors in approximately 30% of cases as well as underestimate the aggressiveness of disease that is identified. The shortcomings of these diagnostics highlight the need not only to accurately identify patients at the highest risk who require treatment, but to avoid over-diagnosis and over-treatment in patients with the least-aggressive or indolent disease.

PI-RADSv2.1 and mpMRI provide a unique image-based opportunity to change the cancer detection and diagnosis pathway. Multiparametric MRI (mpMRI, which includes: T2-weighted imaging T2WI, diffusion-weighted imaging DWI, and dynamic contrast-enhanced DCE perfusion imaging) may be useful for evaluating the type of cancer and finding aggressive disease. Development of the imaging acquisition and reporting guidelines, known as the Prostate Imaging and Reporting and Data System (PI-RADS), support the adoption of mpMRI. Early changes in practice are being seen already; however, there is no U.S. prospective multi-center trial of mpMRI and PI-RADSv2.1 to determine the accuracy of detecting clinically significant disease and no risk prediction model exists that integrates mpMRI and PI-RADSv2.1.

This study will investigate the use of mpMRI and PI-RADSv2.1 to stratify clinically significant versus indolent disease in 852 patients who are newly diagnosed with prostate cancer in a prospective, multicenter design. This will:

- Address the primary clinical concern of appropriately routing patients with prostate cancer for treatment or active surveillance
- Possibly have an impact on clinical practice, including the potential of mpMRI to select men for prostate biopsy
- Possibly demonstrate a positive influence on survival in patients identified to have clinically significant disease while maintaining quality of life in patients with indolent disease who do not require treatment

### EAF151, Change in Relative Cerebral Blood Volume as a Biomarker for Early Response to Bevacizumab in Patients with Recurrent Glioblastoma

There are no validated biomarkers that can be used to determine which patients with recurrent glioblastoma multiforme (GBM) are most likely to benefit after initiation of bevacizumab therapy.

Dynamic susceptibility contrast-enhanced magnetic resonance imaging (DSC-MRI) may help evaluate changes in the blood vessels in patients with GBM. This phase 2 trial of 146 patients studies how well DSC-MRI works in measuring relative cerebral blood volume (rCBV) for early response to bevacizumab (obtaining rCBV at the 2-week time point after treatment initiation) in patients with recurrent GBM.

This trial could change clinical practice by identifying a patient group demonstrating early response that should continue bevacizumab or its biosimilars. The side effects may be treated more aggressively to maintain these patients on therapy versus poor responders who could participate in alternative clinical trials. This trial may support both a new clinical imaging technique and time point that proves helpful for early response assessment in this patient group and the concept of rCBV as an imaging marker for early response of recurrent GBM to bevacizumab or its biosimilars; therefore, positive results may spur further advances in imaging designed to accurately measure this parameter.

### EA1183, FDG PET to Assess Therapeutic Response in Patients with Bone-dominant Metastatic Breast Cancer, FEATURE

This phase 2 trial investigates how well FDG-PET/CT works in assessing the response of patients with breast cancer that has spread to the bones or mostly to the bones (bone-dominant (BD) metastatic breast cancer). Diagnostic procedures, such as serial bone scans, although often included in clinical trials, do not provide accurate measures of response for

patients with BD metastatic breast cancer. FDG-PET/CT may work better in serially measuring and classifying response of bone metastases from breast cancer to systemic therapy compared to other standard imaging tests.

Inclusion of an early 4-week FDG PET/CT time point for predicting PFS was evaluated in a single-institution, prospective study with 23 patients and was found to be highly correlated with the standard-of-care 12-week PET/CT. 12-week FDG PET/CT PET responders had longer PFS (14.2 months vs 6.3 months; P = .53) and overall survival (OS) (44.0 months vs 29.7 months; P = .47) compared with PET non-responders at the 4-week time point.

Positive results of this multicenter trial involving 128 patients will provide prospective evaluation of response criteria for FDG-PET/CT (modified PERCIST) to predict PFS and subsequently be incorporated in therapeutic clinical trials as an integral imaging biomarker for patients with BD and bone only (BO) metastatic breast cancer - a population often excluded from therapeutic clinical trials.

### S1827, MRI Brain Surveillance Alone Versus MRI Surveillance and Prophylactic Cranial Irradiation (PCI): A Randomized Phase III Trial in Small-Cell Lung Cancer (MAVERICK)

Following the completion of first-line therapy for newly diagnosed small-cell lung cancer (SCLC), the optimal central nervous system management strategy for patients without a history of brain metastases has become controversial in the modern era of brain MRI.

MRI scans are used to monitor the possible spread of cancer over time. Prophylactic cranial irradiation (PCI) is RT that is delivered to the brain to prevent the spread of cancer into the brain. The use of brain MRI alone may reduce side effects of receiving PCI and prolong patients' lifespan. Monitoring with MRI scans alone (delaying radiation until the actual spread of the cancer) may work similar to the combination of PCI with MRI scans. PCI has been recommended for patients with both limited-stage (LS) and extensive-stage (ES) SCLC due to consistent reductions in the rates of brain metastases as well as improved OS.

This phase 3 trial is expected to recruit 668 patients and examine whether a strategy of MRI surveillance alone, allowing for early salvage therapy in patients who develop brain metastases, compared to MRI surveillance plus PCI would result in non-inferior OS (primary endpoint) and improved cognitive preservation (secondary endpoints) in patients with LS and ES-SCLC.

The primary endpoint of the study was modified from OS to the key ongoing study endpoint of cognitive failure free survival (CFFS), which is a superiority comparison with the hypothesis that MRI surveillance alone will result in superior CFFS compared to MRI surveillance plus PCI. This modification allowed the study to set a feasible accrual goal of 250 patients for a CFFS superiority design and maintains the potential to provide practice-defining results.

## CO-CLINICAL IMAGING RESEARCH RESOURCES PROGRAM (CIRP)

The mission of the CIRP network is to advance the practice of precision medicine by establishing and disseminating consensus-based best practices for co-clinical imaging and by developing optimized state-of-the-art quantitative imaging methodologies for disease detection, risk stratification, and therapeutic response assessment. CIRP projects include four essential components: animal models (GEMMs or PDXs), co-clinical therapeutic trials, quantitative preclinical and clinical imaging methods, and informatics for supporting web-resources. The goal of the CIRP network is to provide the cancer and imaging research communities with web-accessible resources for quantitative imaging in co-clinical trials and to encourage consensus on how quantitative imaging methods can be optimized to improve the quality of imaging results for co-clinical trials.

# ONGOING STRATEGIES IN IMAGING – NATIONAL STRATEGIC PLANS, INITIATIVES, AND ROADMAPS

The CTB is engaged in the following activity designed to establish national strategic plans and an NCI-specific roadmap to advance the field of medical and biomedical imaging. By serving as lead representatives, CTB defines and develops avenues leading to the discovery of novel scientific breakthroughs and fosters the transfer of new technologies into the product development pipeline while focusing on key societal needs and priorities.

## NATIONAL NANOTECHNOLOGY INITIATIVE (NNI) 2.0

The NNI is a collaboration of 20 federal agencies and cabinet-level departments with shared interests in nanotechnology research, development, and commercialization. These agencies recognize that understanding and harnessing the novel phenomena that occur at the nanoscale is already leading to revolutionary new materials, devices, and structures for the diagnosis and treatment of cancer. These advances are poised to improve human health and quality of life.

Every three years, the NNI agencies develop and update the NNI Strategic Plan. This document represents a consensus among NNI agencies on the high-level goals and priorities of the initiative and on specific objectives to be pursued over the next three years. The purpose of the Strategic Plan is to catalyze achievement in support of the goals and vision of the NNI by providing guidance for agency leaders, program managers, and the research community regarding the planning and implementation of Federal Nanotechnology research and development investments and activities.

CIP staff participate in the Nanoscale Science, Engineering, and Technology Subcommittee of NNI and work with the Office of Science Policy in the NIH Office of the Director to define opportunities and national priorities. Based on a recent NIH-wide portfolio analysis, technical developments at the intersection of nanotechnology and imaging represent an opportunity to plan the future development of this field. The focus will be on the creation of grand challenges and new initiatives that support fundamental discovery, foster innovation of new materials, and accelerate the clinical translation of existing nanomedicine for cancer management.

## COMMUNITY ENGAGEMENT WITH PROFESSIONAL SOCIETIES

CIP staff work continuously with major professional societies of medical imaging in the U.S. to understand and help support areas of need and interest in medical imaging research. Medical officers and program directors from CTB work with societies representing the various imaging modalities essential to cancer imaging, including the Radiological Society of North America (RSNA), the Society of Nuclear Medicine and Molecular Imaging (SNMMI), and the World Molecular Imaging Congress. Examples of community outreach activities with professional societies include:

- Membership and participation of CIP/CTB in various initiatives organized by the Quantitative Imaging Biomarkers Alliance of RSNA
- Offering consultation to the SNMMI on seeking regulatory approval for novel PET agents such as fluorocholine and fluorothymidine
- Workshops with the SNMMI on state of the science in radionuclide therapy and dosimetry
- Giving presentations on relevant medical imaging and regulatory issues at plenary and other scientific sessions at imaging society annual meetings
- Membership in the Research Committee of the European Society of Radiology and the Imaging Committee of the EORTC
- RSNA Crowds Cure Cancer image annotation crowd source experience
- RSNA annual state of research using TCIA data sets
- WMIS imaging biology special sessions

## IMMUNE MODULATION THERAPY AND IMAGING

Immunotherapy is rapidly becoming a successful strategy in treating malignancies. NCI is investing resources to evaluate the role of various immunotherapies – either alone or in combination with other cytotoxic or cytostatic therapies. Assessment of tumor response with anatomic imaging and with the standard RECIST criteria has limitations in

patients receiving immunotherapy. CIP researchers are pursuing alternative methods of tumor response assessment in this setting.

### RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) WORKING GROUP (2006-PRESENT)

The RECIST criteria is a set of voluntary, international standards, which is the de facto method used to evaluate the response to an intervention (such as a novel cancer therapeutic drug) in most cancer-related clinical trials conducted today. RECIST is based on statistically validated work and analysis that categorizes responses to therapy based on changes in tumor size as measured with anatomical imaging modalities, such as a CT or MRI scan. The criteria were originally published in February 2000 by an international collaboration that included EORTC, NCI, and the National Cancer Institute of Canada, and were revised to RECIST 1.1 in 2009. Having a set of standardized, validated response evaluation criteria such as RECIST enables comparative analysis across studies and allows medical imaging data to be used as a surrogate endpoint in clinical trials. CIP Medical Officers participated as committee members in this international collaboration, have been co-chairs on the RECIST FDG PET Working Group since 2007, and are leading the next revision of the RECIST criteria.

### METABOLIC REGULATION OF INFLAMMATION AND ITS RESOLUTION WORKSHOP

In 2021, CIP hosted a trans-NIH workshop to discuss the important role that interactions between metabolic status and immune response (coined as immunometabolism in 2011) play in maintaining homeostasis or promoting disease. Understanding these interactions is critical to develop imaging tools involved in novel therapeutic approaches that can prevent and treat diseases like cancer. This workshop's white paper outlined future directions and funding concept opportunities for cross-fertilization of knowledge in this field.

## FUTURE DIRECTIONS

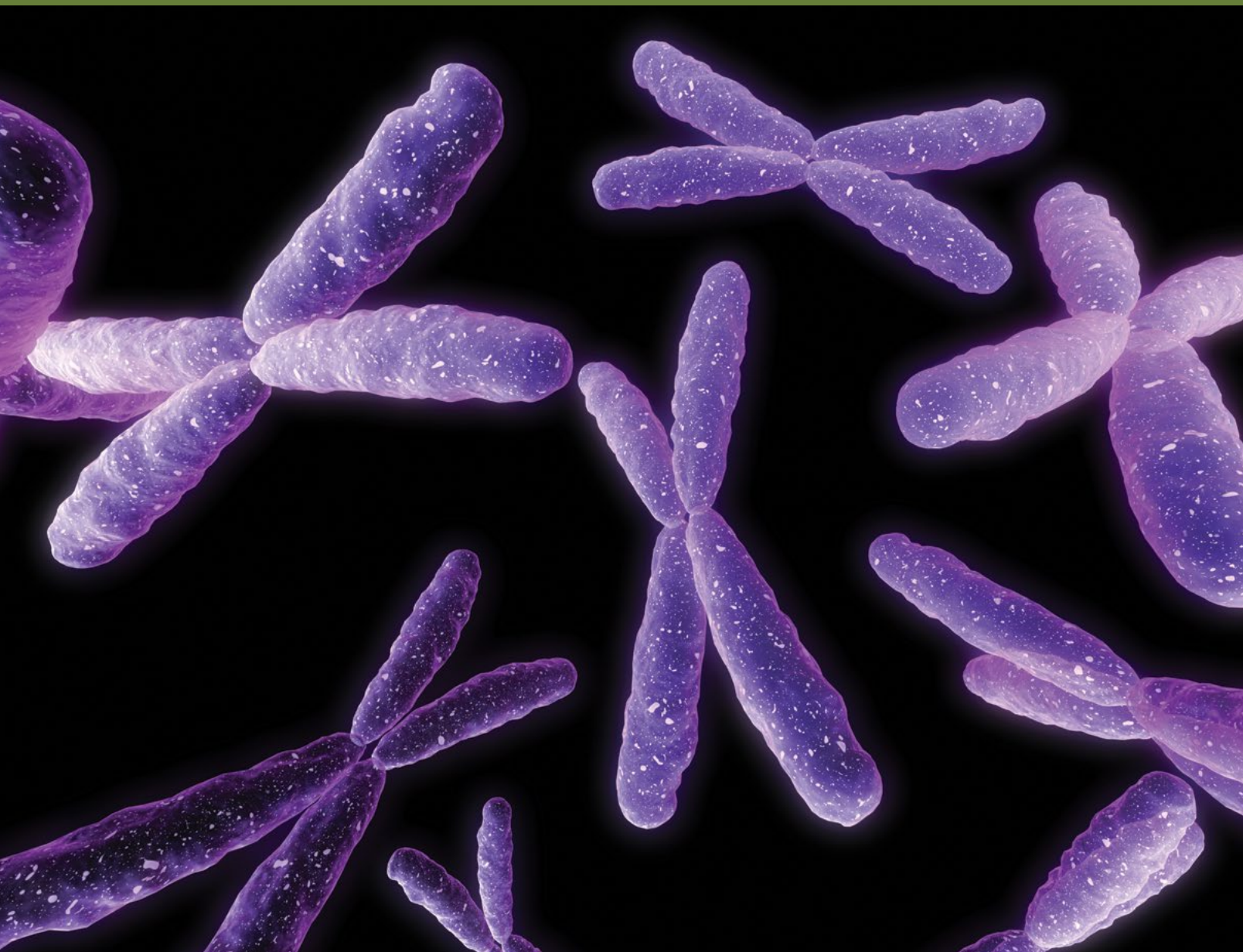
Novel devices, new methods for displaying and using images, and highly targeted imaging agents capable of isolating even the smallest tumors for characterization will continue to transform clinical imaging in cancer. Holographic images coupled with 3-D printing will give surgeons the opportunity to visualize deep seeded tumors in difficult anatomical locations before surgery begins. Imaging probes that remain undetectable in the bloodstream will suddenly activate upon reaching the tumor to reveal the tumor's location. Functional imaging methods will reveal the activity of natural immune responses to tumors. Nanobot devices, molecularly engineered structures capable of performing intercellular tasks, guided through image control will be able to alter damaged cellular communication pathways to prevent the initiation of disease. Implanted devices will be capable of detecting and eliminating circulating tumor cells before metastasis can occur. Such achievements are feasible when imaging is coupled with biological, chemical, and engineering technologies.

As imaging technologies and capabilities move toward these novel goals, tasks for the immediate future include improving methods that will support precision medicine. Major emphasis will be placed on improved methods for directed biopsy, support for clinical studies of imaging agents for tumor augmentation, and quantitative methods to extract phenotype information from tumors, including artificial intelligence techniques. It is critical to address the issue of co-correlation at vastly different physical scales and the integration of disparate data to allow valid alignment of imaging defined phenotypes with biologic characteristics. Developing techniques that minimize the intrinsic errors of random sampling and alignment are essential to advancing our understanding of human cancer and improving outcomes.

Additional challenges in imaging technology development will include methodologies for translating new imaging concepts into the clinical workflow, requiring consensus on standards, and data quality management activities. Improvements in imaging capabilities will continue to be a central focus for technology development, but methods for translation will be emphasized in future support.

PROGRAMS AND INITIATIVES (2020-2023)

# CANCER THERAPY EVALUATION PROGRAM



## OVERVIEW

The Cancer Therapy Evaluation Program (CTEP) coordinates DCTD's clinical treatment program through support and oversight of clinical trial network programs under cooperative agreement grants as well as through management of early-phase, investigator-initiated cancer clinical trials and translational science studies under P01 and R01 grants. CTEP manages a broad range of clinical trials that are closely integrated with preclinical discovery and development fostered by other DCTD programs. Once an approach (drug, surgery, radiation, immunotherapy) has obtained promising efficacy and adequate safety in preclinical testing, CTEP resources may be used to move the therapy from first-in-human safety trials through definitive, randomized, controlled trials conducted in one of the clinical trials networks supported by CTEP that meet U.S. Food and Drug Administration (FDA) requirements for approval.

CTEP staff directly supports and oversees more than 270 actively accruing cancer treatment clinical trials conducted throughout the nation annually. These trials are funded by more than 70 grant cooperative agreements and contracts and involve enrollments of about 19,000 to 22,000 patients annually. This level of activity makes CTEP one of the largest publicly funded clinical trials organization in the United States. As noted above, CTEP also supports studies funded by investigator-initiated trials under P01 and R01 grants. The program is responsible for many of the major studies that have improved cancer treatment over the last three decades. Networks of U.S. and international members that contain considerable scientific expertise and accrual capability conduct these trials. The trial networks, supported in whole or in part by CTEP, are aligned as shown in **Figure 44**.

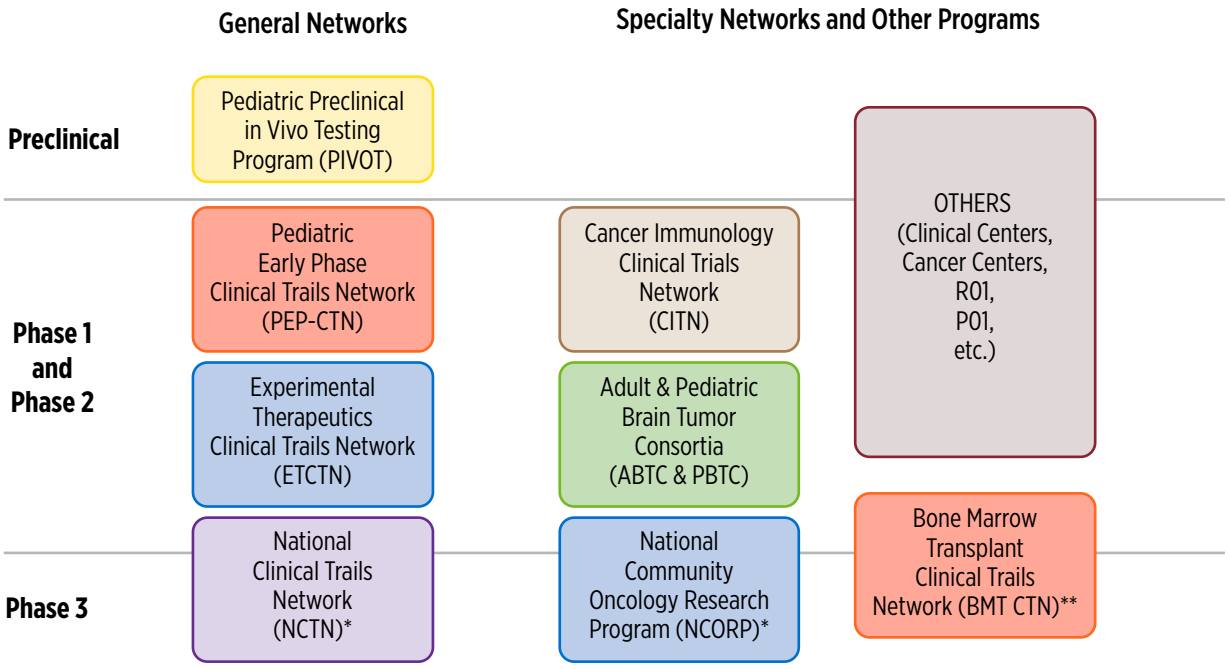



**FIGURE 44: MAJOR NCI CLINICAL TRIALS NETWORK AND PROGRAMS.**

R01, R21, P01 are research project, exploratory & developmental research, and program project grants. CTEP-funded Clinical Trials Networks included the PIVOT, PEP-CTN, ETCN, NCTN, CITN, ABTC, PBTC and BMT CTN.

*NCORP sites also participate in NCTN trials; NCORP is under DCP and not funded by CTEP

**BMT CTN is overseen by NHLBI with co-funding from NCI DCTD/CTEP

# MEG MOONEY
## ASSOCIATE DIRECTOR

Meg Mooney, MD, MS, is the Associate Director of the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis, at the National Cancer Institute (NCI), and she is also the Chief of the Clinical Investigations Branch (CIB) in CTEP.

She received her medical degree from the University of Chicago Pritzker School of Medicine in Chicago and her general surgical training at the Dartmouth-Hitchcock Medical Center in Lebanon, NH. She completed her Surgical Oncology fellowship training at the Roswell Park Cancer Institute in Buffalo, New York, and holds a Master of Science degree in Management from the Massachusetts Institute of Technology in Cambridge, MA.

Dr. Mooney joined NCI in 2002 as Head of Gastrointestinal and Neuroendocrine Cancer Therapeutics in CIB. She was appointed Chief of the branch in May 2009. She is responsible for the direction of the NCI National Clinical Trials Network (NCTN) Program. The NCTN performs large, definitive, practice-changing phase 2 and 3 cancer treatment and advanced imaging trials. In April 2014, she was named the Deputy Associate Director of CTEP. Dr. Mooney became the Associate Director of CTEP in April 2020.

## CTEP STRATEGIC GOALS

- Develop predictive diagnostics in tandem with new agents to enable precise targeting to those patient populations most likely to benefit from the agents
- Conduct controlled phase 1, 2, and 3 trials with the goal of developing new treatments and determining the best treatment approach for a particular cancer or molecular subtype of a cancer

## STRUCTURE AND FUNCTION

CTEP staff comprise physicians, scientists, nurses, pharmacists, and other specialists. By offering support and expertise to extramural investigators, CTEP branches enable the academic community to overcome many of the regulatory, pharmaceutical, and scientific barriers that can hinder the implementation of clinical trials. At the end of 2023, CTEP held 211 Investigational New Drug (IND) applications for new agents, primarily through Cooperative Research and Development Agreements (CRADAs) with pharmaceutical partners, thereby providing latitude to extramural investigators during early-phase trials to explore new schedules, doses, and proof-of-concept/mechanism-of-action studies.

By expanding the number of diseases in which agents developed by pharmaceutical companies are studied, CTEP's early clinical trials program (comprising the phase 1 and 2 programs shown in **Figure 44**) adds significantly to the industry drug development plan, which focuses primarily on supporting FDA evaluation of new agents and agent combinations. Depending on the scope and expertise of the pharmaceutical partner, CTEP-sponsored researchers can either perform trials in common cancers or can focus on areas that are less market driven, such as pediatric and hematologic tumors, complex tumors requiring multidisciplinary approaches, such as head-and-neck cancers and brain tumors, and multiple rare tumors. In addition, CTEP filled a particular niche in recent years involving early combination trials with experimental agents from two or more companies. CTEP has forged multi-company partnerships by creating a novel intellectual property (IP) agreement for collaborators to share IP when they co-develop drug combinations.

Sixty-one novel combinations of targeted investigational agents have entered CTEP-sponsored clinical trials in recent years. When promising signals of biologic activity are seen in phase 2 trials performed by CTEP's early-trials networks, the NCI National Clinical Trials Network (NCTN) moves these ideas into controlled, randomized, phase 3 trials for definite evaluation against the current standard of care. Transitioning from phase 0 to phase 3 studies requires a full complement of clinical trials services that reside in CTEP's seven branches under the Office of the Associate Director.

## INVESTIGATIONAL DRUG BRANCH (IDB)

The Investigational Drug Branch is responsible for the clinical development of anticancer agents that are being developed under NCI sponsorship. NCI fosters research collaborations with pharmaceutical partners to develop anticancer agents in the public interest. Pharmaceutical companies seek NCI collaboration in areas such as the development of therapies for rare cancers and of combination therapies with drugs under development by other companies. In these collaborations, NCI assumes the role of IND sponsor and is responsible for the design, conduct, and safety of trials conducted under NCI-IND. NCI also provides a haven for IP concerns, thereby permitting different companies to overcome industry barriers to co-development of agents. To facilitate the development of NCI-IND agents, IDB coordinates a clinical research network, the Experimental Therapeutics Clinical Trials Network (ETCTN), a UM1 grant-funded network of more than 90 clinical trial sites with expertise in early phase cancer clinical trials. IDB provides oversight of clinical trials of NCI-IND agents, and IDB physicians are the medically responsible physicians for all clinical trials of NCI-IND agents. IDB oversees a portfolio of more than 80 NCI-IND agents.

In addition to their pharmacovigilance role, IDB staff evaluate new agents for potential NCI clinical development, initiate drug development plans, review study proposals, and oversee the conduct and analysis of data from trials conducted under NCI-INDs. IDB physicians meet regularly with pharmaceutical companies, serve on NCI drug development committees, and interact with investigators in academia and industry, as well as FDA regulatory staff. A major focus of CTEP drug development is to explore the combinatorial use of investigational and approved drugs based upon a strong mechanistic rationale and supportive preclinical data.

## CLINICAL INVESTIGATIONS BRANCH (CIB)

The Clinical Investigations Branch coordinates and oversees the definitive, practice-changing clinical trials of innovative oncology treatments and advanced imaging, as well as complex, preliminary, umbrella/basket precision medicine trials and rare tumor trials when an extensive, national patient catchment area is required. These mostly randomized, phase 2 and 3 studies include investigations of single-agent or multiple-agent targeted therapies or combined modality interventions, including surgical and radiation therapy with chemo-, biologic-, and immunotherapies, in the treatment of cancer for adult, adolescent, and pediatric populations, conducted nationally by the extramural scientific community:

- NCI National Clinical Trials Network (NCTN)
- Pediatric and Adult Brain Tumor Consortia (PBTC / ABTC (phased out December 31, 2023))
- Pediatric Early Phase Clinical Trials Network (PEP-CTN; including transition of the disease portfolio of the Pediatric Brain Tumor Consortium into the PEP-CTN)
- Pediatric Preclinical in Vivo Testing Program (PIVOT; previously the Pediatric Preclinical Testing Program)

CIB physicians, nurses, and allied health professionals provide oversight of essential services and collaborations associated with these national clinical trial networks in conjunction with:

- The Cancer Trials Support Unit (CTSU), which provides centralized patient enrollment 24 hours a day, 7 days a week, as well as administrative and regulatory support for trial conduct
- The NCI Central Institutional Review Board (CIRB) for adult and pediatric CTEP and Division of Cancer Prevention (DCP) clinical network and consortia trials
- The Cancer Diagnosis Program (CDP) regarding the collection, banking, and use of clinical biospecimens in conjunction with validated data from multi-institutional clinical trials
- The Center for Coordinating Clinical Trials (CCCT) on identifying and prioritizing clinical treatment trials for disease-specific cancers
- Other NIH and NCI programs, such as the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN),

co-sponsored by NCI and the National Heart, Lung, and Blood Institute (NHLBI)

- Other international clinical trial organizations on treatment trials

## CLINICAL GRANTS AND CONTRACTS BRANCH (CGCB)

The Clinical Grants and Contracts Branch administers and manages grants, cooperative agreements, and contract awards focused on promising cancer therapeutic agents, treatments, and other clinical research proposed by the extramural cancer research community at large. CGCB's portfolio mainly comprises, but is not limited to, investigator-initiated phase 0-2 clinical trials and correlative science projects addressing challenges across a wide range of diseases. Research topics include the assessment of dose, safety, and effectiveness of investigational agents/therapies including surgery/surgical CTN, Childhood Cancer Survivorship Study (CCSS), and the Patient-Derived Xenograft Network (PDXNet) and manages cooperative agreements focused on collaborations with the NIH Clinical Center.

To successfully implement CTEP's extramural programs and initiatives, Program Officers (POs) from IDB, CIB, and CGCB manage the scientific, technical, administrative, and fiscal aspects of these awards. In addition, CTEP staff provide oversight to ensure proper stewardship over NCI-funded clinical investigations and perform outreach activities to further its mission. As a result of these efforts, CTEP has launched new and reissued existing NOFOs and presented clinical outcomes/key findings over the past three years. POs from IDB and CIB manage the scientific, technical, administrative, and fiscal aspects of CTEP's extramural clinical research portfolio consisting of grants and cooperative agreements.

## REGULATORY AFFAIRS BRANCH (RAB)

The Regulatory Affairs Branch comprises two groups, the Agreement Coordination Group (ACG) and the Drug Regulatory Group (DRG), both of which function to facilitate the development of promising anti-cancer drugs as identified via the NCI Experimental Therapeutics (NExT) Program.

The ACG begins this process by developing and negotiating a CRADA with an industry partner, as a foundation for the co-development of an agent. A CTEP-specific CRADA template includes standard, non-negotiable clauses that reduce negotiation time. More recently, the ACG has fostered pharmaceutical collaborations for three NCI-supported precision medicine clinical trials (Molecular Analysis for Combination Therapy Choice (ComboMATCH), MyeloMATCH for patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), and immunoMATCH (iMATCH)), as well as the NCI Formulary. Other types of agreements put in place to support our IND studies include Material Transfer Agreements (for preclinical studies), Clinical Trial Agreements (e.g., NCI-MATCH study), International Agreements, Memoranda of Understanding, and Data Use Agreements.

As part of the co-development process, CTEP takes on the role of IND sponsor, and all the responsibilities required by FDA. The DRG within RAB is responsible for filing the necessary INDs to support all clinical trials under the auspices of a CRADA. Moreover, this group is responsible for ensuring that these studies comply with FDA regulations.

As of December 2023, there are 211 IND applications used to support our ETCTN and NCTN trials. IND-related activities include Safety Reporting (expedited and annual reporting), new protocols and amendments, and responses to FDA queries. In addition, DRG coordinates End-of-Phase 2 meetings between the FDA and CTEP-NCTN-Pharma for all studies intended to support a new indication or label change. DRG also plays a central regulatory role regarding investigational biomarker assays used in conjunction with investigational drugs. Specifically, this group ensures that pertinent Investigation Device Exemption (IDE) regulations are followed for those studies using investigational, treatment-determining assays. In addition, this group coordinates meetings with FDA's Center for Devices and Radiological Health (CDRH; e.g., Pre-submission meetings).

## PHARMACEUTICAL MANAGEMENT BRANCH (PMB)

The Pharmaceutical Management Branch is a unique resource for experimental and investigational oncology agents in support of DCTD clinical research efforts. PMB provides the extramural community with specific pharmaceutical services, regulatory oversight, and administrative support. PMB pharmacists manage approximately 180 investigational agents, negotiate with pharmaceutical collaborators to ensure appropriately labeled investigational agent supplies and associated drug information are available, and support thousands of domestic and international clinical sites that enroll patients to NCI-funded clinical trials.

## CLINICAL TRIALS MONITORING BRANCH (CTMB)

The Clinical Trials Monitoring Branch manages quality assurance and quality control of the following:

- Early-phase clinical trials (phase 0, phase 1, and phase 2 studies) conducted by the ETCTN
- Late phase clinical trials (phase 2 and phase 3 studies) conducted by the NCTN
- Prevention trials sponsored by DCP

CTMB establishes standards for quality assurance activities and for overseeing the on-site auditing activities to assure the integrity of the data, patient safety, and compliance with protocol requirements and Good Clinical Practices (GCP). CTMB also provides education to clinical research sites that are experiencing performance issues.

### CTMB Accomplishments (01/01/2020 – 10/15/2023)

- 3,087 NCTN Group audits reviewed
- 62 AMC audits
- 4 PBTC audits
- 72 University of Rochester Cancer Center and Wake DCP Research Base audits
  - 29 Cancer Center Site Visits coordinated and performed
  - 70 PEP-CTN monitoring conducted by the clinical trial management service (CTMS) and reviewed by CTMB staff
  - 575 phase 1 and phase 2 audits involving 3,901 patient cases
  - Development and implementation of a specimen tracking system used for 128 ETCTN studies
  - Revision to CTMB Audit Guidelines to address remote auditing and monitoring
  - Expansion of Source Document Portal to facilitate remote auditing
  - Enhancements to Web Reporting and the CTMB-Audit Information System
  - Development of the Cancer Screening Research Network Auditing Guidelines
  - Recompetition of the Clinical Trials Monitoring Service contract

### CLINICAL TRIALS OPERATIONS AND INFORMATICS BRANCH (CTOIB)

The Clinical Trials Operations and Informatics Branch improves protocol development and conduct by providing efficient business practices, informatics tools, as well as central review of clinical trials for human safety and protection, and process evaluation methods. CTOIB includes the Protocol and Information Office (PIO), Clinical Oncology Research Enterprise (CORE), the CTEP Enterprise System (ESYS), Biomarker review and tracking, the Cancer Trials Support Unit (CTSU), Centralized Protocol Writing Support (CPWS), the NCI Central Institutional Review Board (CIRB), the standard Clinical Data Management System (CDMS), and the Protocol Tracking System (PTS). CTOIB also supports process evaluation and data-analysis efforts for the NCTN systems.

## FINANCIAL INVESTMENTS IN GRANTS AND COOPERATIVE AGREEMENTS

In summary, CTEP has invested $353 million to fund a total of 312 awards in fiscal year 2023. This investment included $69 million for R01 Research Projects, $50 million for Program Projects, and $219 million for cooperative agreements. Figure 45 shows the distribution of awards in terms of number of awards and funding. Based on this analysis, CTEP continues to support a strong grant portfolio based on research plans that follow the R01 mechanism.

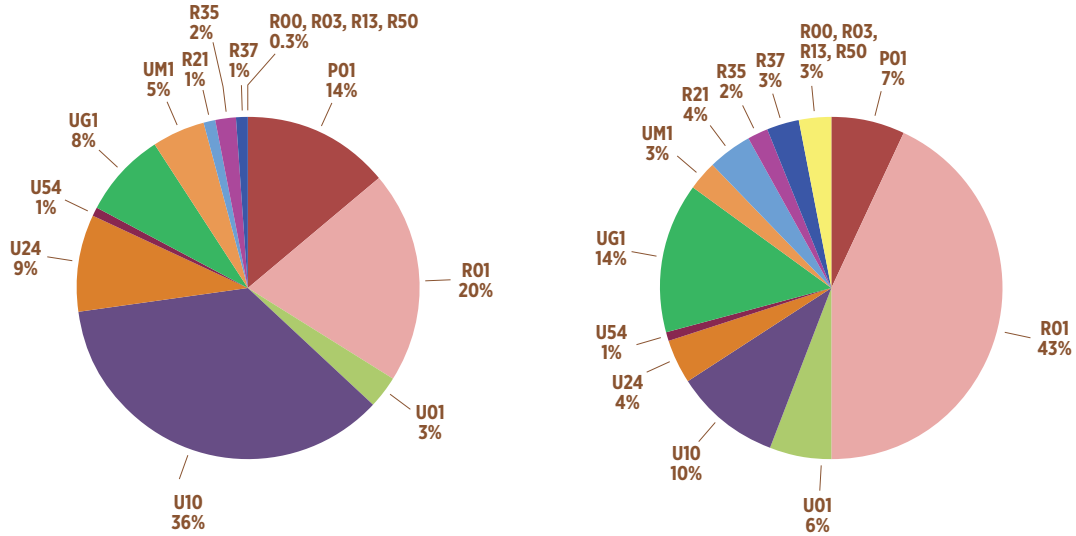
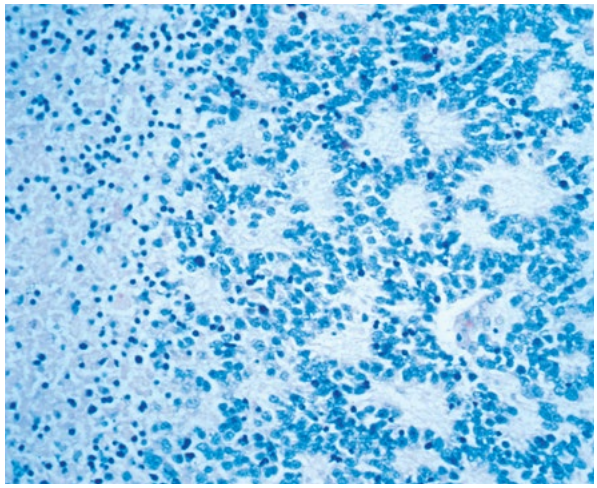



FIGURE 45: DISTRIBUTION OF CTEP 2023 GRANT FUNDS (LEFT) AND NUMBERS OF GRANTS (RIGHT) BY MECHANISM.

CANCER THERAPY EVALUATION PROGRAM CTEP



## FOSTERING CAREER DEVELOPMENT OF JUNIOR CLINICAL INVESTIGATORS

The Early-Stage Investigator (ESI) LOI program is designed to facilitate career development by providing a competitive advantage for junior investigators submitting LOIs. The program provides mentoring in the LOI development and review process, including expert commentary on clinical trial proposals. Of the almost 800 ESI LOIs submitted through the end of 2023, approximately 35% have been approved. Moreover, virtually all members of CTEP Drug Development Project Teams are junior faculty/mentor pairs. ESIs have been submitted through all funding mechanisms, reflecting broad acceptance of the ESI process.

Ten to twenty U.S. and international fellows and junior faculty rotate at CTEP each year, during which they participate in:

- CTEP scientific review of LOIs and protocols
- Scientific presentations by biotechnology and pharmaceutical companies seeking CTEP collaboration
- Mentoring subprojects from CTEP early-phase trial data

CTEP also sponsored its first LOI writing workshop for ESIs in September 2019. CTEP staff and extramural mentors staffed the workshop, which was attended by 20 ESIs. Didactic session topics included preclinical data, trial design, biomarker considerations, and statistical plans. Additional virtual workshops have been held annually beginning in 2020.

## CLINICAL TRIALS PROGRAM

### NCI NATIONAL CLINICAL TRIALS NETWORK (NCTN)

For a comprehensive review of the NCTN, see the NCTN section in the Major Initiatives chapter.

### COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENTS (CRADAS)

Following are the numbers and types of agreements for 2020–2023:

- CRADAs Executed: 54
- Total Active CRADAs: 107
- CTAs Executed: 2
- Total CTAs: 18
- International Agreements Executed: 3
- Total International Agreements: 6
- INDs Filed: 74
- Total Active IND Portfolio: 211
- IND Amendments:
  - 1843 Protocol Amendments
  - 109 New Protocols
  - 1491 Expedited Safety Reports
  - 51 Annual Reports

## IP AND BIOMARKER DEVELOPMENT

To facilitate precision medicine trials and biomarker-driven targeted therapy, DCTD developed the CTEP IP Option to Collaborator, which describes the data and IP rights of both the diagnostic assay companies and pharmaceutical collaborators under the scope of a CTEP study. Biomarker and clinical outcome data are shared per the multiparty data provisions of all agreements to allow both the collaborators and diagnostic companies any further development of their proprietary products.

## NCI DRUG DEVELOPMENT PROJECT TEAMS

Highly ranked drug development proposals submitted through the NExT Program and approved for the development of collaborative research agreements with NCI may require the assembly of an NCI Drug Development Project Team to design the scope of NCI's initial multi-institutional, multi-disciplinary drug development plan for the proposed agent(s). To identify the appropriate team members, CTEP solicits and reviews Project Team Member Applications (PTMAs) from investigators in CTEP's clinical trial networks. The Project Team members are selected based upon their qualifications and the expertise they can provide to the Project team. They determine which clinical trials will be conducted across the CTEP clinical trials network sites, and how best to approach critical translational studies.

Extramural investigators included on the Project Teams may fill one or more of the following roles:

- **Clinician scientists** lead the clinical trials recommended by the NCI Drug Development Project Team and create protocol study committees for execution of these studies. These trials can be conducted through any of the clinical trials networks managed by CTEP. Junior investigators and their mentors are encouraged to submit Career Development Project Team Member Applications (CrD PTMAs), similar to the prioritization of ESIs in other CTEP and NCI initiatives.
- **Translational scientists** provide guidance on prioritization of biomarkers for the studies under development, including recommendations for technologies and platforms that meet increasingly stringent requirements for integral and integrated biomarkers.
- **Basic scientists** provide scientific guidance for the study design based on the mechanism of action of the investigational agent and help prioritize the clinical study choices based on published literature and unpublished data. Basic scientists on the team will have access to the agents to conduct additional laboratory studies deemed important for supporting the proposed clinical trial(s) of the agent.

Once convened, the NCI Drug Development Project Team meets regularly over an 8-10-week period to finalize the drug development plan for presentation to the Investigational Drug Steering Committee (IDSC). Upon approval of the project development plan and the requisite funding by the NExT Program Senior Advisory Committee (SAC), the clinician and translational scientists on the Project Team submit LOIs to CTEP. CTEP subsequently makes the agent available to qualified investigators, contingent on approval from the agent applicant. Network and non-network sites not on the Project Team may submit unsolicited LOIs for clinical trials or request the agent for preclinical studies (**Figure 46**).

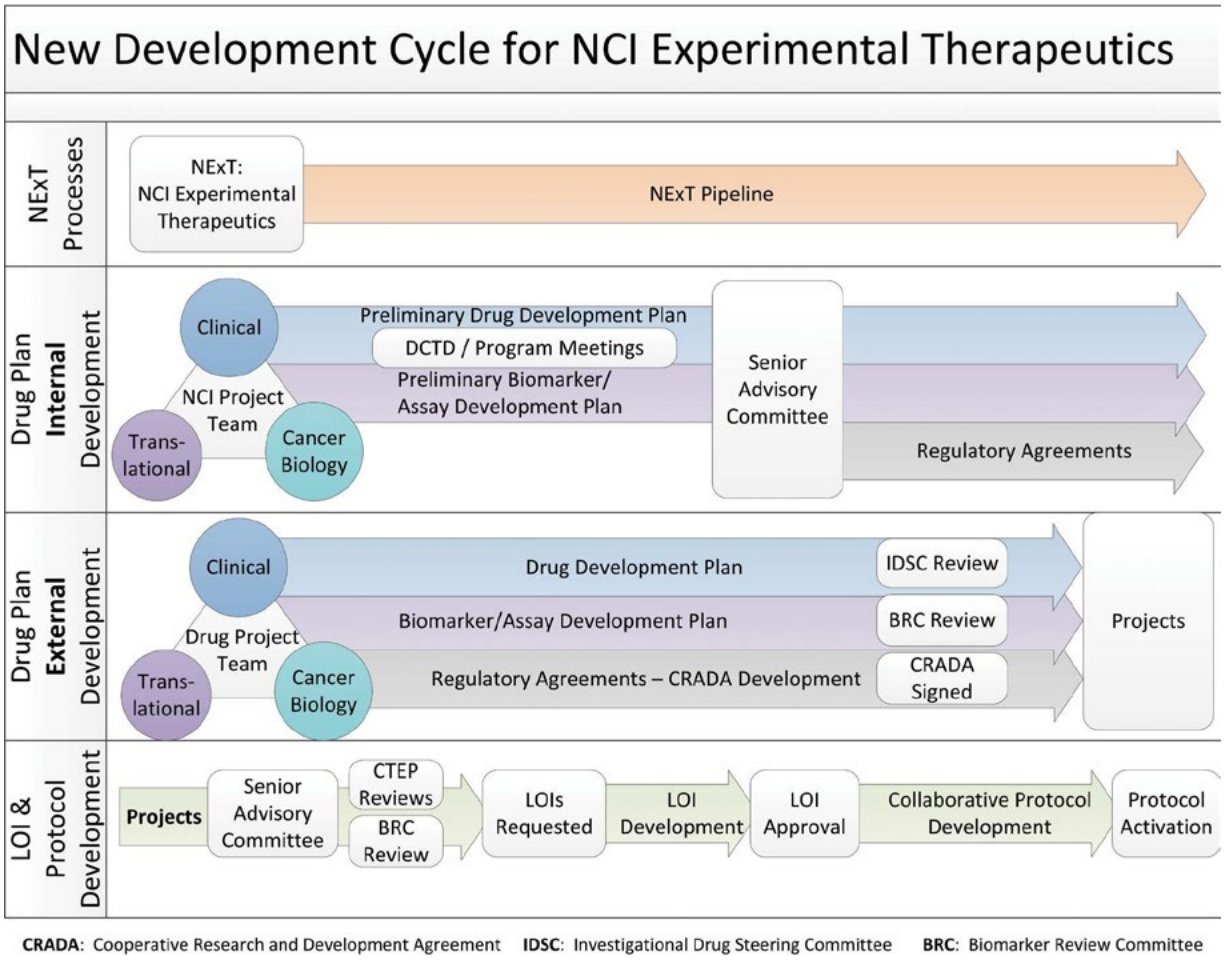



FIGURE 46: WORKFLOW FOR THE PROJECT TEAM-DRIVEN APPROACH TO NCI CLINICAL TRIALS.

**Table 29** shows the Drug Development Project Teams assembled in 2020-2023.

| Year | Agent | Mechanism of Action | Target |
|---|---|---|---|
| 2020 | zlpatasertib | an ATP-competitive AKT inhibitor, blocks the phosphoinositide 3-kinase (PI3K)/AKT pathway | PI3K/AKT |
| 2020 | Selinexor | Selective Inhibitor of Nuclear Export | XPO1 |
| 2022 | CBX-12 | Alphalex conjugate that contains a topoisomerase I inhibitor exatecan | TOPO1 |

TABLE 29: NCI DRUG DEVELOPMENT PROJECT TEAMS (2020-2023).

CTEP has also acquired agents that, due to a very limited drug development plan, have not required a Drug Development Project Team (**Table 30**).

| Year | Agent | Mechanism of Action | Target |
|---|---|---|---|
| 2019 | AZD6738 | Inhibits Ataxia Telangiectasia and Rad3 related (ATR) serine/threonine protein kinase | ATR |
| | Darolutamide | A novel nonsteroidal androgen receptor (AR) antagonist | AR |
| 2020 | ASTX727 | DNA methyltransferase (DNMT) inhibitor | HDAC |
| | CA-4948 | Inhibits TLR and IL-1R signaling; Inhibits myddosome signaling; inhibits NFkB activity | IRAK4 |
| | AMG-510 | Inhibits G12C-mutated KRAS | KRAS |
| | Capivasertib | binds to and inhibits all AKT isoforms | AKT |
| 2021 | Mosunetuzumab | Simultaneously targets CD20 on B-cells and CD3 on T-cells by redirecting endogenous T-cells to engage and eliminate tumor-specific CD20-expressing B-cells. | anti-CD20/CD3 |
| | Tiragolumab | Binds and inhibits T cell immunoreceptor with Ig and ITIM domains (TIGIT) expressed on the subsets of activated T cells, natural killer (NK) cells and tumor-infiltrating immune cells. | TIGIT |
| | Eltanexor | Selective Inhibitor of Nuclear Export | XPO1 |
| | M1774 | Selectively inhibits ataxia telangiectasia mutated and Rad3 related (ATR) protein kinase | ATR |
| | Nemvaleukin Alfa | Binds to the IL-2R complex to preferentially activate memory cytotoxic CD8+T cells and natural killer (NK) cells without expanding CD4+ Tregs. | IL-R2 |
| | Iberdomide | Immunomodulatory therapeutic | |
| 2022 | Giredestrant | Selective estrogen receptor degrader (SERD) | SERD |
| | Actimab-A | Antibody Radioconjugate comprising the alpha-particle emitting radionuclide actinium-225 (Ac225) conjugated to lintuzumab, a humanized anti-CD33 monoclonal antibody | anti-CD33 |
| | Acalabrutinib | selectively inhibits Bruton's tyrosine kinase (BTK) with minimal effects on TEC, EGFR, and ITK signaling. | |
| | Inavolisib | Selectively inhibits the Class I PI3Kα isoform (p110α), with minimal inhibition of the Class I PI3K β, γ, and δ isoforms | Human Epidermal Growth Factor Receptor 2 (HER 2) |
| | Cirtuvivint (SM08502) | Inhibits CDC-Like Kinases (CLK) and Dual-Specificity Tyrosine-Regulated Kinases (DYRK) | FGFR |
| | Glofitamab | promotes T-cell activation, proliferation, and tumor cell killing upon binding to CD20 on malignant cells | radiopharmaceutical |
| | Amivantamab | Inhibits EGFR and MET signaling | CD47 Receptor |
| 2023 | Fianlimab and Cemiplimab | Inhibits immune checkpoint receptor LAG-3<br>Inhibits programmed death receptor-1 | Anti-CD33/Anti-PD1 |
| | REGN5093 | Binds to two distinct epitopes of MET, thus blocking HGF binding and induces internalization and degradation of MET | METxMET |
| | Mezigdomide | binds to cereblon (CRBN), thereby affecting the ubiquitin E3 ligase activity, and targeting certain substrate proteins for ubiquitination | CELMod |

TABLE 30: NCI AGENTS WITH LIMITED DRUG DEVELOPMENT (2020-2023).

## REGISTRATION OF CLINICAL TRIAL SITE RESEARCH STAFF

More than 23,000 physician investigators are registered with PMB to participate in clinical investigations, of which approximately 20,000 (87%) are domestic and 3,000 (13%) are international researchers. In addition, approximately 54,300 trial-associated health care professionals are registered with NCI. The help desk manages more than 64,000 inquiries and communications annually in support of the registry. Registration is accomplished via the NCI Registration and Credential Repository database, which documents that the appropriate education, training, and qualifications of research staff required to conduct DCTD-sponsored and funded research are obtained and current. Additional PMB registration activities are listed in **Table 31**.

| Activity | Details and Accomplishments |
|---|---|
| Investigational agent shipments authorized in support of DCTD-sponsored and supported trials worldwide | Average of 22,000 shipments annually, 20,000 of these to domestic sites |
| Blinded study/patient-specific supply order shipments (for 8 active blinded, placebo-controlled, and patient-specific clinical trials) | Approximately 2,000 annually |
| Open-label study standard order shipments | 20,000 annually |
| Specialized resources to support shipment of agents to international clinical trial sites | During the reporting period, agents were shipped to Australia, Canada, Israel, Japan, South Korea, New Zealand, Saudi Arabia, Singapore, and Trinidad and Tobago. |
| Specialized resources to support randomized, placebo-controlled, and patient-specific supply clinical trials, including the development, implementation, support, and monitoring of blinded and patient-specific clinical trials | At the end of 2023, there were 8 active blinded and patient-specific trials and more in development. |
| Investigator Community Service-Support Projects | • Online tools allow the investigator to meet regulatory requirements, including the Treatment Referral Center that can improve the accessibility of CTEP IND agents for certain patients.<br>• PMB After Hours is an e-mail address for investigators and research staff to send questions 24/7/365 (16,000+ e-mails and 400+ telephone inquiries addressed annually).<br>• Maintenance and secured distribution of Investigator Brochures (IBs) that the investigator and research staff need to develop and conduct clinical investigations<br>• Training videos support site education for investigational agent management and reinforce PMB policies and procedures.<br>• AURORA is PMB's comprehensive and innovative agent inventory management application that allows investigators and research staff to order investigational agents, monitor shipments, access stock recovery notifications and IBs, and maintain drug accountability records in a future enhancement.<br>• Enhanced investigator and sub-investigator registration website and resources to support the NCI Registration and Credential Repository<br>• Development and maintenance of the NCI Formulary website<br>• Meet regulatory requirements to support agent distribution processes for IND Exempt clinical investigations |

TABLE 31: PMB REGISTRATION ACTIVITIES.

# CLINICAL TRIALS OPERATIONS AND INFORMATICS BRANCH (CTOIB) ACTIVITIES

## PROTOCOL AND INFORMATION OFFICE (PIO)

The PIO collects, processes, tracks, and monitors (**Table 32**) all protocol-related information between CTEP and its extramural collaborators, as well as with other CTEP and NCI programs to:

- Facilitate the development and conduct of quality clinical trials in the most efficient and expeditious manner possible
- Minimize the administrative burden related to clinical trial development, conduct, and management on CTEP staff and the extramural community
- Capture protocol-related keywords and milestones into CTEP ESYS to assist with CTEP decision making
- Promote, inform, and educate all concerned parties regarding NCI programs, policies, and objectives related to clinical trial development, conduct, and management

| Item | 2020 | 2021 | 2022 | 2023 |
|---|---|---|---|---|
| LOIs | 100 | 90 | 86 | 78 |
| Concepts | 72 | 84 | 58 | 64 |
| New protocols | 76 | 82 | 89 | 82 |
| Protocol revisions | 371 | 249 | 315 | 305 |
| Protocol amendments | 802 | 805 | 693 | 729 |

TABLE 32: ITEMS PROCESSED BY THE PROTOCOL AND INFORMATION OFFICE (CY 2020-2023).

## CTEP CLINICAL ONCOLOGY RESEARCH ENTERPRISE (CORE)

The CTEP CORE increases collaboration and is an integrated solution across multiple IT systems and contractors. CTEP CORE supports evolving and more complex science, emphasizes harmonization, and streamlines integration. The CTEP-CORE comprises integrated applications from CTEP ESYS, the CTSU ESYS, and applications (e.g., MediData RAVE) that work together to support NCI clinical trial conduct and reporting.

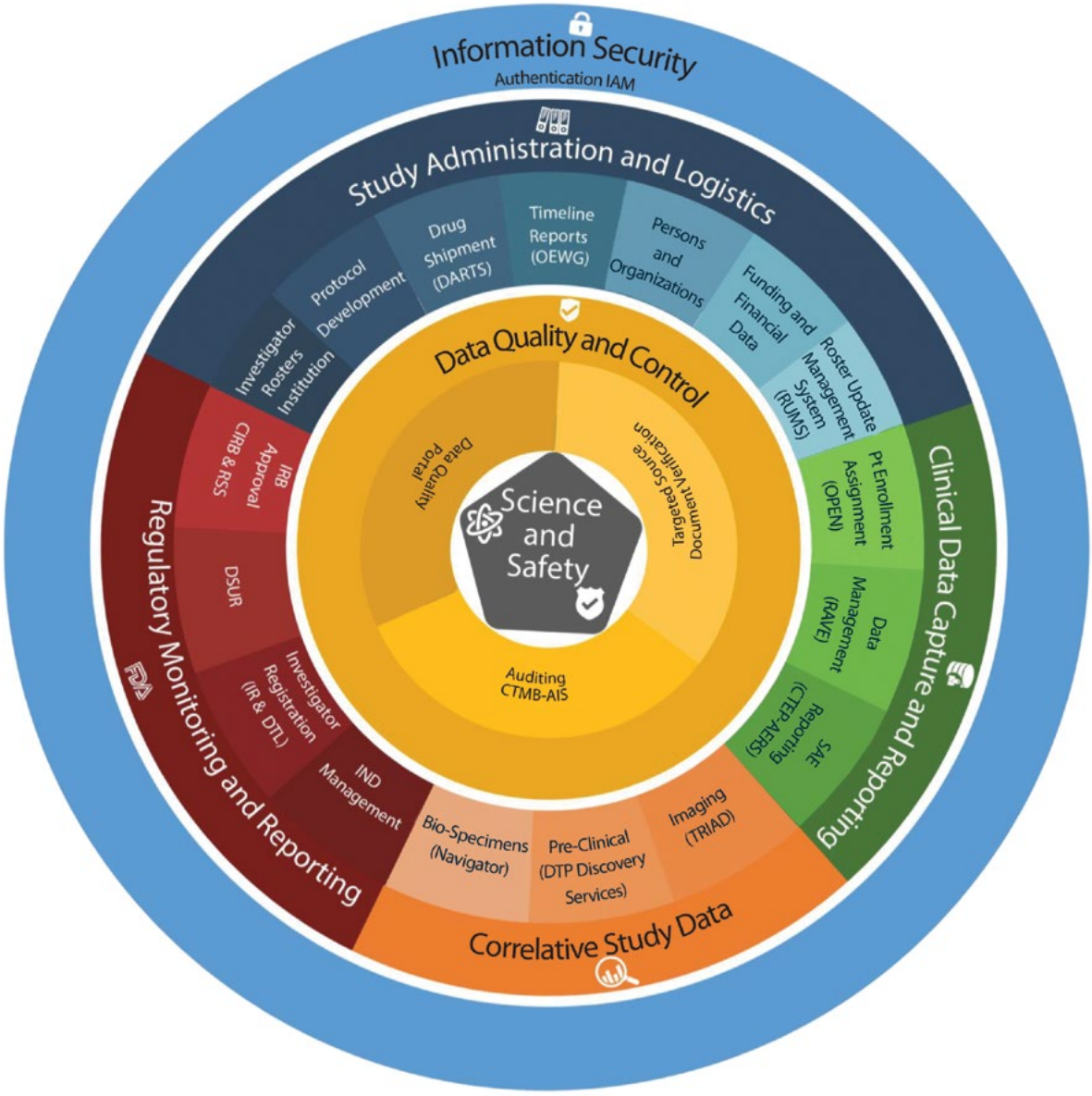



**FIGURE 47: CTEP CLINICAL ONCOLOGY RESEARCH ENTERPRISE (CORE).**
Provides secure, flexible, and scalable operational infrastructure to a robust clinical trials program.

## CTEP ENTERPRISE SYSTEM (CTEP ESYS)

The CTEP ESYS is a multi-application system that fosters broad investigator participation, patient safety, and scientific advancement. It facilitates clinical trial conduct and management by:

- Capturing data and translating it into a usable and streamlined format to address scientific, safety, regulatory, and administrative requirements of clinical trials
- Eliminating data redundancy throughout the oncology community through integrated data systems
- Improving communication between CTEP and its collaborators
- Assuring the security and confidentiality of proprietary and patient information
- Supporting broad patient access to clinical trials
- Expediting the protocol development and review process within both clinical trial organizations and reviewing bodies

The CTEP ESYS updated several systems (new and enhanced) used for submitting and tracking clinical trial information to CTEP. Tools are being upgraded to broaden their use for diagnostic imaging, cancer prevention, and cancer control. Additional flexibility is being incorporated to support evolving scientific needs, including translational research, precision medicine, and other genomic initiatives. Software upgrades will ensure that CTEP ESYS applications remain secure, flexible, and relevant with technology, operational, and scientific advancements.

CTEP staff updated the following systems:

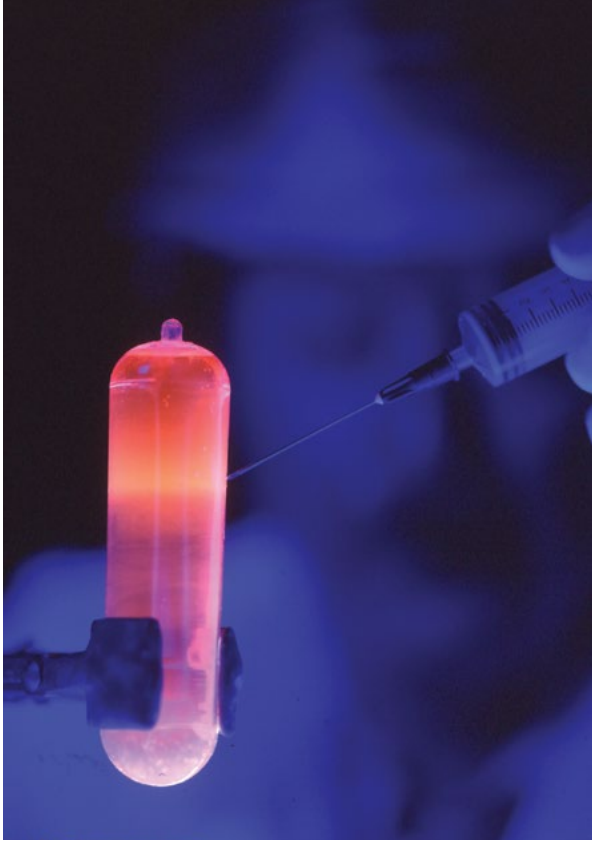
- AURORA—Consolidates PMB's inventory management system and inventory management activities with clinical trial sites' inventory management activities in one centralized system.
- CTEP Adverse Event Reporting System (CTEP-AERS)—Following the FDA's new requirements (in line with the ICH guidance), the CTEP-AERS system requires the external community (clinical trials staff at sites) to have either an IAM (Identity and Access Management) or ID.me account to access the system.
- Identity and Access Management (IAM)—Securely manages access to applications by the external community and CTEP, allows single-source sign-on to all CTEP-managed applications, and is required to include Identity Proofing/Verification (IP) and Multi-factor Authentication.
- Study Abstraction Review & Tracking System (START)—Allows CTEP to enter, modify, and retrieve data on study documents such as LOIs, concepts, protocols, revisions, and amendments received from researchers conducting clinical trials through the protocol lifecycle, from review and approval to activation and completion.
- CTMB Audit Information System (AIS)—Schedules and performs audits at sites conducting CTEP-sponsored studies
- Multiple Systems—Integration support to accommodate Targeted Radiopharmaceutical Facilities (TRFs) and Imaging and Radiation Treatment Facilities (IRTFs)

## BIOMARKER REVIEW AND TRACKING

CTOIB supports the review and tracking of biomarker plans for early-phase CTEP sponsored trials under IND. This includes identifying and tracking biomarker plan review requirements, coordinating review processes, receiving and cataloging biomarker-review related documents, and coordinating with colleagues within CTEP and CDP to ensure efficient biomarker review processes. CTOIB also maintains and provides quality control oversight for a repository of the biomarker plans for early-phase CTEP-sponsored trials under IND in START. A new module for START was developed and implemented to track biomarker review for early phase CTEP-sponsored studies under CTEP IND. It allows for the monitoring of the individual steps for specific biomarker review processes, such as the Biomarker Review Committee (BRC), from initial requirement identification to completion. Features within the Biomarker Module enable tracking of biomarker-related funding and use of NCI resources, such as the National Clinical Laboratory Network (NCLN) laboratories and the Early-Phase and Experimental Clinical Trials (EET) Biobank.

## CANCER TRIALS SUPPORT UNIT (CTSU)

The goals of the CTSU are to increase physician and patient access to NCI-sponsored clinical trials, reduce the regulatory and administrative burden on investigators and site staff par-



ticipating in clinical trials, identify and implement operational efficiencies, and standardize operational processes through informatics solutions. The CTSU coordinates with NCI, other NCI CORE services (e.g., Central Institutional Review Board (CIRB)), and the lead protocol organizations to simplify admittance to NCI-funded clinical trials for qualified clinical sites and support the conduct of those clinical trials.

More than 50,968 registered CTSU members have access to a range of information and support services such as the Oncology Patient Enrollment Network (OPEN), which is a web-based patient enrollment system that can enroll patients 24/7. The CTSU also offers the Regulatory Support System (RSS), which serves as a centralized repository for regulatory documents for NCI-supported clinical trials. The CTSU facilitates several integrations with Medidata Rave, the clinical data management system used for the entry and management of clinical data that supports the collection of clinical trial data across the NCI-supported networks and improves data quality. The CTSU developed and supports the National Clinical Trials Network (NCTN) Navigator, is responsible for Awareness, Education, and Training (AET) activities to facilitate clinical trial enrollment and execution, facilitates the creation of National Coverage Analysis (NCA) Documents, and generates Electronic Medical Record (EMR) extractions for trial requirements.

## CENTRALIZED PROTOCOL WRITING SUPPORT (CPWS)

CPWS provides centralized support for protocol and informed consent document writing and editing, from the LOI approval through study closure (**Table 33**). The CPWS also provides support for writing revisions, and CIRB and FDA requested changes, to meet Operational Efficiency Working Group (OEWG) timelines. The CPWS works directly with the PI and members of the protocol Study Team to:

- Draft the initial protocol, informed consent document (ICD), and associated documents (protocol submission worksheet [PSW]) for submission to CTEP.
- Draft revisions and changes associated with the protocol and ICD.
- Monitor protocol review and submission timelines for protocols it authors, to facilitate protocol activation by OEWG deadlines.

| Item | 2020 | 2021 | 2022 | 2023 |
|---|---|---|---|---|
| Original protocols | 23 | 19 | 22 | 14 |
| First revisions | 18 | 21 | 23 | 14 |
| Other revisions | 92 | 77 | 57 | 52 |

TABLE 33: NUMBER OF PROTOCOLS DRAFTED AND REVISED FROM 2020-2023.

## NCI CENTRAL INSTITUTIONAL REVIEW BOARD (NCI CIRB)

The NCI CIRB helps reduce the administrative burden on local IRBs and investigators while continuing a high level of protection for human research participants. The CIRB, with one centralized review, enables investigators to enroll patients into network trials significantly faster than when employing the traditional method of assessment, which requires trial investigators in each site to obtain approval from a local IRB.

The CIRB consists of four Boards: Pediatric, Late Phase Emphasis, Early Phase Emphasis, and Cancer Prevention. The CIRB reviews nearly all clinical trials conducted via the NCTN, ETCTN, NCORP, and DCP Phase 1-2 Prevention Consortia programs. Thus, all study phases, treatment modalities, participant ages, cancer diagnoses, related conditions, and interventions across the entire cancer continuum can be coordinated. From 2020-2023 (**Table 34**), the CIRB maintained the established review timelines even with an increased number of studies to review.

As of August 31, 2023, 616 signatory institutions representing 2,292 sites were enrolled in the CIRB. This includes 99% of the NCTN, 99% of the ETCTN, and 99% of the NCORP institutions. The CIRB has covered more than 50,000 protocols since its inception in 2001.

| Year | Number of New Studies Approved |
|---|---|
| 2020 | 98 |
| 2021 | 94 |
| 2022 | 84 |
| 2023 | 84 |

TABLE 34: NUMBER OF NEW STUDIES REVIEWED BY CIRB (2020-2023).

## COMMON NETWORK-WIDE CLINICAL DATA MANAGEMENT SYSTEM (CDMS)

NCI deployed Medidata Rave, which is a standard CDMS, in the spring of 2012 across its clinical trial networks to improve operational efficiency, participant safety, and scientific advancement. Rave is integrated with multiple NCI applications (**Figure 48**), including the Cancer Therapy Evaluation Program Identity and Access Management (CTEP-IAM) Single Sign-On (SSO), OPEN, CTEP-AERS, Data Quality Portal (DQP), Site Audit Report (SAR), Central Monitoring Portal (CMP), and Core Data Repository (CORE-DR), and CTSU Enterprise Transaction Engine for Rave (CENTER). Future integrations will support specimen tracking and site performance evaluation (using the auditing and central monitoring data).

The goals of using a common CDMS and related systems are to improve efficiency of multi-center trial operations through communication, elimination of duplicative effort, and the development and use of standard systems and processes for trial sponsors and participating sites. With the standard CDMS, NCI has been successful in facilitating a consistent adoption of Medidata Rave within the NCTN community, and it is now providing a broad package of support to users as they conduct clinical trials using Medidata Rave within the NCI Enterprise Systems environment.

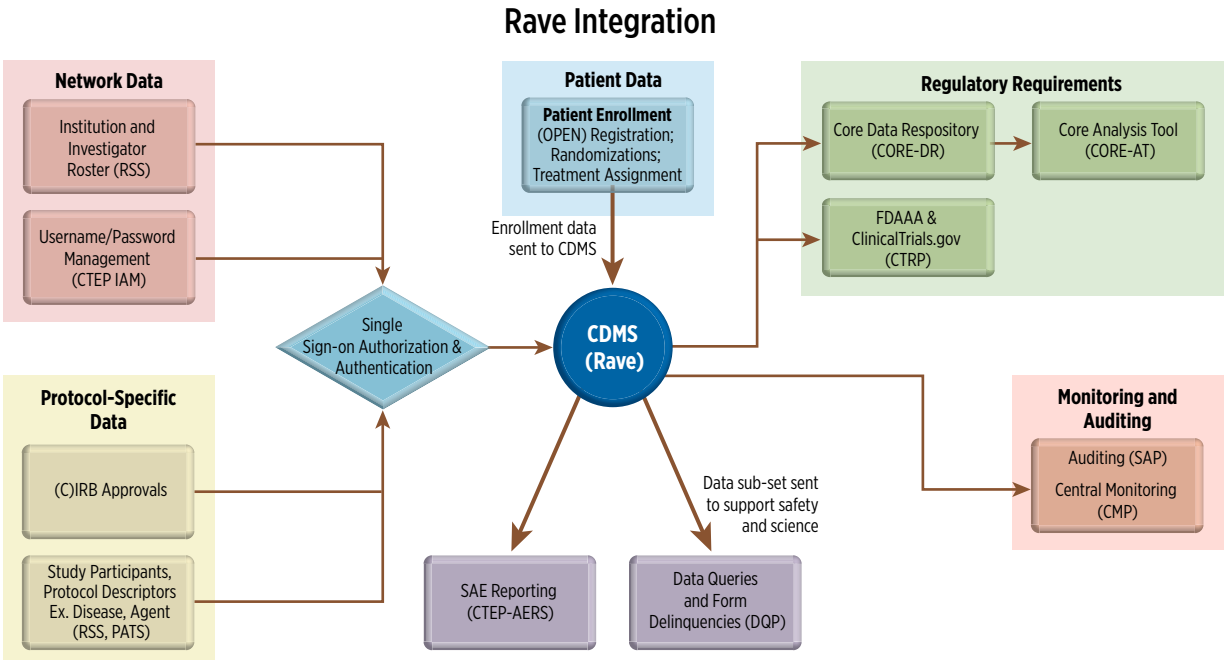



FIGURE 48: INTEGRATION OF THE METADATA RAVE CLINICAL DATA MANAGEMENT SYSTEM (CDMS) INTO THE NCI CLINICAL TRIALS IT INFRASTRUCTURE.

# PEDIATRIC CLINICAL TRIALS

CTEP supports a comprehensive research program for children with cancer that ranges from discovering new therapeutic targets, to definitive clinical evaluation of new therapeutic strategies in phase 3 trials, to studying the late effects of successful cancer treatment in long-term survivors of childhood cancers. This pediatric research program is critical because, despite the progress made in pediatric drug development through the RACE for Children Act, it remains challenging for pharmaceutical companies to conduct all the clinical trials that are needed to advance treatment for children with cancer.

CTEP primarily sponsors pediatric clinical trials through the NCTN COG. Additional pediatric trial consortia include the Pediatric Early Phase Clinical Trials Network (PEP-CTN), and the Pediatric Brain Tumor Consortium (PBTC), with ongoing plans for the PBTC to be transitioned into the PEP-CTN. CTEP also supports a pediatric preclinical testing program (the PIVOT Program) to generate data to facilitate prioritizing agents for evaluation in children with cancer.

## THE NCI PEDIATRIC PRECLINICAL IN VIVO TESTING (PIVOT) PROGRAM

The PIVOT Program systematically tests novel anticancer agents in vivo against pediatric preclinical models to develop datasets that can assist clinical researchers in selecting the agents and combination therapies that are most likely to be effective for childhood solid tumors and leukemias. The PIVOT Program builds upon nearly 20 years of experience achieved through the Pediatric Preclinical Testing Program (PPTP) and Pediatric Preclinical Testing Consortium (PPTC), during which more than 100 anticancer agents were systematically studied, providing the preclinical data that supported the advancement of a number of these agents into pediatric clinical testing. Equally importantly, the PPTP and PPTC identified agents with limited activity for which focused pediatric development could be deferred without additional rationale.

The PIVOT Program began its 5-year funding period in the second half of 2021. Jackson Laboratory serves as the Coordinating Center for this international consortium, which consists of research programs for the *in vivo* testing of agents using patient-derived xenograft (PDX) models in **Table 35**.

Recent accomplishments include:

- Identification of tumor-regressing activity for the HER2-targeting antibody-drug conjugate trastuzumab deruxtecan (DS-8201a) for multiple pediatric solid tumors, including osteosarcoma and Wilms tumor (Hingorani, 2022)
- Identification of activity in osteosarcoma models for an antibody-drug conjugate targeting LRRC-15 (ABBV-085) and for an MT1-MMP-targeted Bicycle toxin conjugate (BT1769) (Hingorani, 2021)
- Demonstration of B7-H3 as a high-priority pediatric solid tumor surface antigen for antibody-drug conjugate development with promise for osteosarcoma, Wilms tumor, neuroblastoma, and rhabdomyosarcoma (Kendsersky, 2021)
- Identification of activity for a DLL3-targeting antibody-drug conjugate in neuroblastoma PDX models; documentation of variability of DLL3 cell surface expression in neuroblastoma specimens with many having limited DLL3 expression (Krytska, 2022)
- Documentation of limited activity for the dual PI3Kδ and PI3Kγ inhibitor duvelisib against pediatric ALL xenografts and for the PI3K inhibitor copanlisib against osteosarcoma xenograft models (Randall, 2023)

| Cancer Program | Lead Investigator(s) | Institution |
|---|---|---|
| Osteosarcoma | Richard Gorlick, MD | MD Anderson Cancer Center; Houston, TX |
| Sarcoma and renal tumors | Raushan Kurmasheva, PhD and Peter Houghton, PhD | Greehey Children's Cancer Research Institute; San Antonio, TX |
| Brain Tumor | Xiao-Nan Li, MD, PhD | Lurie Children's Hospital; Chicago, IL |
| Neuroblastoma | Yael Mosse, MD and John Maris, MD | Children's Hospital of Philadelphia; Philadelphia, PA |
| Acute lymphoblastic leukemia (ALL) Research | Richard Lock, PhD | Children's Cancer Institute; Sydney, Australia |
| Rhabdomyosarcoma and other soft tissue sarcoma | Michael Dyer, PhD and Elizabeth Stewart, MD | St. Jude Children's Research Hospital |
| Solid tumor research | Andrew Kung and Filemon Dela Cruz | Memorial Sloan-Kettering Cancer Center |

TABLE 35: RESEARCH PROJECTS IN THE PIVOT PROGRAM.

## PEDIATRIC EARLY PHASE CLINICAL TRIALS NETWORK (PEP-CTN)

The PEP-CTN was established in 2019 to continue the work of the COG phase 1 Consortium. Its overarching goal is to identify and develop effective new agents for children and adolescents with cancer, through rational and efficient clinical and laboratory research. The PEP-CTN designs and conducts pediatric early-phase trials including phase 1 trials that often include phase 2 expansion cohorts. The PEP-CTN conducts pilot studies of novel agents/regimens to determine their tolerability to enable promising agents/regimens to proceed to definitive testing in phase 3 clinical trials. Important characteristics of the PEP-CTN include:

- Conducts trials with seamless transitions from phase 1 to phase 2 testing
- Uses the Pediatric Early Phase Agent Prioritization Committee (APC) to prioritize agents for evaluation by the PEP-CTN and to expedite the pace at which novel investigational agents enter clinical testing in children with cancer
- Centrally monitors all PEP-CTN clinical trials
- Incorporates relevant biological/genomic evaluations to establish eligibility for PEP-CTN clinical trials and/or to facilitate factors determining the activity of agents studied by the PEP-CTN.

Recent accomplishments include:

- A clinical trial (NCT02304458) evaluating nivolumab as a single agent and in combination with ipilimumab against a range of pediatric solid tumors.[22] The limited activity observed for nivolumab and nivolumab plus ipilimumab for pediatric cancers (excepting Hodgkin lymphoma) is in sharp contrast to the high level of activity observed for these agents against many adult cancers.
- A clinical trial (NCT01922076) evaluating the Wee1 kinase inhibitor adavosertib (AZD1775) with radiation for children with diffuse intrinsic pontine glioma (DIPG).[23] A recommended phase 2 dose was defined, but there was no evidence for prolongation of survival compared to that observed in previous clinical trials for children with DIPG combining radiation therapy with agents that were determined to be ineffective.
- A phase 2 clinical trial of the Wee1 kinase inhibitor adavosertib (AZD1775) in combination with irinotecan for several pediatric solid tumors and CNS tumors.[24] Neuroblastoma was the only cancer for which some level of activity was observed, and little or no activity was observed for CNS embryonal tumors (e.g., medulloblastoma) or for rhabdomyosarcoma.
- Clinical trial results presented at AACR and ASCO describing dosing recommendations and AE profiles for novel agents studied in PEP-CTN clinical trials, including trastuzumab deruxtecan, the NEDD8-activating enzyme inhibitor pevonedistat, and the ATR inhibitor elimusertib.[25,26,27]

## PEDIATRIC BRAIN TUMOR CONSORTIUM (PBTC)*

PBTC's primary objective is to conduct timely phase 1 and 2 clinical evaluations of new therapeutic drugs, local delivery of agents, immunotherapies, and radiation treatment strategies in children with brain tumors. During this reporting period, the PBTC's active clinical trials evaluating novel treatment approaches, include evaluation of:

- the G207 oncolytic virus (NCT04482933)
- A HER2-targeted CAR T cell for children with ependymoma (NCT04903080)
- SurVaxM, which is a peptide vaccine conjugate designed to activate the immune system against survivin (NCT04978727)
- the MET inhibitor salvolitinib (NCT03598244)
- the Optune device that is being used to apply tumor treating fields to diffuse intrinsic pontine gliomas (NCT03033992)

Recent findings from PBTC clinical trials include:

- The MEK inhibitor selumetinib was evaluated in a clinical trial (NCT01089101) that included a cohort for children without NF1 who had recurrent/progressive optic pathway and hypothalamic low-grade gliomas. Selumetinib

[22] Davis KL, Fox E, Isikwei E, et al. Clin Cancer Res. 2022 Dec 1;28(23):5088-5097.
[23] Mueller S, Cooney T, Yang X, et al. Neurooncol Adv. 2022 May 20;4(1):vdac073
[24] Cole KA, Ijaz H, Surrey LF, et al. Cancer. 2023 Jul 15;129(14):2245-2255
[25] Reed DR, Janeway KA, Minard CG, et al. J. Clin. Oncol. 2023;41:Abstract #11527
[26] Ortiz MV, Bender JLG, Minard CG, et al. J. Clin. Oncol. 2023;41:Abstract #e15131
[27] Foster J, Reid JM, Minard CG, et al. J. Clin. Oncol. 2021;39: Abstract #10019

induced responses and prolonged disease stability based upon radiographic response, PFS, and visual outcomes (Fangusaro, 2021).

- The CDK4/6 inhibitor palbociclib was evaluated and a recommended phase 2 dose of 75 mg/m$^2$ for 21 days per treatment course was determined. Higher palbociclib exposure was associated with higher rates of neutropenia, and no objective responses were observed.
- The addition of vorinostat with isotretinoin to intensive chemotherapy for young children with embryonal tumors was found to be tolerable in a PBTC pilot study (NCT00867178), and the Children's Oncology Group is considering pursuing this strategy in a future study.[28]
- The addition of veliparib to radiation followed by temozolomide and veliparib for children with newly diagnosed diffuse intrinsic pontine glioma (DIPG) was tolerated, but it did not improve survival for this patient population (NCT01514201).

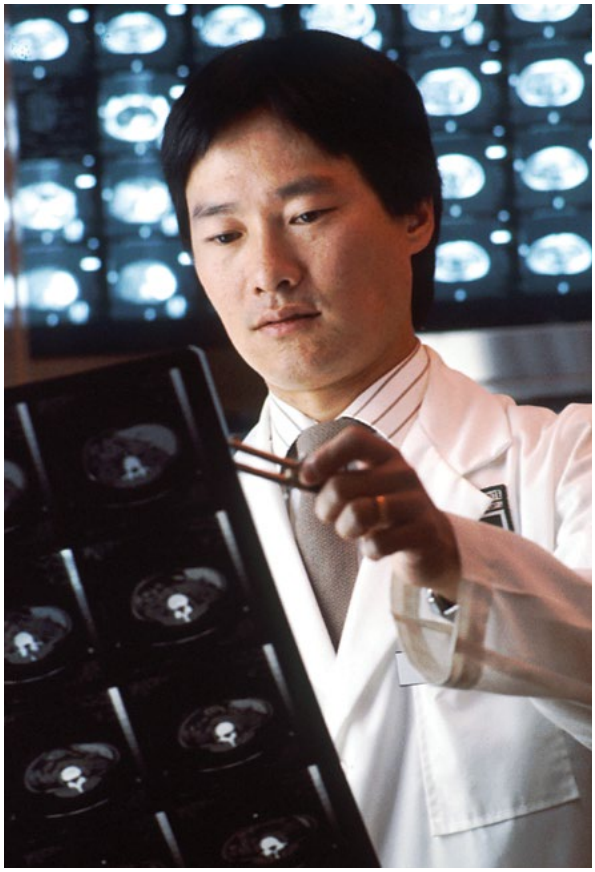
*Note added at time of printing: NCI began to transition the PBTC to the PEP-CTN in late 2025.

## CHILDHOOD CANCER SURVIVOR STUDY (CCSS)

The CCSS was established in 1994 as a multi-institutional, multidisciplinary collaborative research resource funded through the U24 mechanism to systematically evaluate long-term outcomes among children diagnosed with cancer between 1970 and 1986 who survived five or more years from diagnosis. After expansion to include children diagnosed 1987-1999 the CCSS now spans three decades and is the world's largest established open resource for survivorship research, consisting of 38,036 childhood cancer survivors and approximately 5,000 of their siblings.

Major accomplishments of the CCSS are:

- Extensive use by the research community resulting in 450 published or in press manuscripts now cited over 26,500 times, 430 abstracts accepted or presented, 66 investigator-initiated grants totaling $80 million.
- Collaborations with other researchers in the field, including the Children's Oncology Group and six investigator-led randomized intervention trials funded by NCI.



- A recent study in *The Lancet* looked at lifestyle habits and long-term mortality of adults who had cancer when they were children. Cancer survivors who led healthy lifestyles improved their long-term survival by as much as 20% compared to those who did not. This includes positive steps such as maintaining a healthy weight, drinking only moderate amounts of alcohol, not smoking, and exercising at the level recommended by the CDC. Major risk factors for shortened lifespan among survivors included heart disease, high blood pressure, and diabetes, all of which are seen in the general population.
- CCSS investigators have identified that survivors of childhood cancer have higher rates of physiologic frailty than their siblings and are like people decades older who have not had cancer, suggesting they experience an acceleration in their underlying biologic aging. More recently, with two decades of follow-up, investigators

[28] Leary SES, Kilburn L, Geyer JR, et al. Neuro Oncol. 2022 Jul 1;24(7):1178-1190

demonstrated that survivors have an accelerated rate of burden of co-morbidities and new onset cognitive problem as they age, suggesting it is now critical to identify and target these rapidly aging survivors with interventions to prevent or slow the process.

- CCSS has been foundational for developing individual risk prediction models that healthcare providers and survivors can use to estimate their individual risk for long-term outcomes, including recent new risk prediction calculators for: acute ovarian failure, breast cancer development, cardiovascular disease, and kidney failure. A suite of clinically useful risk prediction calculators is available on the CCSS website.
- Evidence for a novel association between anthracycline exposure in childhood and increased risk for subsequent breast cancer was strengthened by identification of a dose response effect between anthracycline exposure and breast cancer risk and discovery of an additive effect between anthracyclines and chest irradiation. This increased risk for breast cancer attributable to anthracycline exposure was recently confirmed in a multi-cohort study published in *Nature Medicine* that included CCSS and will provide new guidance for use of anthracycline chemotherapy.
- A study of late effects in long-term survivors of standard risk ALL found that the incidence of long-term side effects was low. This enables oncologists to reassure children with cancer/families that cure of their child's cancer is not accompanied, in most cases, by a diminished quality of life.
- CCSS collaboration with other large cohorts identified that the dose equivalence of mitoxantrone to doxorubicin to be 10.5:1. Thus, the previous hematologic-based doxorubicin dose equivalency of mitoxantrone (4:1) appeared to significantly underestimate the association of mitoxantrone with long-term cardiomyopathy risk. This finding provides important guidance for the use of mitoxantrone in clinical trials.
- CCSS has been a critical resource for evidence for the COG Guidelines for Long-Term Follow-up of Children and Adolescent with Cancer. To date, 50% of guidelines after chemotherapy and radiotherapy exposure are informed by CCSS publications (82 total CCSS references in version 5.0).

# MAJOR CO-FUNDED NETWORKS

## BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK (BMT CTN)

The National Heart, Lung, and Blood Institute (NHLBI) and NCI co-sponsor the BMT CTN. Established in 2001, the BMT CTN conducts large, multi-institutional trials to improve outcomes of cellular therapies, such as hematopoietic cell transplantation (HCT), cellular vaccines, and chimeric antigen receptor T-cells (CAR-T) for patients facing life-threatening non-malignant and malignant disorders of the hematopoietic and immune systems. The BMT CTN infrastructure encompasses a network of 20 clinical core centers and 75 affiliate centers across the US and is managed by a unique Data Coordinating Center (DCC) consisting of 3 organizations (Center for International Blood and Marrow Transplant Research (CIBMTR), National Marrow Donor Program (NMDP)/Be The Match, and The Emmes Corporation) with extensive cellular therapy research experience. The significance of the network is its function, which provides a forum for research planning, strategy, and priority setting in HCT-related approaches to life-threatening diseases. The co-sponsorship of this infrastructure creates an effective trans-Institute collaboration that spans other funded clinical research networks supported by both institutes.

The BMT CTN's goals are to improve HCT outcomes, evaluate promising novel cell/gene therapies, and rapidly disseminate study results to improve the scientific basis for the treatment of patients in need of HCT therapy as described in two solicitations: RFA-HL-17-018 and RFA-HL-17-019. During this 7-year award period, which began in September 2017 and will end in August 2024, the BMT CTN serves as a national program for evaluating the use of HCT as a curative platform for hematologic malignancies by unifying the HCT community, forming essential collaborations, and defining clinical practices and standards.

The network has contributed to the science of transplantation, to the evolution of clinical practice standards, and to the improvement in clinical management of transplant recipients. For instance, important advances in improving autologous HCT for multiple myeloma (MM) and allogeneic HCT for acute myelogenous leukemia (AML), myelodysplastic syndromes (MDS) and other malignancies have led to changes in standard of care for these patients. Moreover, collaborations with the NCI-sponsored AIDS Malignancy Consortium (AMC) provided evidence for the use of autologous and allogeneic HCT for HIV+ patients with lymphoma

and leukemia, respectively. Collaborating with the NCTN introduced new HCT concepts developed by the NCTN and/or the BMT CTN based on novel CAR T-cell therapy and drug combinations to improve survival in patients with lymphomas. BMT CTN protocols are also being used by CMS for Coverage with Evidence Development to provide Medicare reimbursement of HCT in patients with MDS and sickle cell disease (SCD), thus extending access to curative therapies. Highlighted in the section below are examples that illustrate such significant findings from recently completed trials and the potential to impact clinical outcomes/practice from ongoing trials.

- *BMT CTN 1102 – Reduced-Intensity HCT for MDS NCT02016781 – COMPLETED]*: This biologic assignment trial compared allogeneic HCT with non-HCT standard of care in patients with MDS, assigning patients based on having (or not) a human leukocyte antigen (HLA)-identical donor. Results indicated a significant survival advantage with HCT, without compromising quality of life. This data has been incorporated into recommendations for MDS therapy in the current National Comprehensive Care Network guidelines.
- *BMT CTN 1506 – AML FLT3 Maintenance Therapy [NCT02997202 – COMPLETED]*: This is a randomized study of FLT3 inhibition with gilteritinib versus placebo after allogeneic HCT for FLT3+ AML. This critical trial will assess whether the maintenance therapy would lead to improved relapse-free survival.
- *BMT CTN 1702 – Alternative Donor Cell Cohort [NCT03904134 – ACTIVE]*: This is an interventional and observational study to understand factors affecting the likelihood of transplantation in patients without a human leukocyte antigen (HLA) matched family donor and to compare outcomes associated with pursuing an HLA-identical unrelated versus other alternative donor graft sources. Patients with AML, ALL, MDS, NHL, HL, SCD, or acquired aplastic anemia are eligible and enrolled at the time of search. The study recently completed accrual.
- *BMT CTN 1902 – MM CAR-T to Upgrade Response [NCT05032820 – ACTIVE]*: This phase 2 study is evaluating the efficacy of an anti-B cell maturation antigen CAR-T therapy for MM patients with sub-optimal response after autologous hematopoietic cell HCT and maintenance lenalidomide, a group with demonstrated poor progression-free survival (PFS) with standard HCT approaches.
- *BMT CTN 2101 – Immunogenicity of COVID-19 Vaccines [NCT01166009 - COMPLETED]*: This is an observational study done in collaboration with the CIBMTR that will describe both antibody and T-cell responses to COVID-19 vaccination in patients receiving allogeneic and allogeneic HCT and CAR T therapy.

## BMT CTN and NCI Collaborative Studies

- *BMT CTN 1304/Dana Farber – Early AutoHCT for MM [NCT01208662 – ACTIVE]*: This phase 3 trial was designed to evaluate PFS between groups randomized to immunomodulatory-based therapy alone compared to autologous transplant to treat MM. The primary objective is finished with published results demonstrating that in MM there is a PFS advantage unaccompanied by any survival advantage demonstrating that transplants for

myeloma can be delayed in the era of modern myeloma therapeutics.[29]

- *BMT CTN 1903/AMC – HIV T-Cell Therapy [NCT04975698 – RECRUITING]*: This is an ongoing phase 2 trial of autologous transplantation followed by administration of HIV-specific T-cell therapy to treat HIV associated lymphomas. This study is funded by NCI specific funds for HIV/AIDS research and is part of the NIH HIV Cure Initiative.

On June 21, 2023, NHLBI and NCI published RFA-HL-24-010 and RFA-HL-24-011 to fund the fifth reissuance of The BMT CTN program.

## CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANT RESEARCH (CIBMTR)

The CIBMTR is a network composed of more than 350 US and international transplant centers that submit outcomes data for patients receiving cellular therapies. The CIBMTR Statistical Center provides data acquisition and management and information technology services to maintain a unique contemporary clinical outcomes database and facilitates observational and interventional research through scientific and statistical expertise necessary to support analyses of these data. NCI, with some funding from NHLBI and NIAID, is supporting the CIBMTR to ensure the database remains available to the public and to improve the treatment, survival, and quality of life for patients diagnosed with cancer and non-malignant blood disorders. The CIBMTR collects real-world outcomes data on every allogeneic transplantation performed in the U.S. as required by law. U.S. transplant centers also voluntarily submit autologous transplantation and cellular therapy data to the registry. Transplant centers worldwide also voluntarily submit both autologous and allogeneic transplantation data.

As of December 2020, the clinical database contained information from more than 575,000 patients with the following distribution: 51% allogenic transplants, 48% autologous transplants, and 1% non-transplant cellular therapy. CAR-T cell therapies represent 70% of the non-transplant research. Most of the CAR-T data entry is due to the FDA long-term follow-up requirement. New additions to the registry include the collection of COVID-19 infections and corresponding treatment data from ~1,132 patients. Now with data from more than 675,000 patients, more than 1,800 publications, and about 200 ongoing studies and clinical trials, the CIBMTR is at the forefront of research to increase access to cellular therapies and to improve outcomes for this patient population. Several CIBMTR studies have impacted clinical practice and have contributed to the scientific literature, including providing data important to the design of myeloMATCH.[30]

On June 14, 2022, NCI issued the following solicitation, RFA-CA-22-026, titled "*A Data Resource for Blood and Marrow Transplants and Adoptive Cellular Therapy Research*" to continue the resource development and utilization of programs of the CIBMTR with an emphasis on adoptive cellular therapies. The U24 competing renewal award was issued to the Medical College of Wisconsin on April 26, 2023.

## CANCER IMMUNOTHERAPY TRIALS NETWORK (CITN)

The CITN was established in 2010 through a cooperative agreement award to the Fred Hutchinson Cancer Research Center. This award created a consortium of the leading investigators and institutions with expertise in tumor immunology and cancer immunotherapy to develop and implement early phase clinical trials in this field. The CITN consisted of a Central Operations and Statistical Office, 43 clinical member sites, and a central immune oncology laboratory to support other laboratories with standardize assays and correlative studies. The CITN also established a pediatric consortium (Ped-CITN) in 2017 to conduct multicenter immunotherapy trials focused on childhood and young adult cancers. Of the four trials open during this reporting period, two have completed accrual and are in follow up or evaluating immune response data (NCT02267603; NCT03063632), and two are actively accruing participants (NCT03513952; NCT02595866).

The CITN fulfilled its original purpose of accelerating early-stage development in a then-emerging field during the 2010 to 2023 period. As the field of immunotherapy matured, especially with the FDA approval of checkpoint inhibitors (anti-CTLA4 and anti-PD1/PDL1) for several cancer types, immunotherapy became a more common treatment modality and the CITN was phased out as a separate network starting

[29] Richardson PG, Jacobus SJ, Weller EA, et. al. N Engl J Med. 2022 Jul 14;387(2):132-147.
[30] Menghrajani, K., et al. (2021). "Risk classification at diagnosis predicts post-HCT outcomes in intermediate-, adverse-risk, and KMT2A-rearranged AML." Blood Advances

in 2023 with the research aims of evaluating immunotherapies in cancer treatment integrated into the broader CTEP-supported early-phase and late-phase clinical trials network programs (e.g., NCTN and ETCTN).

### NCI CLINICAL TRIALS QUALITY ASSURANCE PROGRAM

The Clinical Trials Monitoring Branch is responsible for managing quality assurance and quality control of the ETCTN phase 1 and phase 2 and NCTN clinical therapeutic trials sponsored by DCTD and of prevention and screening trials sponsored by the Division of Cancer Prevention.

This program includes:

- Establishing standards for evaluating the conduct of research and the reporting of audit findings
- Monitoring the conduct of clinical trials by performing audits to ensure data quality, compliance with the protocol, and adherence to regulatory requirements, NCI policies, NCI guidelines, and GCP requirements
- Continuing education of investigators and research staff at sites through audits to share information on data quality, data management, and other aspects of quality assurance

#### Scope of Program

The Quality Assurance Program (QAP) includes institutions conducting ETCTN phase 1 and phase 2 trials, NCTN Groups, NCORPs, Cancer Centers, and all other institutions conducting clinical research trials sponsored by CTEP and NCI. The program provides oversight and coordination of audit procedures for international sites participating in CTEP or DCTD clinical trials (**Table 36**).

| Organization/Type of Study | Audits | Patient Cases |
|---|---|---|
| Phase 1/2 studies | 594 | 3,916 |
| NCTN Groups & Other Consortia (AMC, PBTC) | 3,376 | 18,356 |
| Cancer Centers and Single Institutions | 29 | 229 |
| PEP-CTN | 76 | 205 |

TABLE 36: NCI QAP AUDIT STATISTICS (2020-2023).

## NEW INITIATIVES AND RECENT ACCOMPLISHMENTS (1/1/2020-12/31/2023)

- Revisions to the 'NCI Guidelines for Monitoring the Experimental Therapeutics Clinical Trials Network (ETCTN) and Other Early Phase CTMS-Monitored Studies,' commonly referred to as Monitoring Guidelines
- Establishment of a DSMB (Data Safety Monitoring Board) for ETCTN randomized phase 2 clinical trials
- Implementation of a Specimen Tracking System for the ETCTN for shipment of specimens from participating sites to the ETCTN Biobank

## FUTURE DIRECTIONS

CTEP will focus on four key areas over the next 5 years:

- Expand efforts in biomarker-driven, targeted therapeutics, immunotherapy, and combination therapy in early-phase trials
- Assist in the ongoing evolution of the NCTN groups into a highly integrated system capable of performing cutting-edge, definitive trials with molecularly targeted agents and combination therapy, including umbrella/basket trials requiring screening of large numbers of participants
- Implement a strategic vision for more flexible, faster, simpler, less expensive, high impact trials that seamlessly integrate with clinical practice by focusing on
- reducing the complexity of clinical trial procedures and data collection (including electronic extraction from existing data sources)
- Shift the performance of appropriate trial procedures/assessments remotely or via telehealth
    - improve accrual and access to NCI clinical trials, especially for minority and underserved participants
    - enhance the efficiency of statistical design and analysis
    - continue to improve the timelines for trial development and accrual
    - Increase contributions to mentoring the next generation of clinical investigators

PROGRAMS AND INITIATIVES (2020-2023)

# DEVELOPMENTAL THERAPEUTICS CLINIC

# OVERVIEW

The DTC focuses on the incorporation of pharmacodynamic (PD) endpoints—direct measurements of drug effect on target molecules and/or pathways within a tumor—into the early development of new cancer agents. The goal is to assess whether the agents are reaching the tumor and are modulating the biology in accordance with their mechanism(s) of action (MOA). These data inform decisions about the clinical activity of the agents, as well as the design of subsequent trials, through targeted patient selection, improved scheduling of agents, or generation of novel combinations.

DTC physicians collaborate closely with other clinical and preclinical colleagues to develop new PD assays specific to the clinical trial design and oncologic agent being evaluated. Over the last decade, DTC staff have expanded their expertise, and the clinic is now a referral center for sarcoma and rare tumors. The team has developed a series of trials targeting rare tumors, individually and collectively. At any one time, 25+ early-phase or rare tumor clinical trials are being conducted in the DTC to facilitate the development and clinical evaluation of novel cancer therapeutics, combinations, or dosing regimens.

DTC also participates in the NCI Experimental Therapeutics Clinical Trials Network (ETCTN) and the NCI National Clinical Trials Network (NCTN) to provide options to their patients. Although services were limited during the COVID-19 crisis, DTC received 362, 485, 427, and 389 referrals, performed 228, 209, 175, and 143 screening visits, and enrolled 141, 140, 115, and 107 patients onto trials in 2020, 2021, 2022, and 2023 respectively. DTC's referral base arises predominantly from the continental US; however, for specialty trials, like alveolar soft part sarcoma (ASPS), DTC receives international referrals. Referrals from other NCI Center for Cancer Research (CCR) clinics on the Bethesda campus have increased over the last few years due to DTC's wide assortment of trials. This is especially true for DTC's rare tumor trials that can provide treatment for patients who have no options within the CCR's medical oncology teams.

# ALICE CHEN
## HEAD

Alice Chen, M.D. became Head of the Developmental Therapeutics Clinic (DTC) in 2015. With more than 25 years of experience as a clinical investigator, she has led numerous early-phase clinical trials, including the first-ever phase 0 trial conducted under the U.S. Food and Drug Administration's exploratory initiative, as well as multiple "first-in-human" phase 1 studies.

Dr. Chen is widely recognized for her expertise in rare tumors and precision medicine. As molecular characterization has become increasingly central to cancer therapy, Dr. Chen has served as the national co-principal investigator for three major NCI Precision Medicine Initiatives: Molecular Profiling-based Assignment of Cancer Therapy (MPACT), NCI Molecular Analysis for Therapy Choice (MATCH), and Combo-MATCH—involving thousands of investigators, sites, and patients across the country.

Recently, she led a pivotal phase 2 clinical trial, published in the *New England Journal of Medicine*, evaluating atezolizumab for alveolar soft part sarcoma (ASPS). This work directly supported the U.S. FDA approval of atezolizumab for unresectable or metastatic ASPS. She also directed an international trial of selumetinib in adults with NF1 plexiform neurofibromas, with results published in *The Lancet*.

Dr. Chen has co-authored more than 190 peer-reviewed publications in leading journals, including *NEJM*, *The Lancet*, *Journal of Clinical Oncology*, and *Nature Medicine*. She has received 14 NCI/NIH Awards of Merit in recognition of her contributions to international collaborations, development of CTCAE and PRO-CTCAE, the Precision Medicine Initiative, and clinical research leading to new drug approvals in desmoid and ASPS.

# DTC CLINICAL TRIALS

| Tissue Procurement/Correlative Pharmacodynamic Support Studies |
|---|
| Tissue procurement Protocol for the Developmental Therapeutics Clinic, NCI |
| Longitudinal Sample Collection and Tracking for the Developmental Therapeutics Clinic |
| **Phase 1 Trials** |
| Combination of Bortezomib and Clofarabine in Adults with Relapsed Solid Tumors, Lymphomas, or Myelodysplastic Syndromes |
| Phase 1 Study of Recombinant Interleukin 15 in Combination with Checkpoint Inhibitors Nivolumab and Ipilimumab in Subjects with Refractory Cancers |
| Phase 1 Trial of 5-aza-4'-thio-2'-deoxycytidine (Aza-TdC) in Patients with Advanced Solid Tumors |
| A Phase 1b Study of Nivolumab in Patients with Autoimmune Disorders and Advanced Malignancies (AIM-NIVO) |
| Phase 1 Trial of Gemcitabine Combined with the BAY 1895344 ATR Inhibitor with Expansion Cohorts in Advanced Pancreatic and Ovarian Cancer |
| A Phase 1 Trial of the ATR Inhibitor BAY 1895344 in Combination with Cisplatin and with Cisplatin plus Gemcitabine in Advanced Solid Tumors with an Emphasis on Urothelial Carcinoma |
| Phase 1/1b Trial of ATR Inhibitor BAY 1895344 in Combination with FOLFIRI in GI Malignancies with a Focus on Metastatic Colorectal and Gastric/Gastroesophageal Cancers |
| BAY1895344 Plus Topoisomerase-1 (Top1) Inhibitors in Patients with Advanced Solid Tumors, Phase 1 Studies with Expansion Cohorts in Small Cell Lung Carcinoma (SCLC), Poorly Differentiated Neuroendocrine Carcinoma (PD-NEC) and Pancreatic Adenocarcinoma (PDA) |
| A Phase 1/2 Study of Tiragolumab and Atezolizumab in Patients with Relapsed or Refractory SMARCB1 or SMARCA4 Deficient Tumors |
| First-in-Human Phase 1 Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological and Clinical Activity of Metarrestin (ML-246) in Subjects with Metastatic Solid Tumors |
| **Phase 2/3 Trials** |
| DURVA+: Evaluation of the Safety and Pharmacodynamics of Anti-PD-L1 Antibody MEDI4736 (Durvalumab) in Combination with Chemotherapy in Patients with Advanced Solid Tumors |
| A Phase 2 Study of Anti-PD-L1 Antibody (Atezolizumab) in Alveolar Soft Part Sarcoma |
| Phase 2 Trial of the MEK1/2 Inhibitor Selumetinib (AZD6244 hydrogen sulfate) in Adults with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas |
| Rapid Analysis and Response Evaluation of Combination Anti-neoplastic Agents in Rare Tumors (RARE CANCER) Trial: RARE 1 Nilotinib and Paclitaxel |
| Pilot Study of DS-8201a Pharmacodynamics in Patients with HER2-expressing Advanced Solid Tumors |
| A Pharmacodynamics-Driven Trial of Talazoparib, an Oral PARP Inhibitor, in Patients with Advanced Solid Tumors and Aberrations in Genes Involved in DNA Damage Response |
| Phase 2 Study of Rogaratinib (BAY 1163877) in the Treatment of Patients with Sarcoma Harboring Alterations in Fibroblast Growth Factor Receptor (FGFR) 1-4 and SDH-deficient Gastrointestinal Stromal Tumor (GIST) |
| Rapid Analysis and Response Evaluation of Combination Anti-Neoplastic Agents in Rare Tumors (RARE CANCER) Trial: RARE 2 Talazoparib and Temozolomide |
| Testing the Combination of ZEN003694 and Nivolumab with or without Ipilimumab in Solid Tumors |
| A Phase 2 Study of Atezolizumab with or without Selinexor in Alveolar Soft Part Sarcoma (AXIOM) |
| Rapid Analysis and Response Evaluation of Combination Anti-neoplastic Agents in Rare Tumors (RARE CANCER) Trial: RARE 3 Tiragolumab + Atezolizumab |
| Molecular Analysis for Combination Therapy Choice (ComboMATCH) |
| Phase 2 Study of Intravenous and Intraperitoneal Paclitaxel and Oral Nilotinib for Peritoneal Carcinomatosis from Colorectal, Appendiceal, Small Bowel, Gastric, Cholangiocarcinoma, Breast, Ovarian, or Other Gynecologic Primary Cancer |
| Randomized Phase 2 Study of Cabozantinib, Ipilimumab, and Nivolumab in Patients with Soft Tissue Sarcoma |
| A Phase 3, Multicenter, International Study with a Parallel, Randomized, Double-blind, Placebo-controlled, 2 Arm Design to Assess the Efficacy and Safety of Selumetinib in Adult Participants with NF1 who have Symptomatic, Inoperable Plexiform Neurofibromas (KOMET) |

TABLE 37: ACTIVE DTC CLINICAL TRIALS IN 2023.

**Table 37** lists clinical trials that were active in DTC in 2023. DTC has played a prominent role in precision medicine studies. DCTD led the multicenter NCI-MPACT trial (Chen, 2021) and participated in NCI-MATCH, a national clinical trial that analyzes each person's tumor in search of genetic abnormalities for which there are targeted therapies available. In the follow-up trial, ComboMATCH, DTC is leading Arm E4 and participating in other arms. DTC also developed and is leading trials in precision medicine in the ETCTN system with DS8201 in HER2 amplification and talazoparib in the population with aberrations in their response to DNA damage and repair (DDR). These patients are participating in the FGFR alteration or succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumor (GIST) trial testing rogaratinib. To provide diversity in age, DTC assists CCR's Pediatric Oncology Branch (POB) in enrolling pediatric patients with SMARCB1- or SMARCA4-deficient tumors with tiragolumab (an antibody to the T cell immunoreceptor with Ig and ITIM domains (TIGIT) that inhibits T cells and NK cells) and atezolizumab (an antibody that blocks PD-L-1 as an immune checkpoint inhibitor) that POB may not be able to enroll or prefer to manage (due to co-morbidities). A clinical trial of non-small cell lung cancer showed increased survival when tiragolumab was combined with atezolizumab compared to atezolizumab alone.

In collaboration with the Pharmacodynamic Assay Development and Implementation Section (PADIS), the Molecular Characterization Laboratory (MoCha), and the NCI Patient-Derived Models Repository (PDMR) at the Frederick National Laboratory for Cancer Research, DTC is developing clinical trials evaluating combinations of agents that showed promising pre-clinical activity when tested in mice implanted with rare tumor models from the PDMR. The RARE CANCER (Rapid Analysis and Response Evaluation of Combination Anti-neoplastic Agent in Rare Tumors) series of clinical trials will help gather information about the:

- Translation of preclinical activity into patients
- Collection of specimens for molecular characterization of rare tumors as patients are treated through the series
- Resistance of tumors to oncology drugs
- Development of new treatments for patients with rare tumors

Three trials are open in this series, of which one has completed accrual, with more trials in development. DTC investigators also led an NCI trial that resulted in the FDA approval of atezolizumab in the rare cancer Alveolar Soft Part Sarcoma (ASPS). The patients benefitted both in shrinkage of their tumor as well as prolonged disease stabilization. The results of this trial were published in the *New England Journal of Medicine* (Chen, 2023).

Having pre- and post-treatment biopsy tissue of adequate quality to measure drug effect is a critical component of PD-based clinical evaluation. With a preponderance of PD endpoint trials requiring biopsy material in the DTC (PD expansion of Phase 0/1 trials, MPACT, and NCI-MATCH), there is a major collaborative effort between the DTC and the NIH Clinical Center interventional radiologists to improve the quality and quantity of biopsy tissue collected for research. Weekly dialogues continue to improve the quality of specimens obtained from the DTC, and workshops have improved PD specimens/results. Based on the need for PD and molecular characterization endpoints, DTC successfully obtained 310, 619, 581, and 412 specimens in 2020, 2021, 2022, and 2023 respectively, from patients on the clinic's trials.

## DTC COLLABORATIONS

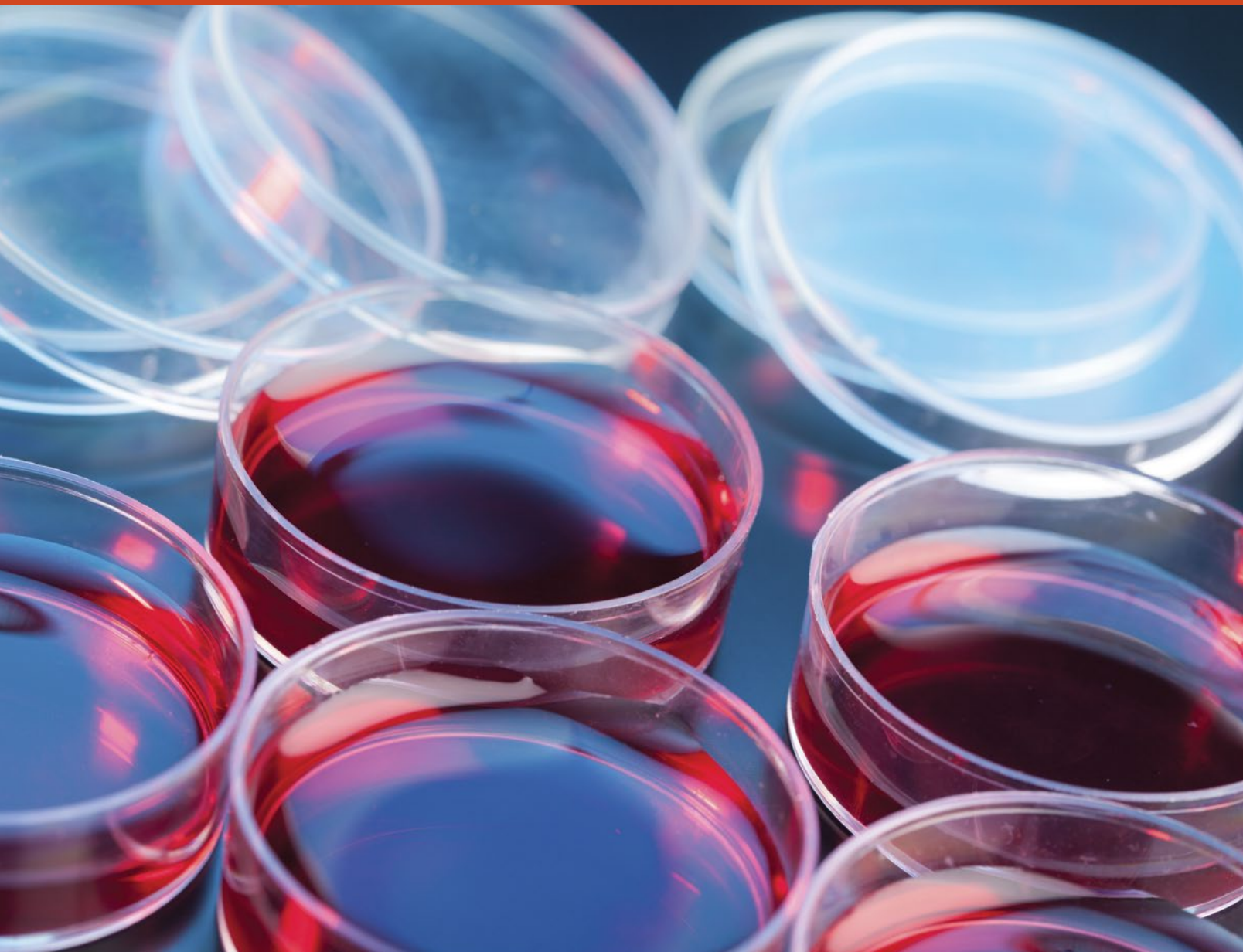
DTC staff also capitalize on collaborations with the outstanding researchers within the NIH Clinical Center. In collaboration with the POB, children can enroll onto several DTC-sponsored adult trials, and the DTC can provide care to adults enrolled on POB trials. This collaboration was essential for the FDA approval of atezolizumab in pediatric patients with ASPS mentioned above. Lately, the most recent collaboration with POB built upon NIH's Rare Tumor Initiative, with trials in development to offer treatment options for people with rare tumors. Investigational imaging agents have also been incorporated into several trials to address efficacy and MOA via collaboration with NIH Radiology and Imaging Sciences investigators. DTC is collaborating with the Surgical Oncology Branch evaluating the use of intraperitoneal and systemic nilotinib and paclitaxel in the Phase 2 Study of Intravenous and Intraperitoneal Paclitaxel and Oral Nilotinib for Peritoneal Carcinomatosis from Colorectal, Appendiceal, Small Bowel, Gastric, Cholangiocarcinoma, Breast, Ovarian, or Other Gynecologic Primary Cancer. Dr. Rudloff of the POB has opened a first-in-human trial testing metarrestin in the DTC.

# ADVANCED DEVELOPMENTAL THERAPEUTICS TRAINING PROGRAM (ADTTP)

Acknowledging the increasing complexity of early-phase clinical trials and the development of novel therapeutic agents, DTC created the Advanced Developmental Therapeutics Training Program (ADTTP). This program is designed to provide specialized early drug development training for medical oncologists by providing an opportunity to develop innovative early-phase clinical trials. Past graduates have taken on leadership roles in conducting trials in both academic centers and the pharmaceutical industry. In addition to the ADTTP, DTC extends its training offerings to CCR medical oncology fellows who are keen on expanding their knowledge in early-phase drug development. DTC has also participated in the NIH Summer Internship Program and continues to offer research opportunities for interested students. DTC's global standing has attracted international investigators, who have approached the organization seeking sabbatical opportunities. This recognition highlights the esteemed reputation that DTC has earned in the field of oncology research and its unwavering commitment to advancing the frontiers of early-phase drug development.

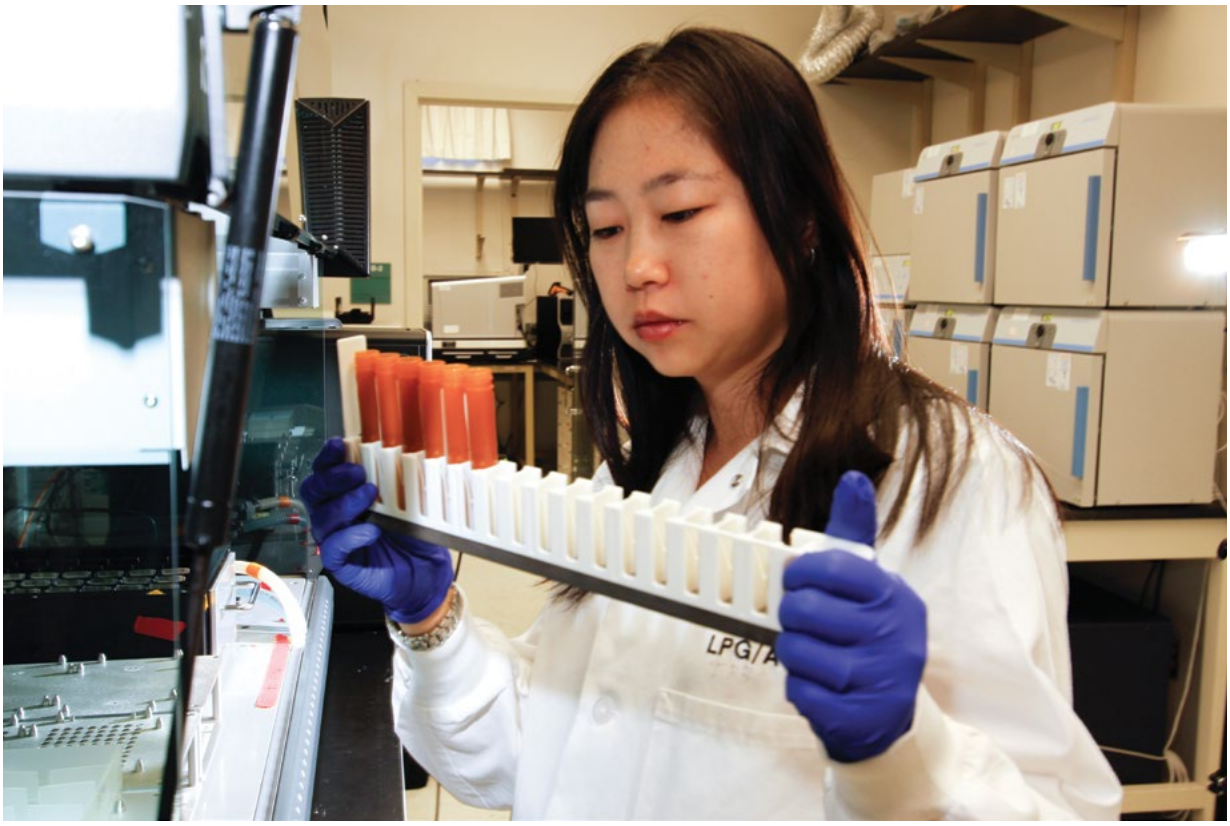
PROGRAMS AND INITIATIVES (2020-2023)

# DEVELOPMENTAL THERAPEUTICS PROGRAM



# OVERVIEW

The mission of the Developmental Therapeutics Program (DTP) is to support and assist the extramural community in promoting the translation of new therapeutic concepts toward clinical use. Created by Congress in 1955 as the Cancer Chemotherapy National Service Center (CCNSC), DTP manages and oversees one of the largest research grant portfolios at the NCI. DTP is also a resource for the generation of preclinical data and research materials, including vialed and plated compounds, human and mouse tumor models, natural products extracts, as well as bulk and formulated drugs and biopharmaceuticals along with the safety data necessary to support Investigational New Drug (IND) Applications. DTP has been directly involved in discovering or developing many anticancer therapeutics on the market today. While the academic and pharmaceutical sectors are currently responsible for most of the anticancer therapeutics discovery and development, DTP continues to provide valuable support for their efforts through a variety of mechanisms.



# ROSEMARIE AURIGEMMA
## ASSOCIATE DIRECTOR

Dr. Aurigemma has been a programmatic leader in drug development for more than 25 years. Her tenure as the Deputy Associate Director of DTP resulted in the launch of the Stepping Stones preclinical development program as well as the initiation and expansion of biopharmaceutical manufacturing support for adoptive cell therapies. She served as Acting Associate Director of DTP beginning in January 2021 until her permanent appointment in September 2021. As Associate Director, she manages the oversight and coordination of the programmatic, financial, and administrative functions for DTP's ten branches.

Dr. Aurigemma initially joined NCI in 2001 as a Program Director in the Biological Resources Branch of DTP where she spent eight productive years directing programs for novel biopharmaceutical products leading to successful phase 1 clinical trials both nationally and internationally. In 2009, Dr. Aurigemma joined the Offices of Biodefense, Research Resources and Translational Research with the National Institute of Allergy and Infectious Disease (NIAID). At NIAID, Dr. Aurigemma served as Chief, Drug Development Section from 2009-2017 where she led a diverse anti-infectives drug discovery and development portfolio, initiating nearly two dozen clinical trials and resulting in several biodefense drugs reaching market approval and placement in the federal Strategic National Stockpile. In 2017, she rejoined NCI as DTP's Deputy Associate Director. She also served as Acting Chief of the Immuno-Oncology Branch (2017-2020) and Biological Resources Branch (2017-2019) until those positions were filled.

Prior to joining NIH, Dr. Aurigemma held positions as Research and Discovery scientist and Clinical Research Manager in the private biotechnology sector and served in academic roles of various disciplinary departments such as microbiology and experimental immunology at Cornell University and pharmacology and biology at Pennsylvania State University. Dr. Aurigemma holds a PhD in Microbiology from Colorado State University and a BS in Biology from Cornell University.

## STRUCTURE AND FUNCTION

DTP is functionally organized into ten branches under the oversight of the Office of the Associate Director (OAD). DTP provides various forms of cancer drug discovery and development infrastructure to the broader extramural cancer research community, including:

**Grants**

- More than 1,000 active grant awards managed in 2023

**Repositories**

- Samples of individual chemical compounds and biologics for research use
- Large plated sets of compounds for high-throughput screening (HTS)
- Genomically and transcriptionally characterized and established human tumor cell lines and patient-derived tumor models along with extracts (DNA, RNA)
- Natural product crude extracts and plated subfractions for HTS
- Web-based databases of chemical compounds and anti-cancer activity information

**Services**

- *In vitro* HTS of compounds submitted by investigators using the NCI-60 tumor cell panel
- Manufacturing and development of clinical grade drugs and biopharmaceuticals
- Development services such as GLP toxicology studies to support use in human clinical trials
- Data mining tools, such as COMPARE, and the Molecular Targets Program

Extramural and intramural investigators can access DTP development resources primarily through the NCI Experimental Therapeutics (NExT) Program (see Major Initiatives). In addition, DTP's Stepping Stones Program (see Major Initiatives) assists extramural investigators within the grants portfolio with drug candidate characterization to help propel novel drug candidates toward the IND-enabling stage of development.

## OFFICE OF THE ASSOCIATE DIRECTOR

The OAD organizes and coordinates activities across DTP to expedite the discovery and preclinical development of new anticancer therapeutic agents. In addition, the OAD manages broader NCI activities involving DTP staff and support to the extramural community, such as the Consultation on the Development of Experimental Cancer Drugs. In the past five years, DTP has led over 260 consultations with academia and industry investigators. By submitting a simple online form, extramural investigators can request a consultation with DTP's drug development experts on critical path activities for the preclinical development of new therapeutics, including nonclinical safety and good manufacturing processes for small molecules, biologics, and imaging agents. DTP has also created the Stepping Stones Program to help extramural NCI grantees identify gaps in their drug discovery/development path and provide expertise on how to remediate them. Ultimately, investigators are encouraged to consider applying to the NExT Program to request access to NCI resources for performing the activities discussed if they do not have the capabilities themselves.

## PRECLINICAL THERAPEUTICS GRANTS BRANCH (PTGB)

PTGB manages the biochemistry and pharmacology grants portfolio within DTP. PTGB grants support preclinical research related to therapeutic intervention, including chemistry, natural products, mechanisms of drug action (MOA), pharmacology, toxicology, nanomedicines, and the co-development of drugs and biomarkers to support the new era of precision medicine. The portfolio emphasizes the modulation of targets and pathways that drive tumors, consistent with the goal of accelerating the discovery, development, and evaluation of agents to treat cancer. PTGB manages more than 700 active extramural investigator-initiated research grants and provides counsel to hundreds more potential applicants each year. PTGB analyzes the portfolio to identify areas of innovative drug discovery and development that would benefit from focused support and develops new initiatives and Notices of Funding Opportunity to encourage greater extramural participation in those innovative areas. PTGB staff lead and co-lead the following initiatives:

- Assay development and screening for discovery of chemical probes, drugs or immunomodulators
- Glioblastoma Therapeutics Network
- Next Generation Chemistry Centers for Fusion Oncoproteins
- Advancing the development of tumor site-activated small molecules

PTGB staff have been integral to the following initiatives:

- Public webinar series on Drug Development
- Stepping Stones Program that helps extramural investigators advance their preclinical drug candidates to the clinic
- DCTD Consultation of Experimental Cancer Drugs service for investigators from academia or small biotech companies

## MOLECULAR PHARMACOLOGY BRANCH (MPB)

MPB focuses on cell-based models of cancer and provides mechanistic understanding of drug combination responses in patient-derived cell lines and organoids that inform potential early clinical trials. A major focus is on improving the treatment of rare, recalcitrant, and neglected cancers through interactions with the cancer research community and other NCI laboratories. In support of this mission, MPB oversees the work of laboratories at the Frederick National Laboratory for Cancer Research (FNLCR) that use state-of-the-art HTS, molecular imaging, and other techniques to identify therapeutic targets and genomic vulnerabilities, screen potential new agents, and develop potential therapeutic combinations.

The Target Validation and Screening Laboratory (TVSL) seeks to elucidate the MOAs of drug combinations, which may result from the independent actions of each agent or through the interactions of the agents' activities. The Translational Support Laboratory focuses on critical intracellular targets, especially tubulin. This laboratory performs detailed analysis of tubulin binding sites, thus providing an understanding of whether two agents act antagonistically, additively, or synergistically.

The TVSL screens combinations of anticancer drugs and investigational agents in complex tumor spheroids, including tumor cells, human mesenchymal stem cells, and human umbilical cord endothelial cells, to identify promising new drug combinations and unexpected disease sensitivity to drug combinations. The TVSL has developed:

- In-house expertise, automation, instrumentation, and an information technology infrastructure to carry out screening campaigns with an array of molecular and cell-based assay technologies applied to large chemical libraries
- Methods to use complex 3D cell spheroids to assay the response of several recently developed patient-derived cell lines from the NCI Patient-Derived Models Repository (PDMR) to more than 300 compounds as single agents and two-agent combinations in 7-day exposures

Complex spheroid screening is evaluating new molecules that the NExT Program's Chemical Biology Consortium developed and novel, investigational-investigational agent combinations in advance of the Cancer Therapy Evaluation Program's (CTEP) early-phase clinical trials. More than 10 screens each including 20-30 cell lines have been screened.

MPB is developing an HTS for panels of PDMR tumor organoids. The panels will be selected based upon disease or genetic alteration. Organoid cultures are being selected based upon their growth characteristics (i.e., ability to be scaled up to screen-able numbers and to proliferate over the 7-day drug or investigational agent exposure time to provide a reproducible readout with cell-titer glo).

The TVSL contributes broadly to collaborative projects through its performance of detailed cell-based studies. A major tenet of cancer therapeutics is that combinations of anticancer agents with different MOAs and toxicities may be effective treatment regimens. Evaluation of drug combinations in cell culture may be used to identify opportunities and assess risk of additive/synergistic toxicity. TVSL develops 3D cell culture models, including tumor, endothelial, and stromal cells in mixed culture spheroids. These models are used for detailed studies in TVSL and screening campaigns by TVSL (**Figure 49**).

MPB engaged in a major effort to modernize the NCI-60 screen and maintains this resource for the cancer research community. In collaboration with the DTP Information Technology Branch (ITB) and Natural Products Branch (NPB), MPB adapted the NCI-60 screen to a high-throughput 384-well robotic screening system with a 3-day compound exposure time and cell-titer glo endpoint. ITB modernized the data capture, storage, and output. A baseline with >1,000 FDA-approved and investigational agents were screened to provide a baseline for this new NCI-60 screen. The switch to the HTS384 NCI-60 screen occurred in January 2024.

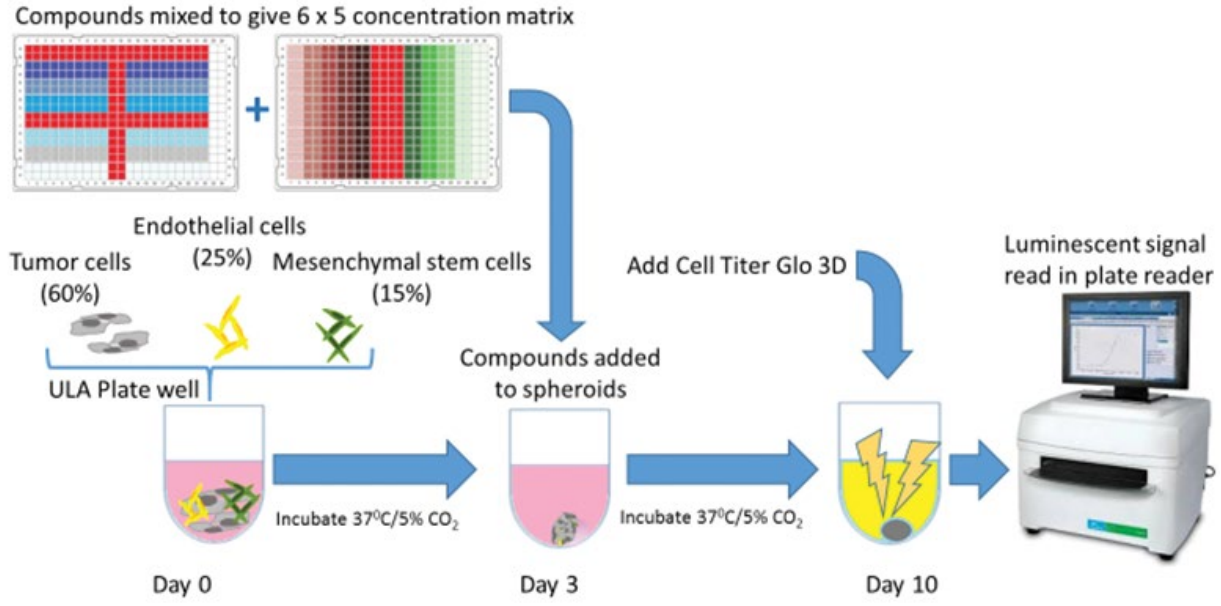



FIGURE 49: EXAMPLE WORKFLOW FOR MIXED CULTURE SPHEROID ASSAYS.

MPB also provides data mining tools, including the Sarcoma project, the Small Cell Lung Cancer project, COMPARE, and the Molecular Targets Program. COMPARE is a group of software tools for searching, displaying, and analyzing results from the NCI-60 screening assay. The global cancer research community uses COMPARE as a discovery tool and in aspects of drug evaluation and decision-making. Versions of COMPARE are deployed to analyze data from the Sarcoma project and the Small Cell Lung project. Over the last decade, DSCB has built a library of more than 1,000 compounds (180 FDA approved oncology drugs and more than 800 investigational agents) annotated with MOAs. Integration of this information into COMPARE allows investigators to discern potential MOAs for compounds active in the NCI-60 screen. The single agent and combination data from the complex spheroid screens are being provided on PubChem.

## COLLABORATIVE EFFORTS BETWEEN BTB AND THE PHARMACODYNAMICS PROGRAM

BTB provided the preclinical animal model support for the development and validation of numerous clinical assays, established methodologies for collecting and stabilizing tumor biopsies for subsequent analysis. These assays and projects included:

- Inhibition of DNA methylation
- γ-H2AX assay
- c-Met assay
- HIF1α assay
- Mer kinase assay
- EMT immunofluorescence assay
- Preclinical development of T-dCyd
- PARP inhibitors project
- Development of multiplex immunofluorescence assays
- Calf intestinal alkaline phosphatase assay
- Topoisomerase 1 complex assay
- Apoptosis 15-plex panel

## BIOLOGICAL TESTING BRANCH (BTB)

BTB provides oversight and technical direction to evaluate the *in vivo* activity of new chemotherapeutic agents, including the development and implementation of new models for drug discovery and testing. To accomplish this, BTB is responsible for:

- Implementing and managing a program to develop patient-derived xenograft (PDX) models – the PDMR - for distribution to the research community as tools for cancer target discovery as well as drug discovery and development
- Planning, directing, and managing a program to screen compounds for evidence of preclinical efficacy in rodent models
- Developing new *in vivo* screening models
- Providing support for preclinical *in vivo* pharmacokinetics (PK) and pharmacodynamics (PD) studies across the DCTD drug development effort
- Implementing and managing a program to develop and characterize syngeneic models applicable to preclinical immune-oncology studies
- Maintaining a repository of experimental animal and human tumor cell lines for use in research performed by DTP and extramural investigators

## DRUG SYNTHESIS AND CHEMISTRY BRANCH (DSCB)

DSCB is responsible for the following activities in support of the discovery and development of novel anticancer agents (**Figure 50**):

- Scientific coordination with universities and industries to stimulate the submission of a variety of synthetic compounds and pure natural products for *in vitro* anticancer screening
- Managing the acquisition, synthesis, storage, inventory, documentation, and distribution of chemical samples for research purposes to NIH and external investigators
- Acquisition of preclinical and clinical anticancer, small-molecule chemotherapeutics for evaluation in various cell line screens and testing *in vivo*, including PDX models

- Synthetic and medicinal chemistry resources and expertise in support of NExT Program development, Stepping Stones, and discovery projects
- Collaboration with DTP's NPB to identify novel chemical scaffolds, as well as develop synthetic methods to generate further supplies for active compounds that have been isolated from natural product extracts

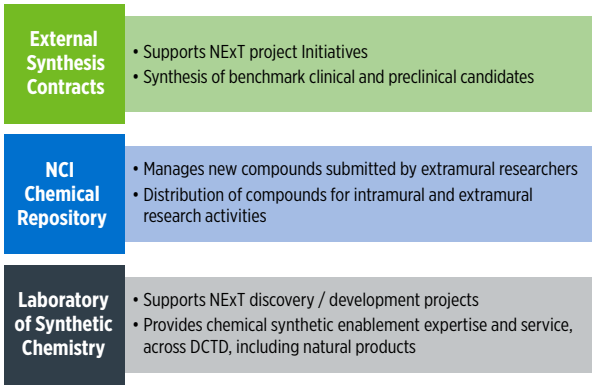



FIGURE 50: CHEMISTRY SUPPORT FOR DCTD.

## NATURAL PRODUCTS BRANCH (NPB)

The primary responsibility of NPB is to obtain natural product materials from terrestrial and marine environments and prepare crude extracts and partially purified fractions for screening in various intramural and extramural screening programs, including the NCI-60 Human Tumor Cell Lines Screen. For example, NPB has provided access to plated screening sets to numerous extramural researchers including through the NExT Program and the NIH HEAL initiative. In addition to maintaining a repository of crude extracts, NPB established the NCI Program for Natural Product Discovery (NPNPD) to create an enhanced pre-fractionated library more suitable for high-throughput targeted screens, increasing the scope and efficiency of natural product drug discovery efforts.

NPB also oversees the operations of the Natural Products Support Group at FNLCR, which side-by-side with NPB research chemists, isolates and chemically identifies the active components from crude extracts or semi-purified fractions that are positive in *in vitro* and *in vivo* anticancer screens and scales-up production of active compounds to support preclinical and early clinical evaluation.

## BIOLOGICAL RESOURCES BRANCH (BRB)

The BRB supports research in biotechnology-based therapies and provides resources to develop potential leads for the treatment of cancer and related conditions. Classes of therapeutic agents include recombinant proteins, monoclonal antibodies and antibody-drug conjugates, genetically modified viruses and virus-like particles, bacteria and mammalian cells, engineered autologous and allogeneic human cells, peptides, and oligonucleotides. These entities may function as cytokines, growth factors, vaccines, adjuvants, or other immune-modifying agents. BRB manages a coordinated portfolio of research grants and contracts that demonstrates the flexible support and expertise in all three components of the discovery, development, and translational process.

The BRB-managed grant portfolio consists of more than 150 grant awards (R-, P-, and U- mechanisms) focusing on the discovery, testing, and development of biotechnology- and synthetic biology-based products for the treatment of, and vaccination against, cancer. The portfolio also includes therapeutic model development and the study of therapeutic MOA. This grant portfolio has a notable history of supporting concepts that successfully compete for further development and translation in resource support programs like the NExT Program.

BRB also oversees the Biopharmaceutical Development Program (BDP) at the Advanced Technology and Research Facility (ATRF), FNLCR. The BDP assists with the preclinical production process development, cGMP manufacturing, testing, and release of all types of biologics for IND- directed preclinical studies through non-pivotal phase 3 clinical trials, including monoclonal antibodies and antibody-drug conjugates, recombinant proteins, viral and RNA/DNA vaccines, peptides, gene therapy vectors, and whole cell-based products such as autologous T cell therapies. The BDP includes comprehensive quality systems (QA/QC) and regulatory affairs expertise to support FDA and EMEA filings, as well as complete technology transfer packages to NCI partners for further commercial development activities.

Surplus production materials from projects within the BDP are provided to the community through the BRB Preclinical Biologics Repository. NCI established this repository in 1988 to acquire, initially by donation, and distribute well-characterized biological reagents to extramural investigators to support more robust preclinical studies and therapeutic concept development.

## TOXICOLOGY AND PHARMACOLOGY BRANCH (TPB)

TPB provides essential toxicology and pharmacology data and expertise for drugs, biologics, and imaging agents in development for clinical trials. TPB manages external contractors to generate PK and toxicology data (e.g., ADME, dose range-finding, and IND-directed toxicology studies) that are essential for filing an IND application with the FDA. This includes organ-specific toxicology studies, such as cardiovascular monitoring and assessment of chemotherapy-induced peripheral neuropathy. TPB also provides toxicology expertise to the extramural community, creating tailored preclinical strategies and study designs for safety assessment. TPB staff guide studies at all stages of product development, from early and rapid *in vitro* or *in vivo* characterization to optimize clinical candidate selection through PK, PD, and safety studies across species to support IND-filing and clinical use. TPB staff also prepare toxicology and pharmacology/PK summaries for inclusion in INDs. Staff also interact with CTEP's Regulatory Affairs Branch and/or external PIs to facilitate assembly of INDs and often participate in pre-IND meetings with the FDA.

### Investigative Toxicology Laboratory

The Investigative Toxicology Laboratory, overseen by the TPB, generates and tests hypotheses as part of target safety and risk assessment efforts to manage safety liabilities and facilitate understanding of toxicity issues in support of the NExT Program. Investigative toxicology evaluations include qualifying fit-for-purpose tools, assays, and *in vitro* model test systems to identify on- and off-target toxicity and better characterize mechanisms of toxicity. The laboratory applies orthogonal data sets (**Figure 51**) that include morphologic, functional, biochemical, and imaging biomarkers to a weight-of-evidence approach to advance research critical for expanded use of new alternative methods by the community of toxicologists.

Establishment of the infrastructure to perform preclinical safety testing of CAR T-cell therapies in support of clinical trials required novel alternative methods (NAMs) developed to assess potential on-target/off-tumor or off-target/off-tumor toxicity in normal human cell types. Such a NAM has been developed and qualified by the Investigative Toxicology Laboratory of TPB at FNLCR (**Figure 52**). This preclinical safety testing approach is intended to support IND packages for first-in-human CAR T-cell therapies.

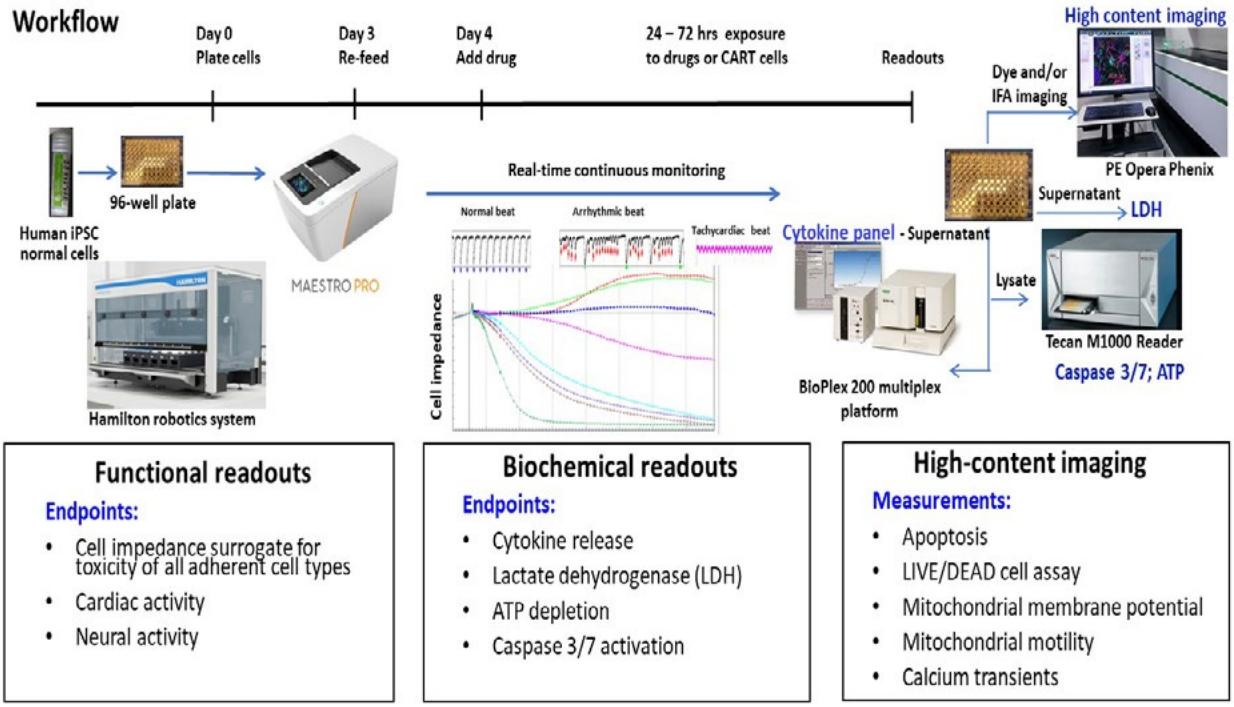



FIGURE 51: INVESTIGATIVE TOXICOLOGY ACTIVITIES IN SUPPORT OF DRUG DEVELOPMENT.

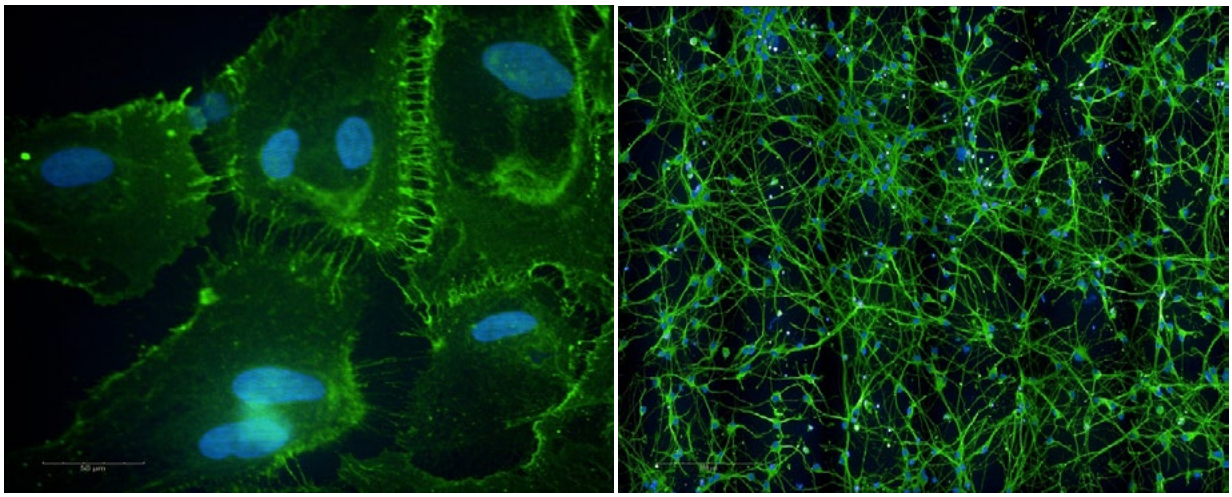


FIGURE 52: IN VITRO HUMAN CELL MODELS.

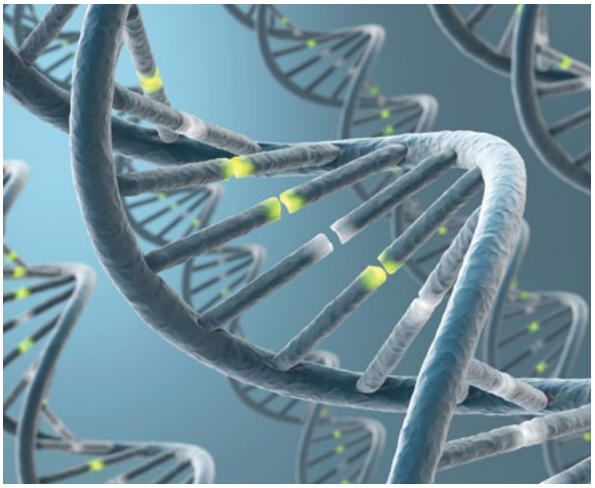
Human induced pluripotent stem cell-derived neurons were immunolabeled to show characteristic β-tubulin III protein expression in axonal processes (left panel). Human induced pluripotent stem cell-derived endothelial cells show fine detail of characteristic CD31 protein expression in cellular projections in a high-power image (right panel). Such cell models are used as surrogates of normal cell types to study on- and off-target toxicity of experimental cancer therapies.

## PHARMACEUTICAL RESOURCES BRANCH (PRB)

PRB provides comprehensive pharmaceutical services to various DCTD programs and other parts of NCI and NIH. The primary objective of PRB is to supply high-quality chemical substances and formulated products for use in preclinical studies and human clinical trials. PRB accomplishes this objective through the management of external contractors. Most of the data are submitted to the FDA in support of an IND.

PRB staff manage these major contract areas:

- Chemical Resources
  - Small-scale synthesis, including probe runs, process optimization, and large-scale GMP synthesis ranging from relatively short syntheses of one to two steps to complicated and challenging multistep syntheses
- Analytical
  - Development of validated assays to certify the purity, identity, and quality of test agents according to FDA guidelines and industry standards.
  - Preparation of specifications for release of bulk chemical substances for IND-directed cGLP toxicology studies and manufacturing of clinical supplies for bulk chemical substances of all lots
- Pharmaceutical Research and Development
  - Development of dosage forms for use in human clinical trials
  - Evaluation of salts, non-aqueous solvents, and surfactants, with emphasis on newer techniques to improve solubility or stability (emulsions, prodrugs, and complexation)
  - Evaluation of dosage forms for chemical content, activity in rodent models whenever possible, and feasibility for manufacture on production scale
- Pharmaceutical Production
  - Management of a pharmaceutical production contract for parenteral drug products
  - Production of capsules and tablets for oral use; capability to produce creams and gels for topical use
  - Production adheres to strict cGMP guidelines
- Shelf-Life Surveillance
  - Stability programs for each clinical batch of drug certify potency, identify degradation products, and other aspects as required
  - Testing according to FDA schedules and other guidelines to ensure stability throughout clinical use



## INFORMATION TECHNOLOGY BRANCH (ITB)

ITB manages the wide array of systems and computer infrastructure that captures, stores, analyzes, and reports the vast amount of data that DTP generates. On the IT engineering side, ITB staff focus on four priorities:

- Data sharing
- Modernization of all systems and subsystems running DTP IT infrastructure on a 24/7 basis
- Implementation of security measures to protect user data and IP
- Addition of new applications to address the demands of the dynamic DTP research environment

In 2020, ITB started to build a state-of-the-art, cloud-based data warehouse to store internal NCI-generated data sets and combine relevant public data sets. This warehouse will store experimental results for compounds submitted to the NCI-60 testing pipeline for testing on the long-established NCI tumor cell lines and for compounds tested against patient-derived models (PDMs) *in vivo* (mice) or in organoids. The molecular characterization data on the PDMs, cell lines, and organoids are being added to the warehouse. NCI staff can query the integrated data through a web portal and can dynamically plot and chart the data to visualize the results. Future expansion is planned to accommodate a wide range of preclinical data.

Also, ITB is redesigning and upgrading the entire database infrastructure, compound submission system, and internal QC web interface that DTP uses to store experimental results. This is being done to support DCTD's adoption of a new robotic pipeline to test compounds in the NCI-60 framework, as well as for new testing, on a production basis, of submitted compounds against PDMs in organoids.

## IMMUNO-ONCOLOGY BRANCH (IOB)

IOB supports immunotherapy-related projects within NCI and in the extramural research community. The branch manages an immuno-oncology grants portfolio consisting of preclinical and early-phase clinical studies that focus on using or exploiting the immune system for the treatment of cancer. IOB supports a wide range of research aims, including:

- Enhancement of T cell activity by checkpoint inhibition or other mechanisms
- Assessment of CAR-T cell therapy and other cell-based immunotherapies
- Modulation of the immunosuppressive tumor microenvironment
- Modulation of the immune network with cytokines, chemokines, and other molecules
- Reduction of immunotherapy-associated toxicities

IOB also provides the biomedical research community with guidance on the processes required to develop new immunotherapeutic agents, including preclinical and clinical PK and PD, toxicology and pharmacology, drug formulation and production, and IND-directed regulatory requirements.

In addition to administering grants, IOB develops various immunotherapy resources and funding initiatives to advance immunotherapy-related projects in key areas of scientific investigation. The branch is involved in coordinating the following three NCI-funded research networks:

- PRECINCT, the PRE-medical Cancer Immunotherapy Network for Canine Trials and the related effort, the Integrated Canine Data Commons (ICDC), which provides publicly available clinical and correlative canine cancer data
- Pediatric Immunotherapy Network, launched in 2023 collaboratively with DCB's Cancer Immunology, Hematology, and Etiology Branch, focuses on developing novel immunotherapy treatments for pediatric solid tumors
- The Cancer Adoptive Cell Therapy Network, launched in 2023 collaboratively with the BRB, focuses on the use of adoptive cell therapies against pediatric and adult solid tumors

IOB partners with other programs across DCTD as well as other divisions across NCI and other international funding agencies to support a multidisciplinary approach to immunotherapy. Areas ripe for collaboration include:

- Development of monoclonal antibody imaging agents with the Cancer Imaging Program
- Immune biomarker development with the Cancer Diagnosis Program
- Exploration of immunotherapy/radiation therapy combinations with the Radiation Research Program
- Analysis of complex immune responses with the Biometric Research Program
- Use of system immunology approach to advance IO therapy
- Employing microbiota and engineered microbiota to facilitate IO therapy
- Participation in the Cancer Grand Challenge effort (See "Cancer Grand Challenges" on page 82)

The branch has also coordinated several conferences and workshops to facilitate collaboration and data sharing among extramural investigators in the immunotherapy field, including two Workshops on Cell-based Immunotherapy for Solid Tumors held in December 2018 and 2020, the NIH-AACR Cancer, Autoimmunity, and Immunology Conference held in April 2019 (co-organized by NIAID and NIAMS), and the Workshop on Combining Immunotherapy with Radiotherapy to be held in January 2024 (co-organized by NCI-IOTN, SITC, and AAI). IOB is organizing yearly informative sessions of the three networks noted above at the Society for Immunotherapy of Cancer's (SITC) annual meeting.

## DTP GRANTS OVERVIEW

The DTP research port`folio included 1,127 funded grants with a total budget of approximately $468 million during fiscal year 2023. DTP's grants portfolio covers various aspects of the discovery and preclinical development of small molecule and biological therapeutic agents, such as drug discovery screen assays and models, medicinal chemistry, mechanism of actions, biomarkers, cGMP production, and immunotherapy. DTP's grant award mechanisms and their distribution in terms of research support in 2023 are shown in the accompanying graphs and charts. The predominant mechanism is the individual research project grant (R01), followed by exploratory phase grants (R21) (**Figure 53**).

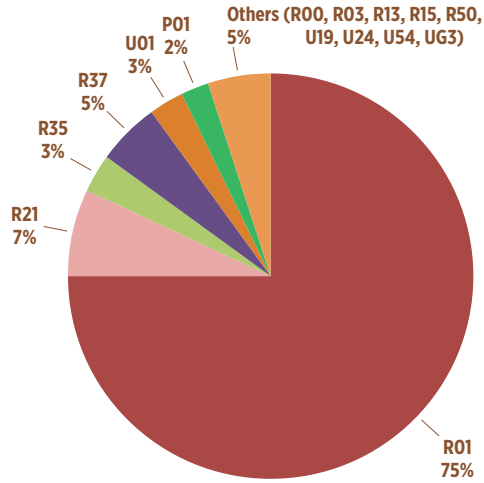



FIGURE 53: DISTRIBUTION OF DTP 2023 FUNDED GRANTS BY MECHANISM.

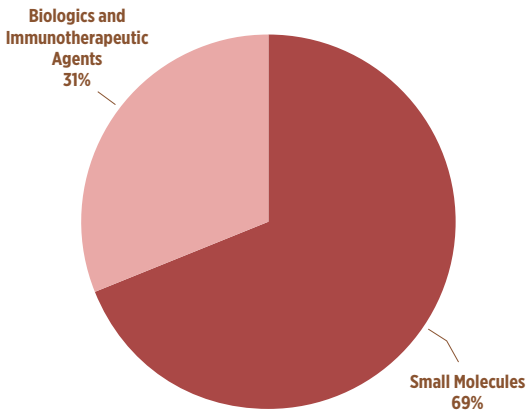



FIGURE 54: DISTRIBUTION OF DTP 2023 GRANT FUNDING BY THERAPEUTIC AGENT CLASS.

| Mechanism | Number of Grants | Dollar Amount |
|---|---|---|
| R01 | 593 | $ 255,646,579 |
| R21 | 108 | $ 22,451,079 |
| R37 | 33 | $ 12,510,214 |
| U01 | 9 | $ 3,932,854 |
| R35 | 11 | $ 10,019,262 |
| R03 | 8 | $ 641,500 |
| R15 | 7 | $ 3,104,735 |
| R50 | 6 | $ 1,013,700 |
| R00 | 7 | $ 1,572,095 |
| P01 | 5 | $ 6,696,334 |
| U19 | 2 | $ 2,916,890 |
| U24 | 3 | $ 1,881,790 |
| U54 | 3 | $ 1,337,011 |
| **Total** | **795** | **$ 323,724,043** |

TABLE 38: FY23 SMALL MOLECULE GRANTS PORTFOLIO.

In 2023, DTP's PTGB grants portfolio contained 795 grants with a total budget of approximately $324 million that support all aspects of small molecule anticancer drug discovery and treatment strategies, including drug design, selective targeting of therapeutic agents, development of new preclinical models for drug discovery, and understanding, preventing, and overcoming drug resistance (**Table 38**). Meanwhile, BRB's and IOB's biologicals grant portfolio contains 313 grants with a total budget of approximately $138 million that supports concept discovery and development for biologic agents, immunotherapy, and cell-based therapies in preclinical models, conducted in parallel with ongoing clinical trials (**Table 39**).

| Mechanism | Number of Grants | Dollar Amount |
|---|---|---|
| R01 | 195 | $ 93,349,997 |
| R21 | 58 | $ 10,153,644 |
| R37 | 22 | $ 11,670,227 |
| U01 | 11 | $ 8,322,209 |
| R35 | 6 | $ 5,323,144 |
| R03 | 5 | $ 476,483 |
| R15 | 3 | $ 1,263,396 |
| R50 | 2 | $ 297,079 |
| R00 | 3 | $ 1,281,431 |
| P01 | 1 | $ 1,411,624 |
| UG3 | 3 | $ 4,125,723 |
| U19 | 0 | $ 0 |
| U24 | 2 | $ 526,576 |
| U54 | 0 | $ 0 |
| R13 | 2 | $ 17,000 |
| **Total** | **313** | **$ 138,218,533** |

TABLE 39: FY23 BIOLOGICAL AND IMMUNO-ONCOLOGY GRANTS PORTFOLIO.

# ASSISTANCE TO THE CANCER RESEARCH COMMUNITY

## NCI-60 HUMAN TUMOR CELL LINES SCREEN

The NCI-60 Human Tumor Cell Lines Screen provides an initial evaluation of the activity of potential anticancer agents. The screen includes cell lines representing nine cancer types: leukemia, melanoma, lung, colon, brain, ovary, breast, prostate, and kidney. The aim of the screen is to identify synthetic compounds and natural product samples, as well as selected biologicals and combinations, showing selective growth inhibition or cell killing of tumor cell lines.

The NCI-60 cell lines have been thoroughly characterized biologically and molecularly through the Molecular Targets Program. There have been more than 300 peer-reviewed publications citing the NCI-60 Cell Line Screen over the past five years. While many of the reports are medicinal chemistry, drug response, and compound studies, an increasing number of publications center on gene expression, genomics, and the development of gene signatures. Other prominent topics include mutation analyses, proteomics, development of bioinformatics methods, biomarkers, microRNAs, metabolomics, epigenetics, and pathways analyses.

The NCI-60 HTS384 Human Tumor Cell Lines Screen consists of a three-step process that starts with a single concentration screen against all 60 cell lines. Agents showing activity are further evaluated across a five-log-concentration range. Agents demonstrating a concentration response are then retested in a confirmatory five-concentration assay.

During FY2023 the NCI-60 Cell Line Screen laboratory:

- Performed single concentration testing on more than 6,063 new synthetic compounds and 333 natural product extracts
- Performed five-concentration testing on 1,743 new synthetic compounds and 63 natural product extracts

As an additional service to the extramural research community, Molecular Targets Program investigators received access to and provided molecular characterization for vials of frozen cell pellets, DNA, RNA, or frozen live cells prepared from each of the 60 cells.

## IN VIVO MODEL DEVELOPMENT AND TESTING

From 2020-2022, BTB assessed:

- 257 plus synthetic molecules
- 3 natural product extracts
- 11 unique vehicle formulations for determination of maximum tolerated dose in preparation for *in vivo* efficacy studies

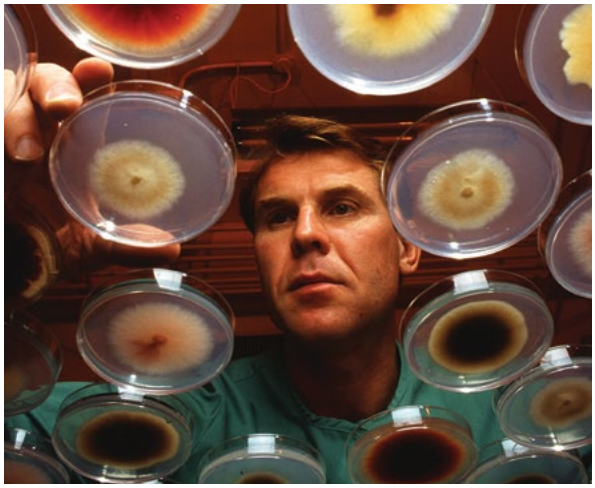
The branch conducted:

- 91 xenograft studies assessing the antitumor activity of small molecules, natural product extracts, and agent combinations, representing more than 70 unique human tumor xenograft models
- 554 drug studies using PDX models to assess efficacy (single agent and/or combination) and/or to collect samples for PD endpoint determinations
- 51 additional mouse studies including general growth assays, assessment of the impact of castration/ovariohysterectomy on estradiol sensitivity and tumor growth, assessment of cloned cell line growth compared to parental cells, and tumor target studies
- 25 studies evaluating the growth of PDX tumor lines in athymic nude rats to assess the utility of using PDX tumors in rats for pharmacological or other studies where a larger experimental animal may afford scientific advantages

As of the end of 2022, the branch received more than 11,000 patient samples (blood or tumor) for implantation into mice to generate PDXs. More than 1,050 PDX models have been created and cryopreserved (>35 distributable vials/model) for distribution through the PDMR. At the end of 2022, 794 PDX models, 305 organoid models, 308 tumor cell lines, and 375 cancer-associated fibroblast cell lines are available to the research community through the PDMR.

## TUMORS, CELLS, CELL LINES, AND MICE

BTB prepares and ships 325–375 orders annually, representing a distribution of more than 2,200 vials of cells, tumor fragments, and cell pellets to individual investigators in the scientific community. The branch published a comprehensive listing of the response data, dosing regimens and toxicities for over 70 approved drugs thus giving access to a large database for the research community to draw upon as they plan preclinical studies (Hollingshead, 2022).



## COLLECTION AND DISTRIBUTION OF SYNTHETIC COMPOUNDS

DSCB maintains a repository of synthetic compounds and pure natural products that are available to investigators for preclinical research purposes (**Table 40**). The repository collection is a uniquely diverse set of more than 250,000 compounds that have been either submitted to DTP for biological evaluation or synthesized under DTP auspices.

| Year | No. of New Submitted Compounds (NSCs) | No. of Compounds Shipped | No. of Plates Shipped* |
|---|---|---|---|
| 2013 | 6,989 | 24,682 | 2,138 |
| 2014 | 4,298 | 20,290 | 1,991 |
| 2015 | 5,560 | 22,190 | 1,912 |
| 2016 | 6,441 | 23,619 | 1,846 |
| 2017 | 6,846 | 21,414 | 1,765 |
| 2018 | 8,870 | 19,156 | 1,624 |
| 2019 | 10,473 | 18,926 | 1,786 |
| 2020 | 3,831 | 5,707 | 720 |
| 2021 | 6,056 | 8,672 | 912 |
| 2022 | 6,002 | 6,425 | 1,457 |
| 2023 | 7,096 | 720 | 1,108 |

TABLE 40: COMPOUND REPOSITORY DISTRIBUTION AND PROCUREMENT SUMMARIES (2013-2023).

* Plates include approved oncology drugs set, structural diversity set, mechanistic diversity set, and natural products set.

## ACQUISITION OF SMALL MOLECULE ONCOLOGY AGENTS

As part of its mission, DSCB acquires samples of investigational oncology agents comprised primarily of targeted small molecules currently in clinical and/or preclinical anticancer studies. These compounds are provided for evaluation in the NCI-60 Human Tumor Cell Lines Screen, as well as to other DCTD programs, such as PADIS and the Molecular Pharmacology Lab in MPB, and to investigators in NCI's Center for Cancer Research (CCR). As oncology treatment moves toward personalized targeted therapeutic agents, the various DCTD human tumor cell line panels are an ideal community-wide tool for further understanding of the disease targets of new agents. All DCTD panel cell lines were thoroughly characterized at the molecular level under the Molecular Target Program, with both in-house and crowd-sourced characterization, including exome sequence mutations, SNPs, DNA methylation, metabolome, mRNA, microRNA, and protein expression. This molecular characterization dataset enables interrogation of patterns of growth inhibition by the investigational drug set looking for characteristics of the cell lines that determine sensitivity. It is anticipated that comparison between drug sensitivity profiles from this data set could lead to the elucidation of common mechanistic targets or pathways, associations with potential response biomarkers, the confirmation of mechanism of action or identification of novel mechanisms, and the uncovering of unexpected "off-target" activities.

Solid samples (5 mg) of most FDA-approved oncology drugs, as well as a plated set of the most current FDA-approved drugs, are available for transfer to external investigators without cost for preclinical research purposes through the DSCB repository.

## LABORATORY OF SYNTHETIC CHEMISTRY

DSCB provides synthetic and medicinal chemistry resources and expertise in support of NExT Program development and discovery projects, the DTP Stepping Stones Program, and the DCTD Acquisition of Oncology Agents initiative. DSCB resources and expertise include iterative drug design and synthesis, synthetic method development, and process synthesis development. One such NExT Program project utilizing DSCB resources involved the preclinical synthesis of two DNMT1 inhibitors, currently in clinical development (phase 1 trials) at NCI. The Laboratory of Synthetic Chemistry (LSC) was responsible for the development of much of the synthetic chemistry that allowed for the preparation of kilogram quantities of potential chemotherapeutics. The large-scale synthesis of both agents to support future canine trials was also accomplished with LSC resources.

The LSC also provides support to the DTP Stepping Stones Program, which provides critical resources for the advancement of innovative anticancer therapeutics toward clinical development. These resources have included synthetic chemical enablement of key lead compounds, preparation of target agents for efficacy and PK studies, and evaluation of alternative salt forms. Finally, DSCB has played a key role in DCTD's oncology drug acquisition initiative that acquires gram quantities of both FDA-approved oncology drugs and promising anticancer investigational agents in clinical and preclinical development. The LSC has provided key synthetic chemistry resources for the preparation of several complex investigational agents that are difficult to obtain through external vendors.

## NATURAL PRODUCTS REPOSITORY

Located at FNLCR, the Natural Products Repository is one of the largest and most diverse collections of natural products in the world, housing:

- More than 200,000 extracts from more than 80,000 plants
- More than 20,000 marine organisms from more than 35 countries
- Extracts of fungi and bacteria from soil and marine environments

NPB initiated the Natural Products Repository Program in 1991 to maximize the potential of the plant, microbial, and marine invertebrate extracts derived from the raw materials that NPB collected. NPB continues to establish collaborative programs with qualified research organizations in source countries for the screening of natural product extracts for activity against cancer and human disease, and the preclinical and clinical development of active agents meeting NCI selection criteria. From 1996, these extracts have been made available (for only the costs of shipment) to organizations and investigators interested in exploring their potential in any disease related to NIH interests (**Table 41**).

NPB provides more than 100 vials per year to the NCI CCR Molecular Targets Program for chemical evaluation of extracts identified as active in targeted assays based on CCR-designated molecular targets. Since 2000, NPB has also executed more than 320 agreements with extramural researchers to investigate the bioactivity and chemical diversity of DCTD's Natural Products Repository extracts.

| Year | Vials | Extract Plates | Fraction Plates | 2nd stage Plates | 2nd stage compounds | Cultures | Total Samples |
|---|---|---|---|---|---|---|---|
| 2018 | 394 | 293 | 428 | N/A | | 1 | 176,835 |
| 2019 | 390 | 135 | 5592 | 163 | | 29 | 1,988,264 |
| 2020 | 1220 | 136 | 720 | 155 | | 0 | 2,483,023 |
| 2021 | 158 | 24 | 912 | 311 | | 12 | 657,804 |
| 2022 | 376 | 12 | 1,457 | 162 | 103 | 86 | 1,914,147 |

TABLE 41: NPB SHIPMENTS TO NON-DCTD INVESTIGATORS AND COLLABORATORS (2018-2022).

## NEW NPB COLLECTIONS

In 2016 NPB gained access to a fungal library through an FNLCR subcontract to the University of Oklahoma Institute for Natural Product Applications and Research Technologies (INPART) to obtain recently collected soil fungi from the United States for culture at NCI. Through the contract, NPB has cultured, photographed, and prepared cryovials of more than 24,000, taxonomically typed, non-duplicative fungi. The soil microbe library extracts will be pre-fractionated and supplied to researchers worldwide.

## NATURAL PRODUCTS SUPPORT GROUP (NPSG)

The Natural Products Support Group provides scientific and technical support to the NPB. The group comprises several laboratories responsible for natural product-based support activities including:

- Extraction of plant, microbial, and marine biota
- Pre-fractionation of natural product extracts
- Isolation and identification of biologically active natural products
- Performing cryo-preservations and microbial fermentations
- *In vitro* drug preparations for screening in DTP assays
- Compound management and preparation support to DTP screening efforts through the NPSG Production Laboratory

**Table 42** describes the specialties and FY22-23 efforts of several natural products laboratories.

| Laboratory | Specialties | Efforts in FY22-23 |
|---|---|---|
| Natural Products Chemistry Laboratory | • Isolates and structurally elucidates biologically active small molecules of interest to DTP<br>• Provides analytical chemistry support<br>• Performs medium- and large-scale isolations of natural products to support NPNPD research collaborations and screening programs | • Worked on 8 HTS campaigns from industry and government collaborators<br>• Investigated more than 450 active subfractions to isolate and identify the bioactive principles<br>• Supplied more than 50 pure natural product compounds for follow-up screening and biological evaluations |
| Fungal Metabolites Laboratory | • Ferments small- and large-scale microbial cultures<br>• Optimizes the production of bioactive metabolites from microbial sources | • Processed and determined that more than 2,600 fungal isolates from the University of Oklahoma were pure and viable (15,000+ cryovial stocks available for future fermentations)<br>• Processed and deposited 2,000+ large-scale fungal fermentations and respective extracts into the NCI DTP Repository |
| Automation Laboratory | • Prefractionates plant, marine, and microbial extracts from the NCI Natural Products Repository<br>• Plates samples in 96- and 384-well-plate formats suitable for HTS | • Developed automated methods for the prefractionation of marine aqueous samples to generate a protein-enriched screening library for HTS (first and only library of its kind)<br>• Performed an average of two pre-fractionations per week<br>• Ran and generated 1,232 fractions per week<br>• Prefractionated 84,000 extracts, generating more than 588,000 fractions<br>• Produced 35 replicates of 1,810 unique pre-fractionation 384-well plates ready for HTS |
| Production Laboratory | • Solubilizes, plates, and delivers drugs for in vitro testing within DTP<br>• Performs extractions of natural product samples from plant, marine, and microbial sources | • Processed 4,900 synthetic compounds and 936 natural product samples using the single-dose NCI-60 screen<br>• Processed 978 synthetic compounds and 134 natural products, extracts, and fractions using the 5-Dose NCI-60 screen<br>• Prepared 4 combination experiments (240 total combinations) and 40 copies of the Approved Oncology Drugs 384-well plates for organoid experiments to support DTP Molecular Pharmacology Branch<br>• Delivered the Approved Oncology Drugs and Investigational Oncology Argents for screening (in support of the NCI-60 screen to 384-well Cell Titer-Glo Luminescent Cell Viability Assay transition)<br>• Extracted more than 2,000 fungal fermentations from the Fungal Metabolites Laboratory |

TABLE 42: NPB LABORATORY EFFORTS IN FY22-23.

## CGMP MANUFACTURING AND FORMULATION

PRB produces clinical supplies and chemistry, manufacturing, and control (CMC) data to support DCTD-sponsored INDs (**Figure 55**). Several new clinical candidates are in advanced IND development stages. The branch synthesized several distinct compounds ranging in batch sizes of grams to multi-kilograms, often manufacturing additional batches as the need arose. PRB also validated high-pressure liquid chromatographic (HPLC) analytical methods that were developed for several distinct compounds in advanced development, with individual lots undergoing complete analytical assessment and release for advanced preclinical studies (IND directed) and/or use in preparing clinical dosage forms.

- Z-Endoxifen
- T-dCyd (4'-thio-2'-deoxycytidine)
- Aza-T-dCyd (5-aza-4'-thio-2'-deoxycytidine)
- IPdR (5-iodo-2-pyrimidinone-2'-deoxyribose)
- LMP-400
- LMP-776
- LMP-744
- FdCyd/THU (5-fluoro-2'-deoxycytidine / tetrahydrouridine)
- PU-H71
- DMS-612
- 1-MT
- Fenretinide
- Safingol
- TRC102
- Phenformin
- O6BG
- FAU
- SJG136
- AFP464
- Triapine
- Novobiocin
- TAK-143

FIGURE 55: CLINICAL SUPPLIES RECENTLY PROVIDED BY PRB FOR NEW OR ONGOING TRIALS.

In addition, PRB did the following:

- Prepared parenteral dosage forms, including freeze-dried and liquid-filled products
- Prepared oral dosage forms (mostly capsules) of several compounds in multiple batches and strengths to accommodate dosing needs in ongoing clinical trial conducted shelf-life studies of these preparations at several points each year
- Performed pre-formulation and formulation to identify the conditions required for preparing suitable and stable formulations, with the results transferred to the manufacturers of the clinical supplies
- Synthesized several lots of GMP bulk drugs, requiring quality-control release testing of each batch
- Developed formulations and/or new size configurations manufactured sterile injectable and capsule dosage forms as appropriate for each drug

## THE BIOPHARMACEUTICAL DEVELOPMENT PROGRAM (BDP)

The BDP manufactures cGMP material for IND-directed toxicology and clinical use in phase 1, early phase 2, and non-pivotal phase 3 clinical trials. Established in 1993, the BDP mission is to advance the development of novel therapeutics for treatment of cancer and other diseases by providing manufacturing, process development, process analytics, quality assurance, and regulatory affairs capabilities and expertise. The BRB provides programmatic, contractual, technical, and budgetary oversight of the BDP.

### Facility

The BDP is located at the ATRF, a state-of-the-art research facility at FNLCR with 55,000 ft$^2$ occupied by a process development laboratory, cGMP manufacturing, and fill-finish suites (**Figures 56** and **57**). The cGMP facility contains distinct upstream bioprocessing and purification trains for mammalian and bacterial/yeast products, plus separate isolated suites for viral vector production and cell therapy manufacturing. The BDP facility often serves as a site for the FDA's biologics inspectors training program and maintains cGMP compliance through audits by qualified independent contractors.

### Capabilities

- cGMP manufacturing, filling, testing, and release
- Process development and feasibility studies

- Process Analytics/QC testing
- Quality Assurance oversight
- Regulatory Affairs support
- Development and manufacturing capabilities for biologics, including monoclonal antibodies, recombinant proteins, viral and DNA vaccines, peptides, gene therapy products, nucleic acids, and cell-based products

FIGURE 56: ADVANCED TECHNOLOGIES RESEARCH FACILITY IN FREDERICK, MD.

FIGURE 57: CGMP FILL/FINISH ACTIVITY AT THE BDP, FNLCR.

## Activities

Since 2017, 18 BDP products have been used in IND-supported clinical trials. In that interval, BDP released 21 new product lots including GMP lots, master cell banks, toxicology/engineering lots, diluents/placebos, and other associated products. BDP provides quality control, quality assurance, and regulatory support for its products, including technical packages for pre-IND meetings with FDA; CMC documents for IND applications; post-filing technical and regulatory assistance, as well as ongoing stability studies for the duration of their use in clinical trials. The following are some significant milestones for BDP products in recent years:

- Two novel oncolytic herpesviruses produced at the BDP entered clinical trials for glioblastoma at University of Alabama Birmingham: M032 and C134
- Technology transfer of the recombinant poliovirus (PVS-RIPO) manufacturing and testing from BDP to Istari Oncology for commercial development to treat glioblastoma and other solid tumors
- Production and release of CD33-targeted Chimeric Antigen Receptor (CAR) autologous T-cell therapies for 26 pediatric and young adult AML patients; this multi-center clinical trial was approved in July 2019, with manufacturing by the BDP continuing in support of a planned allogeneic arm (clinical trial number: NCT03971799)
- Successful cGMP production of a novel recombinant FGF-1 molecule, TTHX114, to be evaluated in clinical trials for treatment of Fuchs Dystrophy
- Development and cGMP production of two Epstein-Barr virus (EBV) virus-like particle (VLP) vaccines, EBV-gp350-FN (clinical trial number: NCT04645147) and EBV-gHgLgp42-FN for clinical investigations
- Development and generation of a chimeric monoclonal antibody that targets canine CTLA-4 to be used in clinical trial in pet dogs through the NCI Comparative Oncology Program. This agent is designed to be a canine version of the human drug ipilimumab and a tool in the establishment of the dog as a model for human immunotherapy development and study.

## Training

The BDP provides training on GMP regulations (21 CFR 210, 211). Besides BDP employees, participants in this training have included scientists involved in cGMP manufacturing, quality control, and supporting operations at the NIH and FDA. In addition, the BDP was selected to train reviewers and inspectors from FDA's Center for Biologics Evaluation and Research and Center for Drug Evaluation and Research.

## Partnerships and Service

Technical and regulatory expertise and specialized capabilities in BRB and BDP primarily support the production of biologic agents for DCTD initiatives; however, the BDP is frequently

engaged in collaborations within NCI as well as outside of NCI with the following other government programs:

- CCR for cancer and AIDS vaccines, and autologous cell therapies
- NCI Division of Cancer Prevention for novel cancer vaccines supported by the PREVENT program
- NIAID and the U.S. Army Medical Research Institute for Infectious Diseases for vaccine development to treat or prevent infectious diseases
- National Center for Advancing Translational Sciences for rare and neglected disease treatments and gene therapies

In addition, a range of programs outside DCTD that are involved in drug development frequently seek staff expertise:

- Source Evaluation Groups or Special Emphasis Panels reviewing grant applications and contract proposals for non-NCI initiatives
- Steering committees for new NIH programs in infectious disease or nanotechnology applications
- New biopharmaceutical programs and academic institutions in developing countries for in-plant training of their senior staff
- New foreign production plants collaborating with NIH requiring the conduct of site visits

## BRB PRECLINICAL REPOSITORY

This NCI-sponsored facility stores cytokines, monoclonal antibodies, and other biologic reagents under carefully controlled conditions. The repository provides a uniform, high-quality supply of these reagents to qualified research investigators at academic and non-profit institutions at no charge.

One of the more popular BRB Repository requests is the NIH collection of Recombineering Bacteria Strains and Plasmid Vectors that investigators use to create new molecular entities for further study or manufacturing. Other popular agents developed and manufactured under NCI-sponsored programs that are available through the repository include anti-GD2 ch14.18 and 1A7 monoclonal antibodies, and IL-7, IL-12, and IL-15 cytokines.

BRB negotiates with companies and investigators to obtain, by donation or at reduced cost, new materials to enrich the repository's supply of reagents. Many donated lots are expired commercial clinical materials that BDP retests or revials to enable distribution of high-quality reagents for research and development use only. Online ordering and standard material transfer agreements provide agents to the research community. Since 1996, more than 80,000 vials of different reagents have been shipped domestically and internationally to over 4,000 scientists. Following a significant drop in requests related to the COVID pandemic in 2020-2021, the repository has been completing an increasing number of orders each year (**Figure 58**).

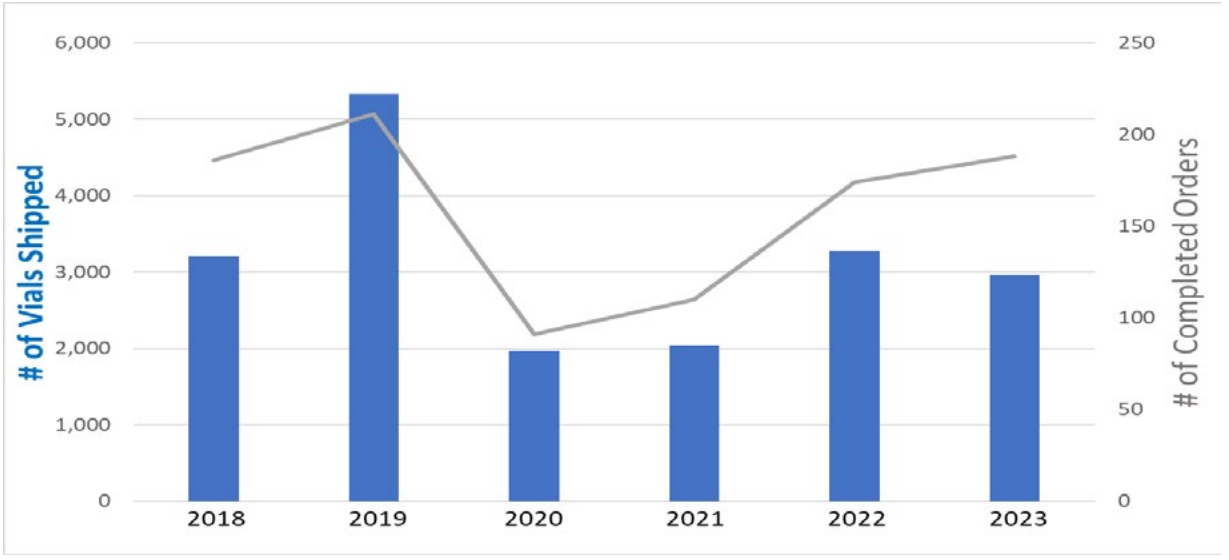



FIGURE 58: NUMBER OF VIALS SHIPPED FROM AND NUMBER OF ORDERS COMPLETED BY THE BRB PRECLINICAL REPOSITORY.

# FUTURE DIRECTIONS

DTP continues to provide more services, resources, and expertise to the academic and private sectors to facilitate the discovery and development of new cancer therapeutic agents. Over the next five years, DTP plans to focus on the following key areas:

## EXPAND OUR PRODUCTION CAPABILITIES FOR BIOLOGICS AND CELLULAR THERAPIES

The Biological Resources Branch will continue expanding its production capabilities of biologics and cell therapy resources by providing a centralized CAR-T cell manufacturing location for clinical trials nationwide. The current turnover time between patient sample reception and shipping of the cell therapy back to the clinical trial site is approximately two weeks. In addition, DTP will expand the development of cell-based assays to assess and understand the therapeutic toxicities of these new cellular therapies.

## ENHANCE THE SUPPORT FOR EXTRAMURAL IMMUNO-ONCOLOGY DISCOVERY AND DEVELOPMENT

The Immuno-Oncology Branch supports peer-reviewed research projects in areas of emerging interest. Among these areas are small molecule immunomodulators, 3-dimensional organ and tumor systems consisting of multiple cell types and structural components, and the role of the tumor microenvironment or the crosstalk between tumor and the microenvironment as one of the modes of action for immune-oncology. DTP will continue to provide valuable resources to the immuno-oncology community by acquiring and distributing well-characterized reagents.

## ENHANCE THE SUPPORT FOR NATURAL PRODUCT DISCOVERY AND DRUG DEVELOPMENT

DTP continues accelerating the discovery of new bioactive compounds from extracts in the NCI Natural Products Repository extracts. The NCI Program for Natural Products Discovery (NPNPD) is a joint endeavor between CCR and DCTD to create an approximately 1,000,000-sample partially purified natural product library for screening by extramural institutions. The Natural Products Branch continues to grow the number of Material Transfer Agreements (MTAs) and Non-Disclosure Agreements (NDAs), with these centers for the isolation and structure elucidation of active natural products.

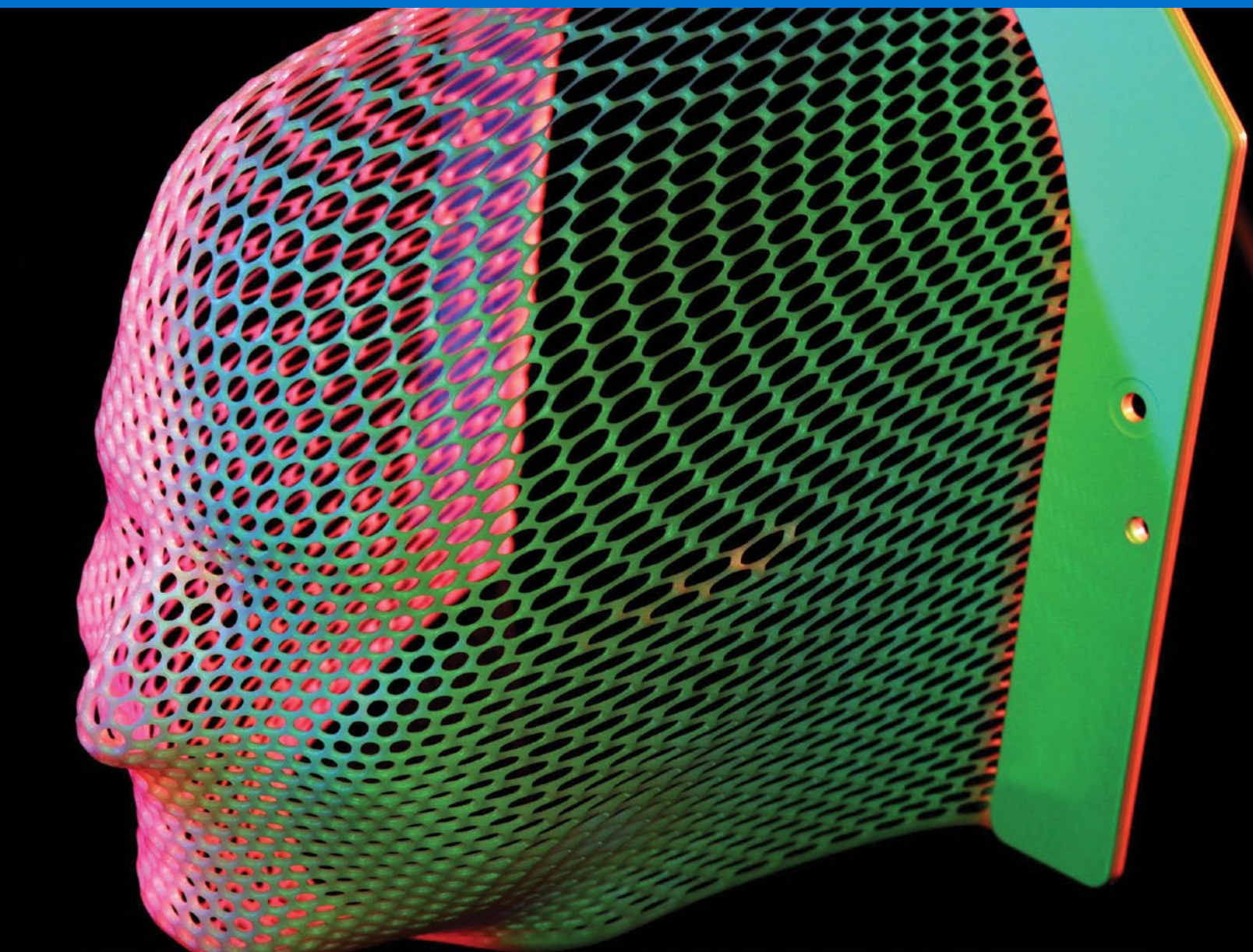
## DEVELOP AND IMPLEMENT AN OPEN DATABASE CONTAINING ALL NON-CONFIDENTIAL DCTD BIOLOGICAL DATA

The next five years will see a boom in the use of Artificial intelligence (AI) models to interconnect and analyze very large and heterogeneous biological datasets. This should lead to the creation of predictive models to guide therapeutic development. DTP is building a modern DCTD Data Warehouse, where large datasets will be publicly available for the external community to use and run in their AI models.

DTP staff will continue to support the best translational research based on peer review and clinical need, catalyze interactions among scientists, educate the scientific community on peer review and grant policy changes, inform grantees about DCTD drug development services such as NExT, and organize workshops. DTP staff will continue their involvement in the NExT Program, serving as team members of working group committees and providing contract-based resources for approved projects where appropriate.

PROGRAMS AND INITIATIVES (2020-2023)

# RADIATION RESEARCH PROGRAM



# OVERVIEW

The field of radiation oncology has a unique scientific and clinical breadth that includes:

- Radiation and stress biology
- Complex tumor and normal tissue systems biology involving cancer care and radiation effects related to space flight (NASA) energy policy (Department of Energy (DOE))
- Innovative technology, electronic data acquisition, and "big data" analysis
- Image-guided therapy
- Particle radiation therapy (RT; protons, carbon ions, and others); neutron capture therapy
- Multimodality cancer treatment and radiation-inducible targets
- FLASH radiotherapy and Spatially Fractionated Radiation Therapy (SFRT)
- Immunology including induction of the immune response
- Radiopharmaceutical therapy (RPT) and theranostics
- Non-ionizing radiation (hyperthermia, ultrasound, photo dynamic therapy)
- Outreach to the underserved and global cancer care
- Health, medical, and societal response to threats from nuclear and radiological disasters, potentially including terrorism involving Administration for Strategic Preparedness and Response (ASPR), National Institute of Allergy and Infectious Diseases (NIAID), Federal Emergency Management Agency (FEMA), and the Departments of Homeland Security, Defense, and State

With its research base in basic biology, physics, chemistry, and clinical care that encompasses the entire spectrum of oncology, radiation oncology has a unique role in multidisciplinary translational science collaboration. More than half of people with cancer receive RT during their cancer treatment, which is effective both as a curative modality and for palliative care. The Radiation Research Program (RRP) is the sole program focused on therapeutic radiation sciences within the extramural programs of NCI.

As part of ongoing efforts to stimulate research in RT and radiation biology, RRP staff support basic, physics, translational, and clinical RT research within DCTD by:

- Providing expertise to investigators and potential grantees who perform cutting-edge research with radiation and other forms of energy
- Helping to organize and lead the RT research community in establishing priorities for the future direction of radiation research, including interagency cooperation and collaboration
- Developing and promoting collaborative efforts among extramural investigators for both preclinical and clinical investigations, including the evaluation of systemic agents that can be used in combination with radiation
- Evaluating the portfolio of radiation research being conducted by NCI grantees
- Advising NCI-funded clinical trial groups and the Cancer Therapy Evaluation Program (CTEP) regarding scientific priorities and quality assurance in clinical studies with RT
- Developing unique models and capabilities to help and mentor medically underserved communities in the United States and worldwide to gain access to cancer clinical trials and follow-up care
- Serving as the NCI liaison and advisor on the mitigation of radiation injury to normal tissue and the development of biomarkers for radiation injury in programs addressing radiological and nuclear terrorism in NIAID and ASPR within the Department of Health and Human Services (HHS)
- Partnering with the Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) programs for advanced development of biological and technical discoveries related to radiation oncology
- Working and coordinating with professional societies to publicize research efforts and findings in radiation oncology and biology

RRP coordinates its activities with other radiation research efforts at NCI, in particular the Divisions of Cancer Biology (DCB), Cancer Control and Population Sciences (DCCPS), Cancer Epidemiology and Genetics (DCEG), and the Center for Cancer Research's (CCR) Radiation Oncology Branch (ROB), Radiation Biology Branch, and Molecular Imaging Program, as well as NIH, other federal agencies, and national and international research organizations. RRP also serves as a focal point for extramural investigators who are concerned with clinically related radiation oncology and biology research.

# PAULA JACOBS
## ACTING ASSOCIATE DIRECTOR

Paula M. Jacobs, Ph.D. is Acting Associate Director, Radiation Research Program (RRP), Division of Cancer Treatment and Diagnostics (DCTD), National Cancer Institute (NCI) and an Adjunct Investigator at the NCI Center for Cancer Research. Dr. Jacobs received her undergraduate degree in chemistry at the Massachusetts Institute of Technology (MIT) and graduate degrees at Tufts University and Northeastern University. Her post-doctoral training was at Northeastern University, MIT, and Peter Bent Brigham Hospital/Harvard Medical School.

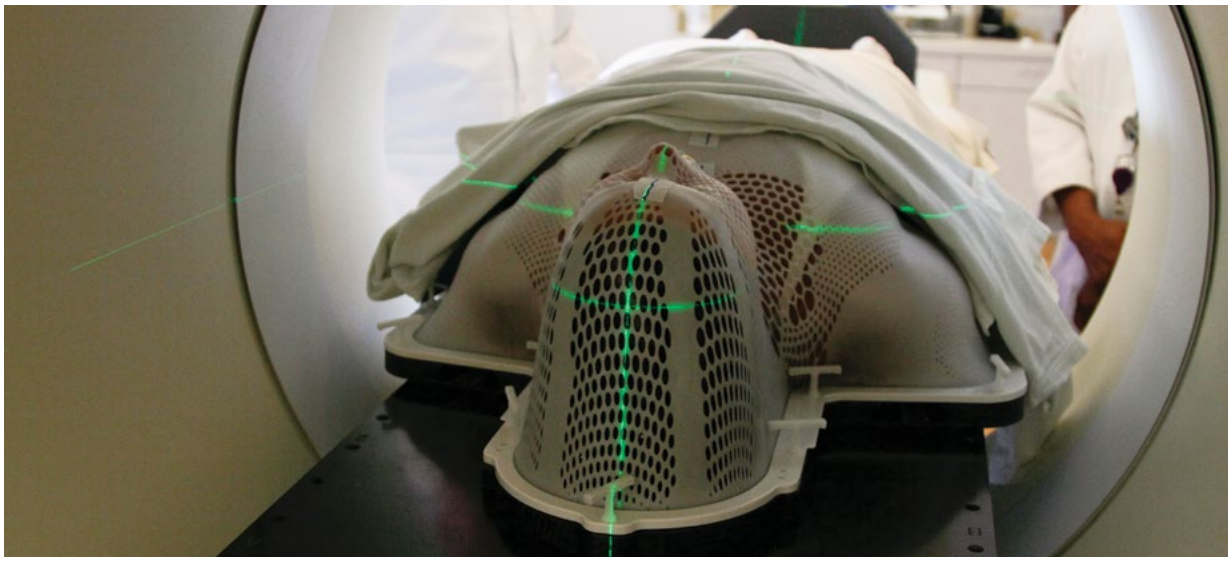
Her responsibilities in RRP include oversight of an extramural grant program in radiation research, including external radiation therapy, radiation biology, and radiopharmaceuticals for targeted radiation therapy.

She is a member of the FDA Medical Imaging Drugs Advisory Committee and on steering/advisory committees for the Integrated Canine Data Commons, the Small Animal Imaging Program at Frederick National Laboratory for Cancer Research, and the NIBIB Medical Imaging Data Resource Center. She is a member of the Editorial Board for Academic Radiology and the SNMMI Artificial Intelligence Task Force. She also directs a radiochemistry facility that prepares preclinical and early clinical radiopharmaceuticals in support of therapeutic drug development and characterization of patient-derived xenograft models of cancer.

Prior to this, she was Associate Director, Cancer Imaging Program, DCTD, where she oversaw an extramural grant program in the areas of molecular imaging, nanotechnology, image-guided interventions, imaging technology, and clinical trials in imaging. She also focused on lowering the logistical and regulatory barriers to investigational use of PET radiopharmaceuticals for therapeutic drug development, developed The Cancer Imaging Archive, a publicly available image archive with associated clinical meta-data for imaging-genomic correlations and development of computer-aided diagnosis software, and encouraged standardization of imaging techniques and quantitative image methods for use in clinical trials.

She joined NCI after 30 years of diverse experience in the pharmaceutical and medical device industries. Her last industrial position was Vice President of Development at Advanced Magnetics where she was a key developer of ultrasmall superparamagnetic iron oxide nanoparticles as magnetic resonance imaging agents and iron replacement therapeutics.

She has published in the areas of organic chemistry, inorganic chemistry, magnetic resonance imaging, PET imaging, regulatory affairs, neuro-oncology, and nephrology.



## STRUCTURE AND FUNCTION

The recently established Office of the Associate Director (OAD) and RRP's administrative staff, led by a program analyst and administrative coordinator, oversee the activities of the two branches comprising RRP's organizational structure:

- Radiotherapy Development Branch (RDB)
- Clinical Radiation Oncology Branch (CROB)

In general, RDB approaches the issues from the biological perspective and CROB from the technical and clinical care perspectives. Since physical energies and perturbations work through biological mechanisms, RRP staff must integrate our expertise across the branches to cover the breadth of the responsibilities included above in the Overview.

The primary responsibility of RRP is to the grantees and contractors of NCI and NIH. In fiscal year 2023 (FY23), RRP administered 208 grant applications. In addition to conducting grants management, RRP staff members advise on and act as reviewers for grants and contracts submitted to the U.S. Department of Defense (DoD) and consult on radiation issues with program staff in NIAID, the Biomedical Advanced Research and Development Authority (BARDA), and the National Aeronautics and Space Administration (NASA).

### RADIOTHERAPY DEVELOPMENT BRANCH (RDB)

RDB is primarily responsible for administering and coordinating grants with the other DCTD programs and NCI Divisions. In addition to their work for NCI, the RDB staff with specific expertise work with colleagues in other aspects of the federal government and coordinate research and development activities with:

- NASA - space biology
- DOE - technology; artificial intelligence (AI); advanced computing; radionuclide therapy
- NIAID and DHHS - normal tissue biology; biomarker development for nuclear/radiological disasters

RDB staff approach the branch's research areas from the biological perspective, by:

- Understanding:
  - The mechanism of RT in the context of molecular and cellular processes to identify therapeutic targets and improve treatment strategies
  - Radiation modifiers, including sensitizers and protectors, and radiation-nanotechnology
  - Normal tissue injury and treatments to prevent or mitigate these injuries
  - Systemic targeted radionuclide therapy also called RPT
  - Non-ionizing radiation-based therapies such as photodynamic therapy, hyperthermia, and focused ultrasound

- Combining the molecular targeted and immuno-oncology therapies with standard and emerging targeted treatments to create new treatment paradigms
- Developing preclinical and clinical multi-modality cancer therapy including diagnosis, predictive and prognostic biomarkers, treatment, and long-term outcomes/toxicity
- Examining how radiation-inducible changes at the physical and molecular scales in both tumor and normal tissues can be used to improve outcomes with drugs and modulators
- Developing and implementing advanced technologies for the production and delivery of radiation (in collaboration with RRP's CROB), as well as sensor modalities to monitor biological changes before, during, and after RT

### CLINICAL RADIATION ONCOLOGY BRANCH (CROB)

CROB coordinates the clinical and translational research grant portfolio in clinical radiation oncology and RPT, the technical and physical aspects of radiation research, and the development of new therapeutic approaches. In addition to grant and program management, a central role for CROB includes working with:

- CTEP and Cancer Imaging Program (CIP) – Assisting with their cooperative clinical trial groups and early-phase trials consortia
- The Coordinating Center for Clinical Trials (CCCT) – Working with steering committees and task forces

The transformation of medicine with advanced technology, information management, big data and AI and machine learning provides novel opportunities and unique roles for radiation-oncology sciences. The efficacy of emerging technologies such as FLASH radiotherapy, SFRT, and particle therapy, highly depend on the biological perturbations they create; therefore, the distinction between physics in CROB and biology in RDB is somewhat artificial, so the program directors work closely on radiation science and technology. The capacity of radiation to focus the RT provides unique opportunities in data acquisition and analysis.

In addition to managing grants, CROB devotes a substantial effort to supporting NCI, NIH, HHS, and government-wide activities, such as technology development and assessment, comparative effectiveness research, and the application of precision medicine.

## RRP EXTRAMURAL INTEREST GROUPS AND INTERACTION WITH PROFESSIONAL ORGANIZATIONS AND SOCIETIES

The RRP program and medical officers collaboratively manage grants that deal with image-guided RT (IGRT), the physics of basic radiation track (beam) structure, and radiation chemistry. Establishing scientific dialogue with radiation oncologists, physicists, and biologists enhances the perspective of those within and outside government leading to new areas of research. This occurs through periodic workshops often co-sponsored by RRP and professional societies and more routine opportunities for dialogue. To that end, RDB and CROB facilitate coordination of scientific interest groups in the areas of brain metastases, colorectal cancer, upper gastrointestinal tract cancer, glioblastoma, sarcoma, hepatocellular carcinoma, radiation-immune system, and imaging. These interest groups interface with extramural radiation oncology researchers to develop radiation modifiers for tumor sensitization and to establish assays for better guidance of clinical trial designs. RDB and CROB also facilitate interest groups on Neutron Capture Therapies (NCT), Targeted Radionucleotide Therapies (TNT), and quantitative imaging, which fundamentally involve both physics and biology.

RRP staff frequently partner with NIAID, BARDA, and NASA and organize strategic workshops and symposia within NCI and at the national and international levels. They highlight emerging areas of RT that interface with cancer biology, prevention, diagnosis, and treatment from the perspective of tumor and normal tissues and address overarching issues in radiation research, such as:

- The future of radiation biology research
- Precision medicine
- Particle and systemic radionuclide therapies
- Reproducibility of preclinical translational research

RRP collaborates with many national radiation-related clinical and research professional societies to facilitate transition of the most promising, radiation-based, experimental therapies to clinical practice such as:

- ASTRO
- Society of Nuclear Medicine and Molecular Imaging (SNMMI)

- Radiation Research Society
- American Association for Physicists in Medicine
- American Association for Cancer Research
- Society for immunotherapy of Cancer
- American Society of Clinical Oncology
- International Atomic Energy Agency
- International Agency for Research on Cancer
- World Health Organization
- Union for International Cancer Control
- Pan American Health Organization
- Consortium of Universities for Global Health

The international collaborations assist countries and provinces with cancer control planning, especially related to human and other resources required for improving cancer detection and management using RT and allied treatments.

## RRP PARTNERSHIP WITH NCI PROGRAMS, DHHS HEALTHCARE RELATED AGENCIES

The RRP OAD coordinates formal and informal relationships beyond RRP including:

- The NCI SBIR and STTR Programs – Establishing priorities for programs involving radiation to help bring new treatments and technology to cancer care.
- The National Cancer Informatics Program, the NCI Center for Biomedical Informatics and Information Technology (CBIIT), and the NIH Center for Information Technology (CIT) – Formulating concepts for demonstration projects using radiation oncology as a platform, including telemedicine with TELESYNERGY®.
- The NCI Center for Global Health (CGH) – Developing topics for conferences and potential research programs involving RT as a component of global cancer research and care.
- The Information Technology for Cancer Research (ITCR) Consortium - Helping to promote IT solutions for cancer treatment involving RT.
- NCI's Center to Reduce Cancer Health Disparities (CRCHD) – Helping with issues relating to the accrual of underserved populations to cancer clinical trials.
- NIAID – Assisting in the identification of opportunities for radiation countermeasure investigators to decrease treatment toxicity in patients with cancer and for the development of biomarkers for whole or extensive partial body exposure for use in triage and medical management.
- The Food and Drug Administration (FDA) – Assisting in identifying needs and opportunities for post-marketing surveillance of devices cleared for use in radiation oncology, and in establishing endpoints and benchmarks for the approval/clearance of new drugs and devices.
- The Agency for Healthcare Research and Quality (AHRQ) and the National Academy of Sciences (NAS) – Assisting in identifying priorities and opportunities for comparative effectiveness research in cancer.
- The DoD Armed Forces Radiobiology and Research Institute (AFRRI) - Discussing ways in which cancer clinical trials may help in licensing of radiation countermeasures.
- DOE – Partnering to promote innovative technology, systems, and big-data analysis.
- The Department of Veterans Affairs – Facilitating quality improvement in radiation oncology at Veterans Health Administration (VHA) facilities, as well as in improving connectivity among various components of the VHA electronic health record and other radiation oncology networks, such as the recently formed NRG Oncology Group (merger of the NSABP, RTOG, and GOG).

## RRP GRANTS OVERVIEW

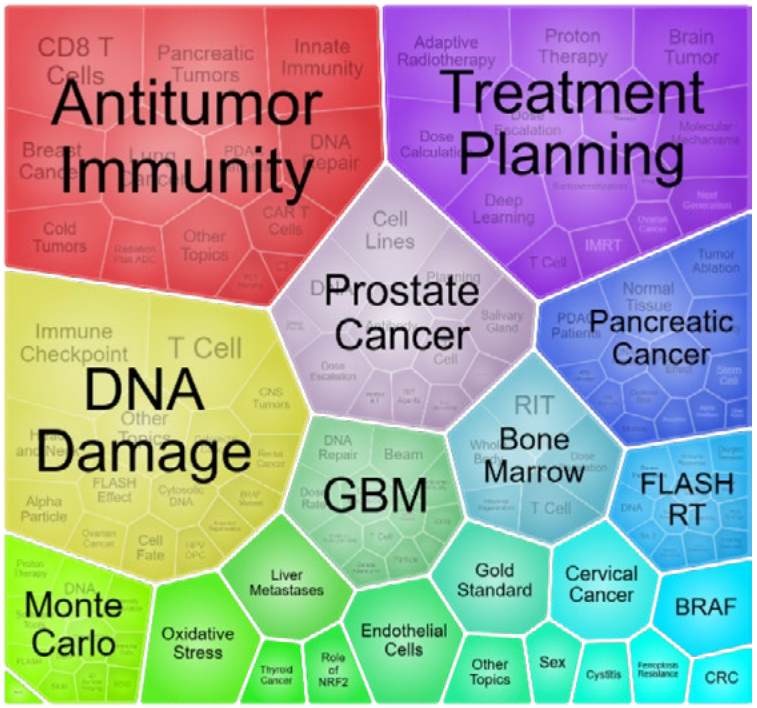



FIGURE 59: RRP 2023 GRANTS - HIERARCHICAL VISUALIZATION OF TOPIC CLUSTERS.

The 2023 RRP research portfolio comprised approximately 208 awarded grants distributed across several areas of radiation research (**Figure 59**). The grant award mechanisms used by RRP and their distribution in terms of research support in 2023 are shown in **Figure 60**. The predominant mechanism is the individual research project grant (R01), followed by research program project grants (P01).

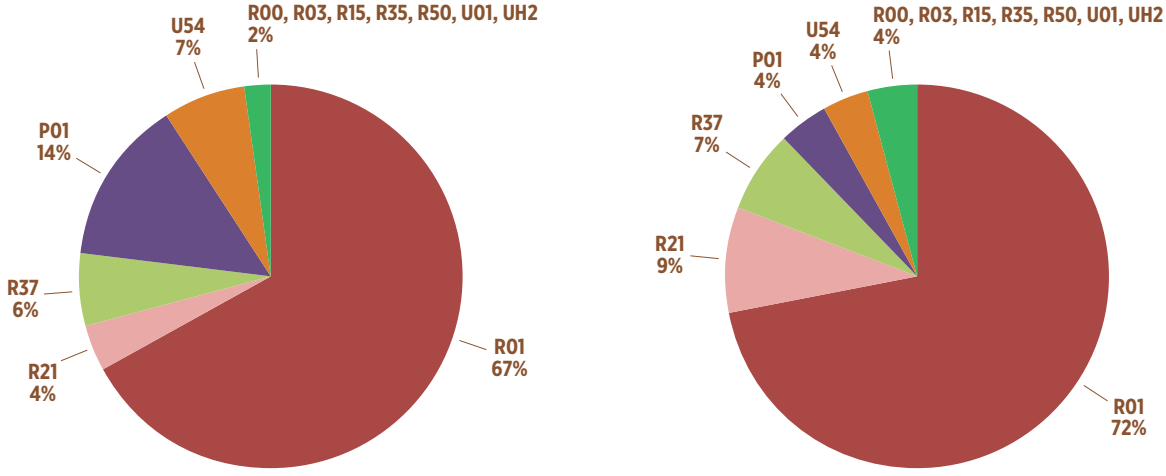



FIGURE 60: DISTRIBUTION OF RRP 2023 GRANT FUNDS (LEFT) AND NUMBERS OF GRANTS (RIGHT) BY MECHANISM.

# ASSISTANCE TO THE CANCER RESEARCH COMMUNITY

## IMAGING AND RADIATION ONCOLOGY CORE (IROC)

The IROC provides integrated radiation oncology and diagnostic imaging quality control programs in support of the NCI's National Clinical Trials Network (NCTN), thereby assuring high quality data for clinical trials designed to improve the clinical outcomes for patients with cancer worldwide. A major strength of IROC is the ongoing development of an IT infrastructure that fully integrates informatics and quality assurance (QA) services across six IROC QA Centers to enable the easy transmission of imaging and RT data sets for receipt, assessment, validation, and archiving using a common web portal for all data entry and a common database of imaging and RT QA data. The NCTN Groups and associated investigators seamlessly share and access the data sets, which support trial outcomes analyses.

Previously funded grants were combined in the NCTN structure to form and provide support for the IROC infrastructure (**Table 43**).

| Location | Expertise |
|---|---|
| **IROC Houston QA Center**<br>MD Anderson Cancer Center | • Interacts with approximately 1,800 national and international research sites through its remote and on-site dosimetry quality audits, extensive RT credentialing programs, QA of brachytherapy treatments, and proton clinical trial QA program<br>• Design, implementation, and analysis of QA anthropomorphic phantoms for credentialing and maintains the only QA database of radiation oncology sites participating in NCI-sponsored research |
| **IROC Ohio QA Center**<br>The Ohio State University<br>Wexner Medical Center and James Comprehensive Cancer Center | • All aspects of imaging in oncologic trials<br>• Participates in the Imaging Response Assessment Teams, the Virtual Imaging Evaluation Workspace (VIEW) consortium, and the Oncology Biomarker Qualifying Initiative |
| **IROC Rhode Island QA Center**<br>Lincoln, RI<br>University of Massachusetts Medical School | • Real-time, on-site, and remote review of imaging and RT objects (e.g., tumor, lymph nodes, and normal tissue organs at risk specified in the study) to prevent research protocol deviations capable of invalidating trial results<br>• Developed a comprehensive, fully validated informatics infrastructure for acquisition, management, and review of imaging and RT objects |
| **IROC St. Louis QA Center**<br>Washington University | • Data exchange formats, data QA processes, and an informatics infrastructure for transmission, receipt, and analysis of imaging and treatment planning data from participating sites<br>• Consensus contouring atlases and supporting secondary analyses |
| **IROC Philadelphia (RT) QA Center**<br>ACR Research Center in Philadelphia | • Broad range of RT protocols involving advanced RT modalities, including 3D-conformal RT (CRT), intensity-modulated RT (IMRT), and IGRT<br>• Collaborates with physicists, dosimetrists, and radiation oncologists in developing protocols and credentialing techniques<br>• Conducts case reviews using a centralized remote review system<br>• Develops and standardizes credentialing for IMRT and lung stereotactic body RT |
| **IROC Philadelphia (Imaging) QA Center**<br>ACR Research Center in Philadelphia | • Imaging trial support for NCTN studies involving positron emission tomography (PET), magnetic resonance (MR), and computed tomography (CT), and most disease sites<br>• VIEW consortium, standardized image management processes, and QA and analysis approaches across the NCTN system |

TABLE 43: IROC LOCATIONS AND EXPERTISE.

## RADIOBIOLOGY BIOTERRORISM RESEARCH AND TRAINING GROUP (RABRAT)

RABRAT is an informal interest group comprising representatives from Federal agencies to discuss opportunities and items of mutual interest on research and training for meeting the challenges of radiation/nuclear terrorism. RABRAT meets three to four times per year.

## WORKSHOPS

### Engineering New Instrumentation for Imaging Unsealed Source Radiotherapy Agents – August 16-17, 2021

This workshop discussed and proposed imaging instrumentation and methods for directly imaging the distribution of a therapeutic agent, and thereby, estimate the delivered radiation dose in real time to the cancerous and normal tissue. The workshop summary report (Zubal, 2022) describes how this would result in the unprecedented ability to assess the biodistribution of the radiotherapy ligand at multiple times and provide highly accurate, direct quantitation of each patient's treatment dose. Improved direct imaging of the therapy agents could verify that the PET imaging analogues have the same pharmacokinetics as the therapy agents they are meant to mimic. The goal is to obviate the use of imaging analogues for future radiotherapy agents, especially for long-lived agents with complicated decays resulting in radioactive daughters.

### NCI Workshop on Neutron Capture Therapy (NCT) for Cancer - April 20-22, 2022

The goals of this workshop were to assess the state of NCT and stimulate new ideas for relevant neutron capture isotopes. NCT involves nuclear capture and fission reactions that occur when an appropriate isotope, e.g., boron-10, is irradiated with low-energy (thermal) neutrons. This requires powerful (high flux) neutron sources and compounds capable of delivering neutron capture isotopes selectively to tumor cells or their microenvironment. Research institutions with nuclear reactors can provide appropriate neutron sources for NCT; however, these sites are typically located away from medical centers where patients receive standard treatment. This limitation has negatively impacted the clinical use of NCT. Following recent technological advances, medical centers can now house relatively small (comparable to proton therapy units), accelerator-based neutron sources. This new development has strengthened interest in developing and testing new NCT delivery agents and testing them in clinical trials.

### Workshop on Shaping the Landscape of Brain Metastases Research - September 29-30, 2022

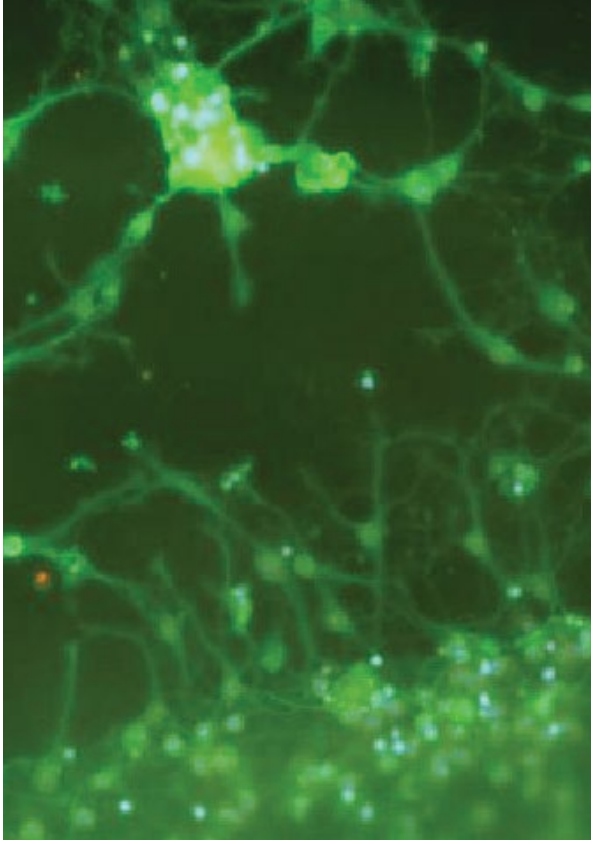
This workshop convened stakeholders across the spectrum of brain metastases research (patients, patient advocates, NCTN group leadership, brain tumor foundations, translational and clinical investigators, professional societies, and NIH leadership) to identify priorities that will shape the landscape of future brain metastases research.

The focus of the workshop included:

- Identifying key challenges limiting advances in the field
- Fostering collaborative research and development of guidance to help shape future research priorities
- Discussing optimal translational and clinical trial study designs incorporating biomarkers, novel radiotherapy or combinatorial strategies, and innovative endpoints to advance scientific understanding and improve outcomes
- Elucidating novel translational concepts and lessons from ongoing work in primary brain tumor research

The workshop topics included:

- Biologic evidence for the development and treatment resistance of brain metastases
- Clinical trial evidence for surgery, radiation, systemic (cytotoxic, immune-modulating, targeted), and other novel treatments of brain metastases and rational combinations of these modalities
- The rationale behind ongoing trial designs investigating combined modality treatment and recommendations for novel endpoints
- Identification of the brain microenvironment as a key area for future investigation to understand the development and progression of brain metastases
- Multi-factorial mechanisms of treatment-related cognitive and functional impairment





### Joint DOE/NIH Workshop – Advancing Medical Care through Discovery in the Physical Sciences Workshop Series: Radiation Detection - March 15-17, 2023

This jointly sponsored DOE/NIH workshop "Advancing Medical Care through Discovery in the Physical Sciences: Radiation Detection" was the second of what is expected to become an annual series. The series is designed to be a forum for discussion of capabilities, challenges, and emerging technologies of interest to both the medical and physical scientific communities. The first workshop was aimed at enhancing an ongoing dialogue of shared information for synergistic advancements. While maintaining the latter dialogue and search for synergy, this second workshop focused on radiation detection, with the following topics:

- Cameras, Detectors for External Imaging – X-rays, Protons, and Beyond
- Cameras, Detectors for Internal Diagnostic Imaging – SPECT, PET, and Beyond
- Cameras, Detectors for Therapeutics
- Electronics and Data Acquisition
- Image Reconstruction, Pre and Post Processing
- Applications of AI

## SPECIALIZED INITIATIVES

RRP is dedicated to advancing scientific knowledge and improving cancer treatments through supporting radiation research. Extramural radiation research funding at NCI includes investigator-initiated grants such as P01, R01, and R21. Several specialized initiatives have also been developed or re-issued to address unmet needs in the field.

**Radiation Oncology-Biology Integration Network (ROBIN) U54** (RFA-CA-21-040, RFA-CA-22-046): see page 42 in the "Major Initiatives" section.

**Systematic Testing of Radionuclides in Preclinical Experiments (STRIPE) R01, R21** (PAR-22-139, 140): The purpose of this Notice of Funding Opportunity (NOFO) is to solicit R01 and R21 research projects using state-of-the-art cancer biology methods and model systems to study the effects of different types of radiation used in radionuclide-based therapeutics (e.g., radiopharmaceutical therapy) on normal tissue, tumor cells, and the tumor microenvironment.

**Precision Approaches in Radiation Synthetic Combinations (PAIRS) R01, R21** (PAR-22-198, 199): Through the PAIRS NOFO, NCI solicits R01 and R21 research projects that seek to investigate actionable synthetic vulnerabilities that can be conditionally paired with tumor responses to radiation therapy. The goal of the PAIRS program is to develop radiation-synthetic combination strategies and facilitate their adoption into the precision medicine toolkit toward building new and effective anticancer treatments.

# FUTURE DIRECTIONS

The role of radiation oncology in the era of precision medicine is both broad and critical to advances in cancer care and quality of survival, and the broad expertise in RRP is essential to maintain these advances (Coleman, 2021). The ability to administer radiation precisely and accurately, which we call "accurate, precision radiation medicine,"[31] greatly improves our ability to specifically kill cancer cells and enhance immunotherapy. In addition, radiation oncologists and biologists repurpose molecular targeted therapies for use in combination with RT, including radiation-inducible molecular and immunological targets. This can potentially extend the use of a drug that has already undergone clinical development. Given the extent of patient data captured as part of routine RT treatment, radiation oncology has robust data sets that, under the appropriate safeguards, could provide well curated information in the emerging era of "big data."

As cells and tissues use complex systems to perform their functions, and as optimal clinical cancer care requires a coordinated system of expertise and functions, RRP approaches its entire portfolio and that of its scientific colleagues as a complex interactive system. Advances in any one area can potentially have an impact on another, and it is the program's strategic vision not only to be aware of advances in radiation and related fields, but also to strengthen existing and develop new links that can accelerate advances (Buchsbaum, 2022). Further, through conferences and workshops, program staff strive to lead the field into new areas of opportunity. With a staff actively engaged in research planning and conduct coupled with the broad collaborations described above, RRP generates a strong level of enthusiasm, collaboration, and innovation among agencies, investigators, and partners. This leadership helps to sustain a critical mass of talent and enthusiasm within government (e.g., the RABRAT group), and with academic, industrial, and global partners.

## RADIOBIOLOGY EDUCATION INITIATIVES

Future progress in the radiation sciences depends upon a cadre of scientists who are both knowledgeable about radiation effects on cells and tissues and technologically trained to a high standard. Classically trained radiobiologists are approaching retirement age, and many of the newer-generation scientists from more focused specialties (such as molecular biology) have not received the broad training that ensures success in radiation-related research. The term "classical" remains as relevant to laboratory technique and safe clinical application of radiation as it does to systemic therapy where dose, timing, and interactions of agents are important. Working with professional societies, RRP will endeavor to assist in education and training of radiation cancer biologists and physicists to bring "accurate, precision radiation medicine" to the clinic as an effective cancer treatment.

In collaboration with NCI's Center for Cancer Training (CCT) and ASTRO, an effort is being made to enhance education in the radiation sciences at a national level through the development of supplemental courses that will incorporate radiobiology, radiation physics, and translational and experimental methodology. Support in preparing applications for programs geared to radiation training is provided on request to extramural investigators. In addition, RRP staff participate in the educational initiatives of national societies and international groups, such as the European Society for Therapeutic Radiology and Oncology (ESTRO). A successful R25E training program at Wayne State University (Detroit, MI) has evolved out of these efforts.

## RADIATION AND IMMUNOTHERAPY

The importance of radiation oncology to the field of cancer immunotherapy is increasingly being recognized. Radiation is now used in combination with cell-based and immune check-point inhibitor therapies to induce robust presentation of antigens, including neoantigens, and to alter DNA damage and repair to enhance the efficacy of immunotherapy, including abscopal effects where the immune system in distal tumors becomes activated by irradiation of a single tumor.

This cross-discipline interaction between radiation oncology and immuno-oncology requires:

- Mutual in-depth understanding of the disciplines of radiation biology, tumor biology and metabolism, and cancer immunotherapy
- An exchange of research materials, including biomarker assays and immune competent models, for preclinical and clinical studies

[31] Coleman CN, Prasanna PGS, Bernhard EJ, et al. Int J Radiat Oncol Biol Phys. 2018 Jun 1;101(2):250-253.

One of RRP's missions is to expand opportunities to expose cancer immunotherapists to the science of radiation oncology/biology to foster the development of strategic initiatives that translate into successful combined modality trials. RRP's staff worked with others in DCTD and extramural investigators to establish the Radiation and Immune Modulation Working Group, which develops sound multi-center clinical concepts. RRP is highlighting the following critical issues that need to be addressed when combining radiation plus immunotherapy:

- Immunomodulation of the tumor microenvironment and tumor cells by radiation
- Effective combinations of radiation and immunotherapy
- Biomarkers of opportune immunogenicity after combined radiation-immunotherapy

## RADIOPHARMACEUTICAL THERAPY (RPT)

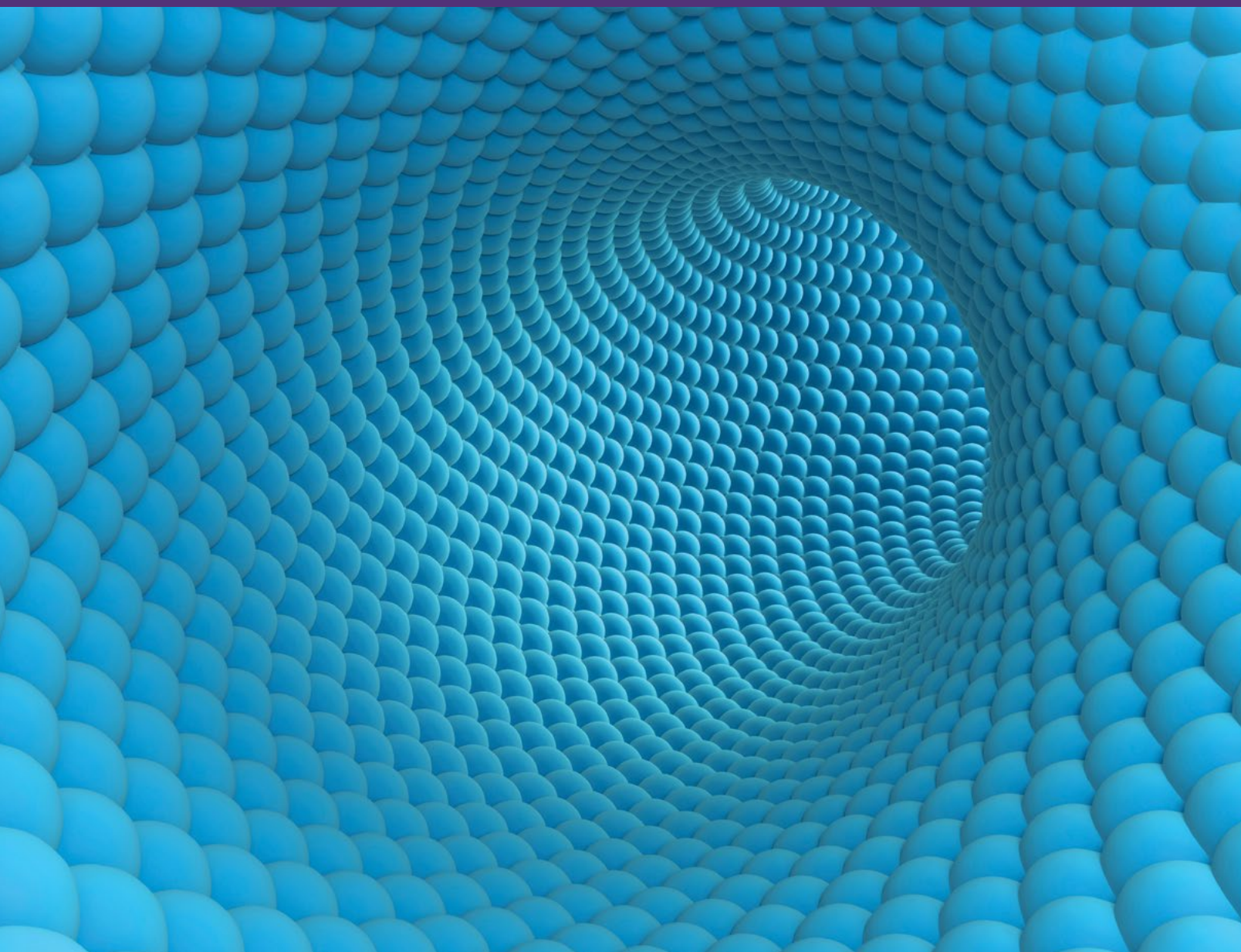
RPT uses cytotoxic radiation delivered to cancer cells or to their microenvironment either directly or via delivery vehicles that bind to cancer-specific targets. The RPT "payload" is a specific isotope with known properties of both half-life (ranging from hours to days) and emitted therapeutic radiation, such as range in the tissue and linear energy transfer (energy deposited on its path). The predictable physics of radionuclides permit for selection of a payload that, for a known duration, emits ionizing particles with a range between several cell-diameters to a few millimeters, thereby maximizing cytotoxicity to tumor cells and the tumor microenvironment with relative sparing of the surrounding normal tissues. RPT has strong potential to eradicate widely disseminated metastatic tumors, including undetectable micro-metastases. FDA has approved RPT for the treatment of several types of neoplasms, including thyroid, prostate, and neuroendocrine cancers. Clinical trials of new radiopharmaceuticals are ongoing and show clinical promise.

## NEUTRON CAPTURE THERAPY (NCT)

NCT is based on the nuclear capture and fission reactions that occur when an appropriate isotope is irradiated with low-energy (thermal) neutrons. The NCT procedure requires powerful (high flux) neutron sources and compounds delivering neutron capture isotopes selectively to tumor cells or their microenvironment. Although other isotopes with a relatively high probability of capturing neutrons were proposed in the literature as potential alternatives, boron-10 ($^{10}$B) was predominantly used in clinical trials, and the treatment modality was coined boron neutron capture therapy (BNCT). The theoretical promise of BNCT – the capability of eradicating individual cancer cells that have spread within normal tissues without causing any adverse effects – prompted multidisciplinary teams of physicists, chemists, radiobiologists, and physicians to test it since the early 1950s. Installation of new accelerator-based NCT systems and approval of BNCT as a standard treatment for head and neck cancers in Japan recently revived interest in BNCT and new approaches to tumor-specific delivery of boron. Ongoing testing of the new boron-containing compounds may identify the best candidates to significantly improve the therapeutic ratio and BNCT efficacy. Other neutron-capture nuclides, emitting radiation with relatively longer range in the tissue, might be combined with $^{10}$B to eradicate large heterogenous tumors.

PROGRAMS AND INITIATIVES (2020-2023)

# TRANSLATIONAL RESEARCH PROGRAM



# OVERVIEW

The Translational Research Program (TRP) is committed to reducing cancer incidence and mortality and improving survival and quality of life for people with cancer. TRP uses advances in the laboratory to develop new clinical approaches for the prevention, diagnosis, and treatment of cancer by fostering interdisciplinary investigations and coordinating the resources of NCI with those of academia, industry, and nonprofit organizations and foundations. Thus, translational research uses knowledge of human biology to develop and test the feasibility of cancer-relevant interventions in humans and/or determines the biological basis for observations made in people with cancer or in populations at risk for cancer. This constitutes a bidirectional character of translational research: from bench to bedside and back (**Figure 61**).

TRP accomplishes its objectives by:

- Supporting the Specialized Programs of Research Excellence (SPOREs) to translate novel scientific discoveries into clinical testing, including early-phase clinical trials and population science studies
- Encouraging a multidisciplinary and bidirectional approach to translational research
- Promoting research in high incidence as well as rare cancers
- Facilitating collaborations for the cross-fertilization of ideas, leveraging resources, and ensuring access of resources to projects and investigators to bring discoveries from the laboratory to the clinic in the most efficient manner
- Supporting additional grant mechanisms for translational research

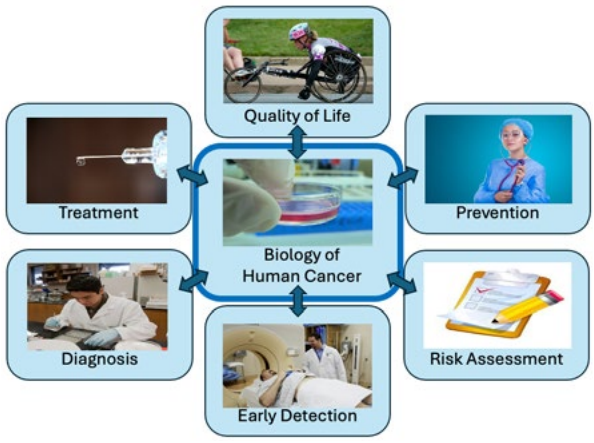



FIGURE 61: MULTIDIRECTIONAL APPROACH TO TRANSLATIONAL RESEARCH.

The SPOREs offer unique approaches to cancer research that are not found in other NCI grant mechanisms. These include:

- All scientific projects (minimum of three) must be translational and reach a human endpoint within 5 years.
- At least one SPORE-based clinical trial is required in at least one scientific project.
- SPOREs are based on a team science approach; they must have at least one basic and one clinical/applied co-leader for each project.
- There is flexibility to terminate projects and to add projects, with NCI approval, within a funding period. This allows the PI to move rapidly to refocus research based upon new knowledge and opportunities in the field.
- SPOREs have a Career Enhancement Program that is not a training program. It allows basic and clinical scientists to become involved in translational research.
- SPOREs include a Developmental Research Program for cutting-edge pilot studies, high risk/high payoff studies, and initiation of collaborations; these are short-term projects with potential to become full scientific projects, if successful, either in the SPORE or as an independent peer-reviewed grant.
- A human biospecimens/pathology CORE is required, which is a source of research specimens and analytic services. SPOREs must share specimens among other SPOREs and with the general scientific community, when appropriate. Many R01s depend upon biospecimen resources in SPOREs.
- SPOREs encourage projects in early detection, prevention, and population science, by providing a funding incentive.
- SPOREs have a requirement to collaborate. A scientific collaboration component, which is scored by peer review, is required.
- SPOREs include the involvement of patient and research advocates with a collective patient perspective.

TRP coordinates interdisciplinary investigations that are based on the biology of human cancer. In addition to SPOREs, TRP manages grants that are part of special initiatives, such as the R50 Research Specialist Career Awards, where the applicant is integral to the work of a funded SPORE. TRP is also involved in the following activities:

- PRE-medical Cancer Immunotherapy Network of Canine Trials (PRECINCT) and the Integrated Canine Data Commons (ICDC)

# TOBY T. HECHT
## ASSOCIATE DIRECTOR

Dr. Toby T. Hecht has led the Translational Research Program TRP, the home of the Specialized Programs of Research Excellence, or SPOREs, since 2008. She has worked in three NIH Institutes–NIDCR, NIAID, and the NCI–for over 45 years. Thirty-seven of those years were spent in NCI Extramural Program activities including biological agent development for the benefit of cancer patients. She has guided several projects from conception to testing in the clinic to approval and licensing. She was the Project Manager for the early stages of cetuximab (2004 approval) and dinutuximab (2015 approval) development, therapies that are widely used for certain EGFR mutant tumors and GD2-bearing tumors, respectively. During her tenure as the SPORE Director, the program grew in budget and scope beyond traditional organ site projects and has been accepting and awarding grant applications in thematic areas, such as cancer health disparities, epigenetics, radiation sensitization, and cancers that rely on similar signaling pathway alterations. She has been overseeing the development and approval of a new RFA for SPOREs in cancer health disparities. In addition, in 2015 she became the Deputy Director of DCTD.

During the ten years of working across DCTD programs, Dr. Hecht instituted a network of canine cancer clinical trials as a model for human immunotherapy and established an Integrated Canine Data Commons (ICDC) as a functional node in the NCI Cancer Research Data Commons (CRDC) so that investigators can use comparative oncology data and analytical tools to gain better insight into the biology and treatment of human disease. She initiated a collaboration across DCTD Programs to establish the Glioblastoma Therapeutics Network (GTN), which develops novel therapeutics and combinations of drugs that can cross the blood-brain barrier and tests them in early-phase clinical trials. Most recently, she led the trans-NCI initiative of grant supplements to encourage research in uterine serous cancer, a disease that is increasing in incidence and mortality in U.S. women. She is a member of the NCI Senior Leadership.

- Small Cell Lung Cancer Consortium (SCLC-C)
- Pancreatic Cancer Microenvironment Network (PaCMEN)
- Pancreatic Adenocarcinoma Stromal Reprogramming Consortium (PSRC)

### TRP MISSION

The mission of TRP is to integrate scientific advancements in the understanding of the biology of human cancer with the development of new interventions for the prevention, diagnosis, and treatment of patients with cancer or populations at risk for cancer. TRP accomplishes this mission by fostering broad interdisciplinary investigations that focus on bringing discoveries from the laboratory to the clinic and coordinating NCI's resources with those of academia, industry, and nonprofit organizations and foundations to reduce cancer incidence, morbidity, and mortality; to extend survival; and to increase the quality of life of people with cancer. To that end, TRP engages in the following activities and initiatives:

- Planning, advising, coordinating, evaluating, and supporting the SPOREs, which use the P50/U54 grant funding mechanism, to translate novel scientific discoveries from the laboratory and/or population studies to the clinic for testing in patients with cancer, to determine the biological basis for clinical observations, and to use specimens from clinical studies to determine correlations between biomarkers and outcomes
- Encouraging and facilitating collaborations among the SPOREs, Cancer Centers, other NCI- and NIH-funded mechanisms and programs, other government organizations, and outside organizations to increase cross-fertilization of ideas, leverage resources, reduce duplication, and ensure access of resources to projects and investigators
- Maintaining the Developmental Research Program and the Career Enhancement Program of the SPOREs to promote high-risk and/or high-payoff projects and to ensure the development of promising researchers who are new to translational research
- Facilitating the involvement of scientists and clinicians from Underrepresented Groups in translational cancer research
- Supporting research in high-incidence cancers as well as rare cancers
- Collaborating with the advocacy community who supports translational science in cancer

# TRP GRANTS OVERVIEW

TRP uses the P50 (and the U54) Specialized Center funding mechanism for the SPORE program. In 2020-23 there were 54 to 60 funded SPOREs, covering organ sites and systems, including one signaling pathway-focused grant (**Figure 62**).

Fifty-three grants used the P50 mechanism, and the remaining grant was funded through a U54. In addition, TRP staff oversee a relatively smaller number of R21, R01, and R50 translational research grants.

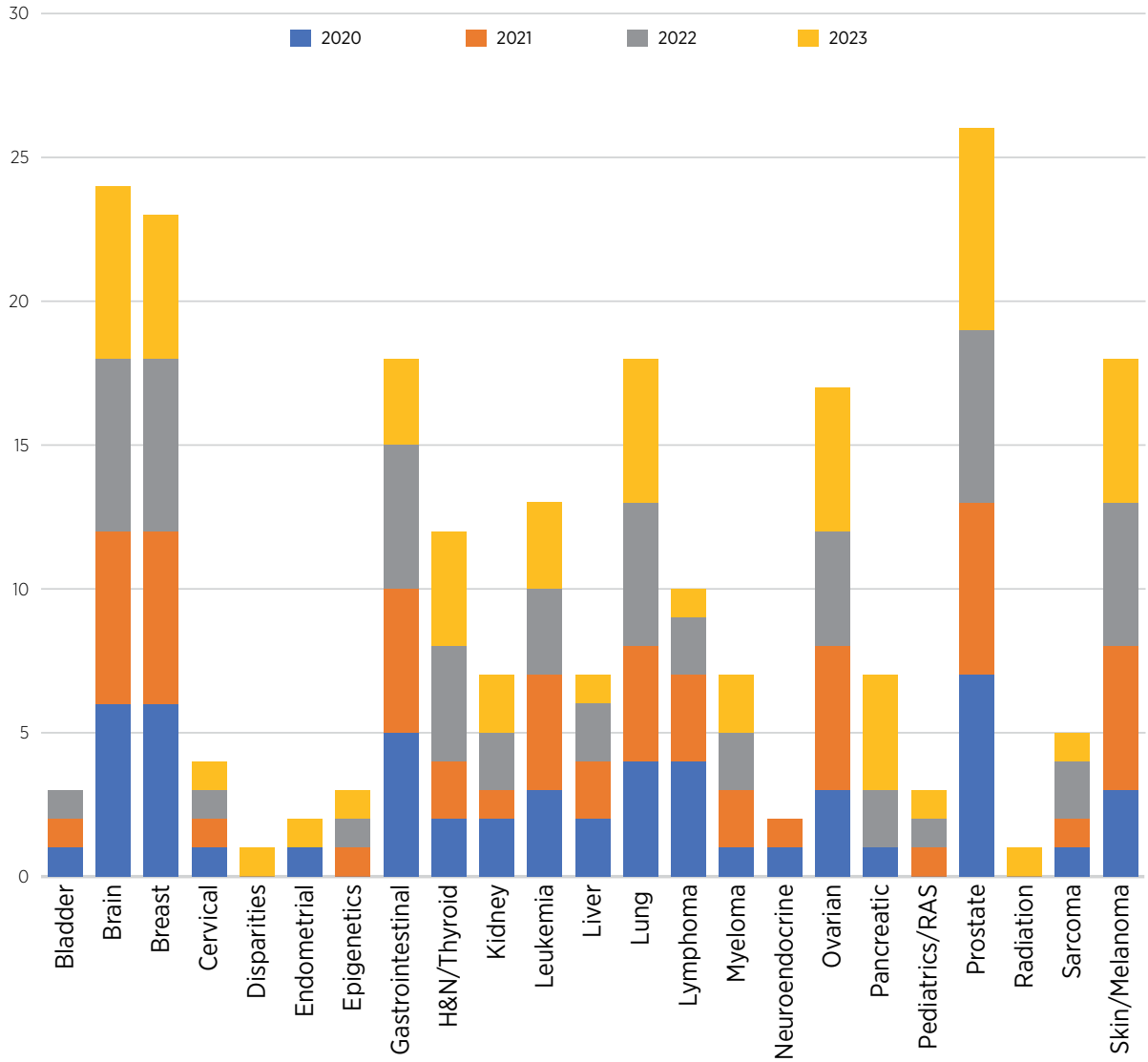



FIGURE 62: 2020-2023 SPORE GRANTS PORTFOLIO BY ORGAN SITES/THEMES.

## ORGANIZED SPORE INVESTIGATOR MEETINGS

**Tables 44**, **45**, **46**, **47**, and **48** describe several recent TRP meetings.

| Date/Location | Organizer/Leaders | Keynote Speaker/Topic | Focus Areas |
|---|---|---|---|
| **June 16-18, 2021**<br>Virtual | Emory University Lung Cancer SPORE<br>Drs. Suresh Ramalingam and Haian Fu | Dr. Nadia Howadler, Cancer epidemiology<br>Dr. Trudy Oliver, SCLC models<br>Dr. Robert Winn, Lung cancer disparities<br>Dr. Christine Lovely, Liquid biopsies | – Lung cancer therapy resistance<br>– EGFR, KRAS, LKB1, and related pathways<br>– Novel targets<br>– Immunotherapy<br>– Molecular profiling<br>– Biomarkers<br>– SCLC |
| **June 16-17, 2022**<br>Virtual | Fred Hutchinson Cancer Research Institute Lung Cancer SPORE<br>Drs. McGarry Houghton and Paul Lampe | Dr. Matt Schabath, Radiomic biomarkers for clinical decision support<br>Dr. Edd Garon, Latest clinical immunotherapy results in lung cancer<br>Dr. Katie Politi, Updates on her work in resistance to EGFR-targeted therapies<br>Dr. Lauren Byers, Advances in SCLC research | – Early detection<br>– Immunotherapy<br>– Oncogene targets<br>– SCLC<br>– Collaborations with the SPOREs, Gateway Foundation, and American Lung Association<br>– Patient advocate presentation by Kim Norris, President, Lung Cancer Foundation of America |
| **June 12-13, 2023**<br>Boston, MA<br>Hybrid | Dana Farber Harvard Cancer Center Lung Cancer SPORE<br>Drs. David Barbie and Lecia Sequist | Dr. Alex Adjei, Overview of the challenges in lung cancer translational research<br>Dr. Valsamo Anagnostou, Blood-based biomarkers of immunotherapy response | – Driver oncogene addiction<br>– Health disparities in lung cancer<br>– Novel immunotherapeutic clinical approaches<br>– Tumor immune interactions<br>– Cancer biology<br>– Lung cancer risk and early detection<br>– SCLC<br>**Special Session**<br>Patient and research advocates Hildy Grossman, Diane Legg, Dr. Laura Petrillo, and Kim Norris |

TABLE 44: LUNG CANCER SPORE INVESTIGATOR MEETINGS (2021-2023).

| Date/Location | Organizer | Focus Areas |
|---|---|---|
| **February 20-22, 2020**<br>Chicago, IL | Northwestern University Brain SPORE | **Keynotes**<br>Dr. William Kaelin<br>Dr. Roel Verhaak<br>**Presentations**<br>– Immunotherapy<br>– Oncolytic viruses<br>– Radiotherapy<br>– Cancer metabolism<br>– Targeted therapy<br>– Epidemiology<br>– IDH mutant gliomas |
| **February 25-26, 2021**<br>Virtual | UCSF Brain SPORE | **Presentations**<br>Summaries of major accomplishments from seven currently and previously funded SPOREs<br>**Breakout Topics**<br>Knowledge gaps and barriers to success in these areas:<br>– Tumor microenvironment<br>– Immunotherapy<br>– Targeted therapeutics<br>– Cell and viral therapies<br>– Tumor genomics<br>– Pediatric gliomas |

TABLE 45: BRAIN CANCER SPORE INVESTIGATOR MEETINGS (2020-2021).

GI and pancreas cancer SPORE meetings included participation from the GI cancer, pancreas cancer, liver cancer, and neuroendocrine tumor SPOREs. Along with SPORE staff, P20 Cancer Health Disparities SPORE planning grant staff were invited to participate.

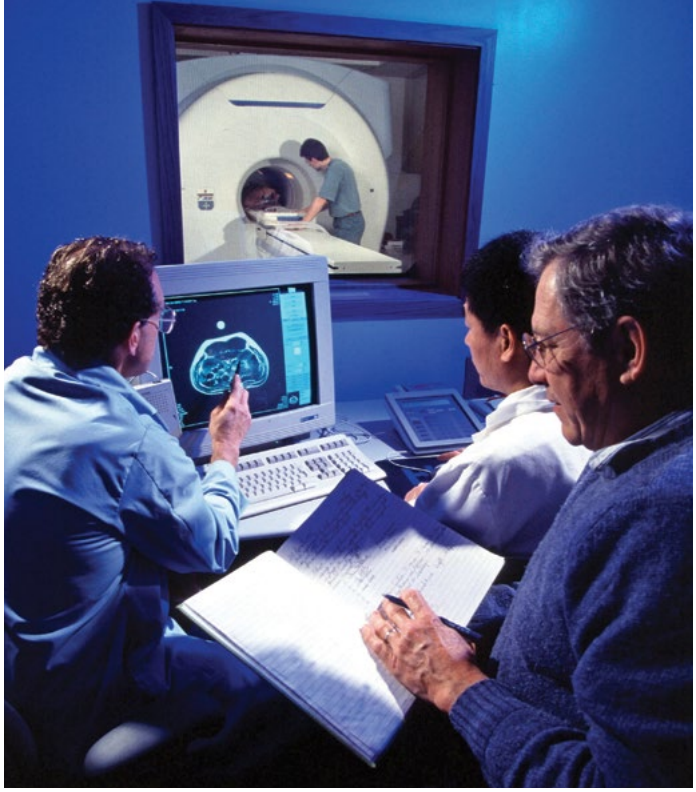
| Date/Location | Organizer/Leaders | Special Sessions |
|---|---|---|
| **November 5-6, 2020**<br>Virtual | MD Anderson Cancer Center GI SPORE<br>Drs. Scott Kopetz and Anirban Maitra and TRP staff | Activities of each component of newly funded SPOREs<br>Research being conducted in P20 programs |
| **November 4-5, 2021**<br>Virtual | Dana Farber/Harvard Cancer Center GI SPORE<br>Drs. Brian Wolpin and Nabeel Bardeesy and TRP staff | Activities of each component of newly funded SPOREs<br>Research being conducted in P20 programs |
| **November 14-15, 2022**<br>Virtual | TRP Program Staff | Activities of each component of newly funded SPOREs |

TABLE 46: GASTROINTESTINAL (GI) AND PANCREAS CANCER SPORE INVESTIGATOR MEETINGS (2020-2022).

Subsequent sessions were organized around specific scientific topics of relevance to all or most of the GI/pancreas SPOREs, including metabolism, immunotherapy, molecular therapies, tumor progression, drug resistance, biomarkers and cancer detection, tumor microenvironment, epidemiology, population studies and early detection, and novel imaging approaches.

| Date/Location | Organizer/Leaders | Topics of Interest |
|---|---|---|
| **June 28-29, 2021**<br>Virtual | NYU SPORE<br>Drs. Iman Osman and Jeffrey Weber | – Neoadjuvant immune therapy for high-risk stage II melanoma<br>– Co-targeting innate and adaptive immunity to overcome resistance to anti-PD1 therapy<br>– KDM5 and its role in resistance, predictive biomarkers<br>– Genomic profiling<br>– Role of NK therapy, liquid biopsies, and the mechanisms and management of ICI-induced arthritis |
| **June 20-21, 2022**<br>Hybrid | NYU SPORE<br>Drs. Iman Osman and Jeffrey Weber | – Determinants of response and toxicity<br>– Role of exosomes in melanoma<br>– ADAR1 and its role in resistance to immunotherapy<br>– Intestinal microbiota signatures of clinical response and adverse events in patients treated with anti-PD1<br>– Development of novel mouse models<br>– Acral melanoma targets<br>– LAG-3 targeting<br>– Non-cutaneous skin cancer such as Merkel Cell and uveal carcinoma<br>– Melanoma brain metastases |

TABLE 47: MELANOMA AND SKIN CANCER SPORE INVESTIGATOR MEETINGS (2021-2022).





| Date/Location | Organizer/Leaders | Topics of Interest |
|---|---|---|
| **13th Annual Meeting**<br>March 1-3, 2020<br>Fort Lauderdale, FL | Dana Farber/Harvard Cancer Center SPORE | – Immunotherapy<br>– Population science and outcome research<br>– Functional genomics and biology<br>– New therapies: Mechanisms, molecules, and resistance<br>– Imaging and biomarkers<br>– Androgen receptor/plasticity |
| **14th Annual Meeting**<br>February 27-March 1, 2022<br>Los Angeles, CA | UCLA SPORE<br>Dr. Robert Reiter | – Immunotherapy<br>– Population science and outcome research<br>– Functional genomics and biology<br>– New therapies: Mechanisms, molecules, and resistance<br>– Imaging and biomarkers<br>– Androgen receptor/plasticity |

TABLE 48: PROSTATE CANCER SPORE INVESTIGATOR MEETINGS (2020 AND 2022).

PROGRAMS AND INITIATIVES (2020-2023)

# OFFICE OF CANCER CLINICAL PROTEOMICS RESEARCH

# OVERVIEW

The emerging field of proteogenomics aims to better predict how patients will respond to therapy by screening their tumors for both genetic abnormalities and protein information, an approach that is possible due to recent advances in proteomic technology. Proteogenomics may help researchers more completely characterize the biologic pathways of cancer development, metastasis, and treatment resistance. Incorporating proteogenomics into patient care or "looking beyond the genome" to the activity and expression of the proteins that the genome encodes, may match patient tumors more precisely to targeted therapies than screening for genomic mutations alone.

## OCCPR MISSION

The mission of OCCPR is to improve prevention, early detection, diagnosis, and treatment of cancer by enhancing the understanding of the molecular mechanisms of cancer, advancing proteome and proteogenomic science and technology development through community resources (data and reagents), and accelerating the translation of molecular findings into the clinic. OCCPR-supported programs such as the Clinical Proteomic Tumor Analysis Consortium (CPTAC), partnerships with federal agencies, and collaborations with international organizations/institutions achieve this mission.

# HENRY RODRIGUEZ

## DIRECTOR

Henry Rodriguez, PhD, MS, MBA is the Founding Director of the Office of Cancer Clinical Proteomics Research at the National Cancer Institute, NIH. Dr. Rodriguez is also a member of NCI's Senior Leadership. Recently, he served as the Assistant Director for Strategic Health and Cancer Science, in the Executive Office of the President at the White House. A cell and molecular biologist with a background in business, Dr. Rodriguez's biomedical research has focused on mechanisms of cancer in basic and clinical science, and the development of measurement science, standards, and technology. Previously, Dr. Rodriguez served as Acting Deputy Director of the Center for Strategic Scientific Initiatives at the NCI, and held multiple roles at the National Institute of Standards and Technology (NIST, Department of Commerce), including Founding Director of the Cell and Tissue Metrology Research Group; Health Sciences Program/Policy Analyst in the Office of the Director that involved coordination with leadership in the Department of Commerce, Congress, and the Department of Health and Human Services Secretary's Advisory Committee on Genetic, Health and Society; and Principal Investigator in the DNA Technologies Group. Accomplishments made in healthcare by the White House Office of Science and Technology Policy during his tenure include the launch of ARPA-H, reignition of the Cancer Moonshot, and modernizing clinical trials to make them more efficient and equitable to all Americans.

Dr. Rodriguez has authored more than 150 original research papers, including co-editing a best-selling book on oxidative stress and aging. Dr. Rodriguez earned his A.A. in biology from Miami Dade Community College, B.S. in biology/chemistry and M.S. in biology from Florida International University, Ph.D. in cell and molecular biology from Boston University, and M.B.A. in finance and management from Johns Hopkins University Carey Business School. Fellowships were conducted at the Scripps Research Institute and City of Hope Comprehensive Cancer Center.

## PROGRAMS AND INITIATIVES

### CLINICAL PROTEOMIC TUMOR ANALYSIS CONSORTIUM (CPTAC)

The Clinical Proteomic Tumor Analysis Consortium is a team-based, national effort to accelerate the understanding of the molecular basis of cancer through the application of large-scale proteome and genome analysis, or proteogenomics.

The CPTAC program was launched in 2006 (CPTAC 1) as part of the Clinical Proteomic Technologies for Cancer initiative to develop standardized proteomic workflows to ensure analytical rigor and reproducibility of proteomic measurements. Highlights of CPTAC 1 include:

- Standardization of mass spectrometry (MS) methodologies for comprehensive proteomics (discovery proteomics)
- Standardization of MS methodologies for targeted proteomics (such as multiple reaction monitoring [MRM])
- Adoption of a MRM assay for thyroglobulin by clinical reference laboratories
- Development of an open-source computational tool (Skyline) for designing assays (such as MRM) that major MS instrument vendors support
- Development of mock 510(k) device clearance documents for regulatory approval of fit-for-purpose targeted proteomic assays in collaboration with the Food and Drug Administration (FDA) and the American Association for Clinical Chemistry (AACC)
- Development of open data sharing policies in proteomics that peer-reviewed journals support

NCI launched the second iteration of the program (CPTAC 2) in 2011 to build upon the successful outcomes of CPTAC 1, using proteomic standards, technologies, standard operating procedures, workflows, and reproducibility metrics for protein identification and quantification by building a multidisciplinary, collaborative team of Proteome Characterization Centers (PCCs). The PCCs fostered multi-institutional and trans-disciplinary interactions using selected retrospective biospecimens from The Cancer Genome Atlas (TCGA) to systematically define the functional cancer proteome derived from alterations in cancer genomes, and to discover and verify protein (and peptide) candidates.

In 2016, NCI expanded CPTAC's infrastructure (CPTAC 3) to include prospective tissue collections (to control for ischemic time, necessary for phosphoproteomic measurements), genomic and proteomic characterization and analysis (global and phosphoproteomics), and resource dissemination through two coordinated sub-programs:

- The Tumor Characterization Program, comprised Proteome Characterization Centers (PCCs) and Proteogenomic Data Analysis Centers (PGDACs)
- The Translational Research Program, comprised Proteogenomic Translational Research Centers (PTRCs)

The goals of this consortium were to:

- Increase the understanding of cancer by comprehensively characterizing tumors (proteomically and genomically)
- Perform pathway and network analysis to further understand cancer biology and potential clinical translation
- Continue to produce public resources (data, assays, images, reagents) that catalyze hypothesis-driven science
- Support clinical research projects (using both sets of omics) that address mechanisms of treatment response, resistance, or toxicity

CPTAC has demonstrated the scientific benefits of integrating proteomic analysis with genomics to produce a more unified understanding of cancer. It has also created open-access resources across several collaborating entities that are widely used by the global cancer community (**Figure 63**).

Most recently (2022), NCI launched the fourth iteration of the CPTAC program with aims to:

- Continue to support an increased understanding of cancer through comprehensive proteogenomic approaches
- Accelerate the translation of findings to clinical practice through public resources (data, assays, reagents, and images) and pilot programs
- Expand support for clinical research projects to implement proteogenomic strategies to understand drug response and development of resistance in the context of a clinical trial

## INTERNATIONAL CANCER PROTEOGENOME CONSORTIUM (ICPC)

The ICPC is a voluntary scientific organization that provides a forum for collaboration among some of the world's leading cancer and proteogenomic research centers. Catalyzed by the effort of the Cancer Moonshot to encourage international cooperation and investments among nations in cancer research and care, as well as new efforts in precision medicine, ICPC was launched in late 2016. In the ICPC, more

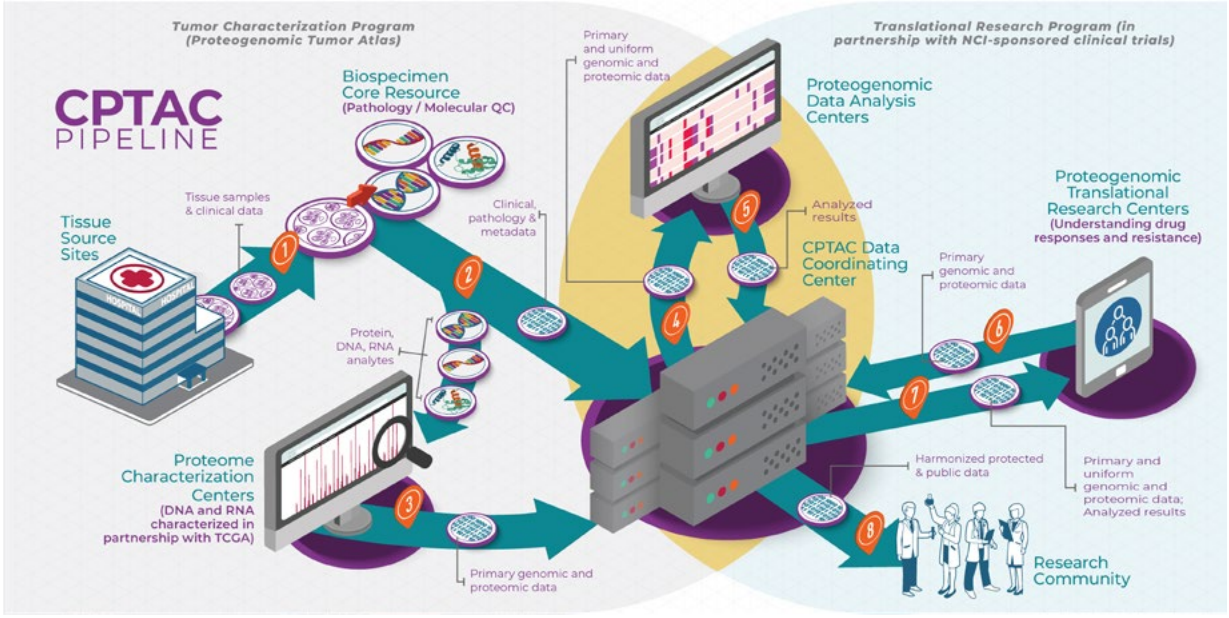



FIGURE 63: CPTAC PIPELINE CHARACTERIZES THE PROTEOMES AND GENOMES OF FULLY QUALIFIED HUMAN BIOSPECIMENS.

than a dozen countries study the application of proteogenomic analysis in predicting cancer treatment success and share biomedical research data and results with researchers worldwide, hastening patient progress.

### THE APPLIED PROTEOGENOMICS ORGANIZATIONAL LEARNING AND OUTCOMES NETWORK (APOLLO)

The APOLLO network is a tri-federal initiative arising out of the Cancer Moonshot™. The program aims to use advanced genomic and proteomic expression platforms on high-quality human biospecimens in near-real-time to identify potentially actionable therapeutic molecular targets, study the relationship of molecular findings to cancer treatment outcomes, and accelerate novel clinical trials with prognostic and predictive value biomarkers. The APOLLO program is designed as a national research pipeline with capabilities ranging from basic science (discovery) to implementation science (in a learning healthcare environment).

## OCCPR GRANTS OVERVIEW

The 2023 OCCPR research portfolio included 12 awarded grants with a total budget of $11.2 million excluding administrative supplements (**Figure 64**). It supports the advancement of proteomic and proteogenomic science to deepen our understanding of cancer and enhance clinical trials. The predominant mechanism is the U24 cooperative agreement, followed by U01.

## ASSISTANCE TO THE CANCER RESEARCH COMMUNITY

### DATA PORTALS AND RESEARCH RESOURCES

One of the core missions of OCCPR is to provide well-annotated proteomic, genomic, and imaging data associated with human tumors to the biomedical research community, as this is vital to accelerating scientific discovery for precision oncology and its clinical translation to patient care. To accomplish this goal, OCCPR-supported centers and collaborators populate the following dedicated data repositories and portals:

#### Proteomic Data Commons (PDC)

The PDC represents the NCI's largest public repository of proteomic data and related data files for human tumors. In addition to providing access to raw MS-based data files, PDC conducts computational processing that uses an internally developed Common Data Analysis pipeline (CDAP) to map spectra to peptide sequences and identify proteins to generate an interactive QC report for each study. In this manner, all data are not only available to the public, but also accessible to non-specialist researchers. The CPTAC, ICPC, and APOLLO proteomic data can be found on the PDC where there are also links to other external resources such as the Genomic Data Commons (GDC), The Cancer Imaging Archive (TCIA) and the Imaging Data Commons (IDC) where complementary omics data are available for individual studies and cases, if applicable.

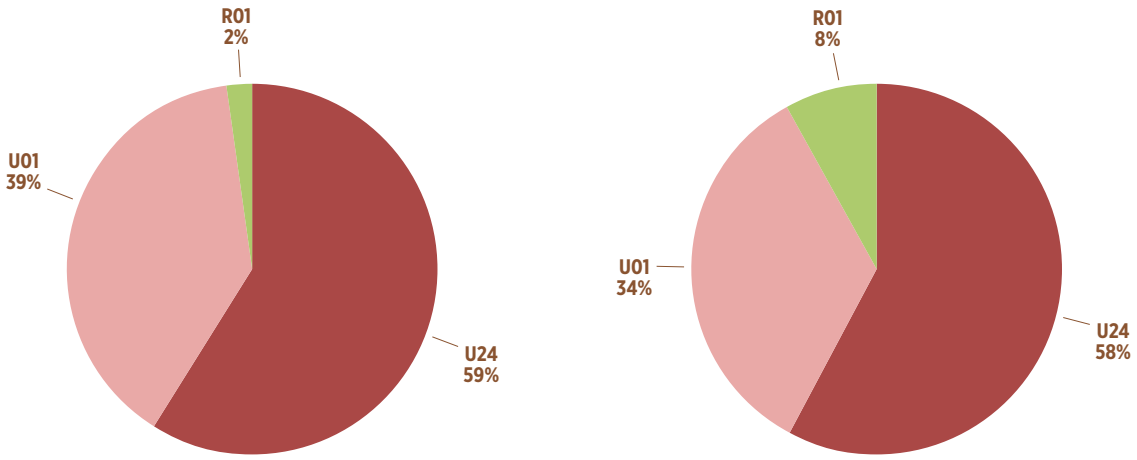



FIGURE 64: DISTRIBUTION OF OCCPR GRANT FUNDS (LEFT) AND NUMBERS OF GRANTS (RIGHT) BY MECHANISM.

### Assay Portal

The Assay Portal serves as a centralized public repository of "fit-for-purpose," multiplexed quantitative MS-based proteomic targeted assays. The Assay Portal aims to widely disseminate highly characterized proteomic assays to the global research community, with access to SOPs and assay characterization/validation data in support of the NIH's Rigor and Reproducibility Principles and Guidelines. Targeted MS assays are characterized according to the CPTAC assay characterization guidelines.

### Antibody Portal and Antibody Characterization Laboratory (ACL)

The CPTAC Antibody Portal serves as an NCI community resource that provides access to many well-characterized renewable affinity reagents (to cancer-associated targets) and accompanying data. All data (positive and negative) are available to the community to allow for understanding of antibody capabilities. All antibodies are deposited at the Developmental Studies Hybridoma Bank (DSHB) for research use only to the scientific community. Antibodies that are used in assays (immuno MRM (iMRM)) on the assay portal are linked.

OCCPR also oversees NCI's Antibody Characterization Program which, every 12 to 18 months, seeks input/requests/applications for cancer-related targets from the scientific community for which NCI should consider for the development, production and characterization of affinity reagents. This work is conducted at the Antibody Characterization Laboratory (ACL) located at the Frederick National Laboratory for Cancer Research (FNLCR). These reagents are generated using a fit-for-purpose philosophy, and the requestor is encouraged to participate in both reagent screening and selection. Regardless of the intended application, each affinity reagent is evaluated using a variety of characterization methods and all data and standard operating procedures are made available on the NCI's antibody portal. The ACL not only characterizes reagent specificity and performance but also ensures alignment with the NIH's Rigor and Reproducibility Principles and Guidelines. The antibodies are made available to the scientific community, where they can be used to standardize results across various labs and studies.

## COLLABORATIONS

### NIH Centers and Federal Agencies

CPTAC collaborates with the NIH Gabriella Miller Kids First Pediatric Research Program to conduct global proteomic and phosphoproteomic characterization of existing pediatric cohorts with samples that have been or are in the process of being sequenced under the auspices of three existing Kids First X01 projects (Brain, AML, and T-ALL leukemia) to elucidate the underlying biology of childhood cancers and structural birth defects with multidimensional omics data. Raw data, Level-1 proteomic data, and associated clinical and phenotypic data will be submitted and shared with the broad research community through the NCI PDC and linked to the Kids First Data Resource Center. CPTAC also collaborates with the National Institute of Standards and Technology on quality control metrics for proteomic data sets.

### Domestic and International Organizations

To raise the analytical standards of fit-for-purpose targeted assays and increase their adoption by the clinical community, CPTAC investigators:

- Organized CME accredited educational sessions at the American Association for Clinical Chemistry annual meetings
- Collaborated with the clinical laboratory community (academia, regulatory, and industry) to develop a CLSI standards document (C64 - Quantitative Measurement of Proteins and Peptides by Mass Spectrometry), a consensus guidance document that describes the design, development, and validation of quantitative assays for proteins and peptides by mass spectrometry, and paves a path to FDA regulatory approval
- Collaborated with Quest Diagnostics/ARUP Laboratories/Mayo Clinic/LabCorp to develop and implement a CLIA thyroglobulin targeted mass spectrometry assay in serum and plasma (laboratory developed test)
- Teamed with UniProt, the leading online protein reference library to include cross-reference links to the NCI CPTAC Assay Portal for fit-for-purpose targeted assays as well cross-reference links to the CPTAC Antibody Portal for cancer associated renewable antibodies. Overall, CPTAC is internationally recognized for being at the forefront of applying standardized state-of-the-art proteomic and proteogenomic approaches to cancer research by producing an additional layer of biology to enhance the understanding of tumor biology and clinical translation.

PROGRAMS AND INITIATIVES (2020-2023)

# OFFICE OF CANCER COMPLEMENTARY AND ALTERNATIVE MEDICINE

# OVERVIEW

The Office of Cancer Complementary and Alternative Medicine (OCCAM) was initially established within the NCI Office of the Director in 1998 to increase NCI's capacity to attract and manage high-quality research on complementary and alternative medicine (CAM) in cancer and improve messaging, accuracy, and usefulness of information products addressing these topics. In 2007, the NCI director moved OCCAM into DCTD, where it promotes and supports research and generation of quality information on the various disciplines and modalities associated with the CAM field as they relate to the diagnosis, prevention, and treatment of cancer. The office also manages a portfolio of grants and other projects evaluating CAM approaches for cancer treatment.

OCCAM has identified four research areas with potential for therapeutic advances. Designed to align with DCTD goals, these areas focus on:

- Identifying novel therapeutics in the pharmacopeia of traditional medical (TM) systems as defined by the World Health Organization
- Using complementary approaches to improve the therapeutic index of standard and investigational anticancer therapies
- Investigating lifestyle modification research (e.g., diet, exercise, mind-body approaches) for their impact on cancer outcomes (e.g., response to conventional cancer therapy, survival)
- Developing the science to support microbial-based cancer therapies

Four organizational components accomplish OCCAM's work:

- Research Development and Support Program – Solicits and manages a grant portfolio predominantly research on cancer treatment involving CAM approaches and microbial-based therapies
- Case Review and Intramural Science Program – Gathers and evaluates information about unconventional cancer therapies to propose next steps and facilitate decisions about therapies warranting NCI-initiated research
- International Research Program – Establishes research collaborations with foreign research organizations predominantly in the areas of natural product and TM product evaluation
- Office of the Director – Supports the other programs, provides topic area expertise for internal and external contacts, manages communication and education activities, performs literature review research and survey projects

## NCI DEFINITIONS OF CAM-RELATED TERMS

**Complementary and alternative medicine (CAM):** Any medical system, practice, or product that is not thought of as standard care

**Complementary medicine:** A CAM therapy used along with standard medicine

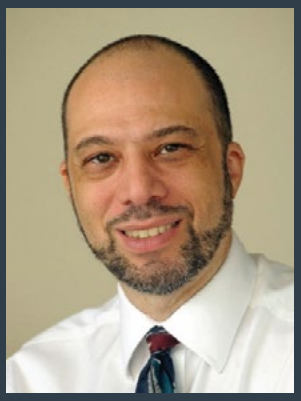
**Alternative medicine:** A CAM therapy used in place of standard treatment

**Integrative medicine:** An approach that combines treatments from conventional medicine and CAM for which there is some high-quality evidence of safety and effectiveness

## MISSION

The mission of OCCAM is to improve the quality of care for people with cancer, those at risk for cancer, and those recovering from cancer treatment by contributing to advances in evidence-based CAM practice and the sciences that support it and by improving the availability of high-quality information for the health care community, researchers, and the public.

# JEFFREY D. WHITE
## DIRECTOR



Jeffrey D. White, MD, graduated from Cornell University with a BS degree in Applied and Engineering Physics in 1979 and received an MD degree from Howard University in 1984. He completed a residency in internal medicine in 1987 and fellowships in oncology and hematology in 1990 at the Washington Hospital Center in Washington, DC.

Dr. White joined the NCI Metabolism Branch in 1990 as a Medical Staff Fellow where he performed laboratory research in immunology and molecular biology and from 1997 to 1998 serving as Director, Clinical Trials and Clinical Care Program, coordinated the development and administration of phase 1 and 2 clinical trials with unmodified and radiolabeled monoclonal antibody constructs.

From 1995 to 1998, Dr. White also served as an oncology consultant to the director of the NIH's Office of Alternative Medicine (precursor to the National Center for Complementary and Integrative Health). In October 1998, he was selected to serve as director of the newly created NCI OCCAM.

## OCCAM GRANTS OVERVIEW

OCCAM is responsible for overseeing, directing, managing, and evaluating a portfolio of preclinical and clinical cancer treatment research grants, cooperative agreements, and contracts related to the use of various dietary and natural product interventions, mostly in combination with conventional cancer therapies. OCCAM contributes to the coordination of CAM activities across NCI divisions and analyzes NCI's CAM expenditures and research portfolio. OCCAM also manages a portfolio of grants exploring the mechanisms of action and therapeutic potential of engineered bacteria.

**Figure 65** and **figure 66** show OCCAM's grant award distribution by research focus areas and mechanisms. The predominant mechanism is the exploratory phase grants (R21), followed equally by the individual research project grant (R01) and conference grant (R13).

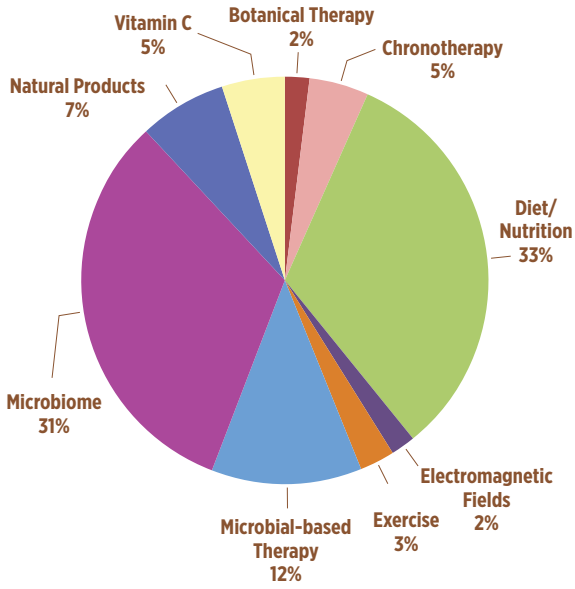



FIGURE 65: PERCENT DISTRIBUTION OF OCCAM FY23 GRANTS BY RESEARCH AREA.

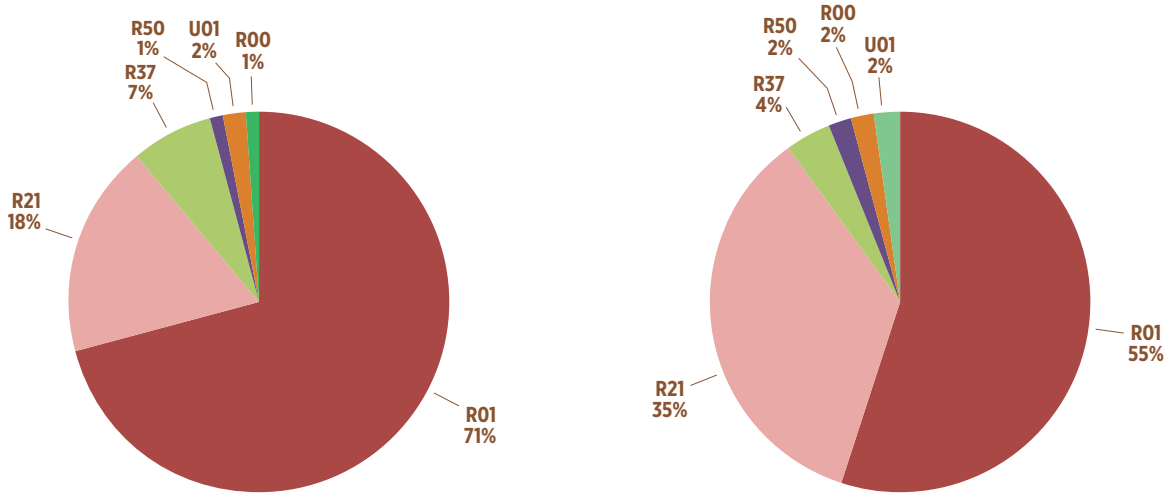



FIGURE 66: DISTRIBUTION OF 2023 GRANT NUMBERS (LEFT) AND FUNDING (RIGHT) BY MECHANISM.

# ASSISTANCE TO THE CANCER RESEARCH COMMUNITY

## MICROBIAL-BASED CANCER THERAPY RESEARCH PROGRAM

To stimulate new research on the mechanism of action of bacteria that are modified to target and kill cancers, two new Notices of Funding Opportunities (NOFOs) were initiated in 2019 and then updated and reissued in 2022: PAR-22-086, aimed at promoting early research without preliminary data, and PAR-22-085, to support more advanced research. The current NOFOs reflect OCCAM's collaboration with National Institute of Dental and Craniofacial Research (NIDCR), NCI's Division of Cancer Biology (DCB), and two other programs in DCTD (CDP and CIP), expanding the scope of this initiative to include microbial treatment of oral cancers and development of innovative microbial-based imaging, diagnosis, and cancer detection applications. This program has attracted new researchers to the field of cancer research.

## MICROBIOME TARGETED INTERVENTION CANCER NETWORK

The microbiome plays an important role in many health conditions and diseases including cancer development and therapeutic outcome. Several preclinical studies of gut microbiota and two recent first-in-human pilot fecal microbial transplantation (FMT) clinical trials suggested that FMT or administration of defined microbial consortia can overcome therapeutic resistance and treat therapy-induced adverse event for patients with cancer treated with immune checkpoint inhibitors (ICI).

NCI convened a workshop in 2019 to discuss the issues and critical research needs to improve the rigor, reproducibility, and generalizability of microbiota research findings for developing FMT and defined-microbial consortia interventions for clinical trials. Recommendations from that meeting included:

- An urgent need to develop an innovative coordinated infrastructure to conduct standardized collaborative multi-center microbiome targeted cancer therapeutic human study and clinical trials

- Establish a cancer FMT national registry for long-term safety and outcome follow up
- Develop a Human Cancer Immunotherapy Fecal Microbiome Atlas and Biobank
- Investigate variables, such as biological, diet, geographic and environmental factors on microbiome targeted intervention outcomes

A NOFO was developed to solicit applications for Microbiome Research and Clinical Trial Centers (MTCC) that will form the collaborative research infrastructure of the Microbiome Targeted Intervention Cancer Network (MTCN). The overall goal of the MTCN is to develop optimal microbiome targeted interventions for conducting early-phase (phase 1/2 or phase 2) safety and efficacy clinical trials to overcome cancer therapeutic resistance and alleviate therapeutic-induced adverse events. The priorities of interventions are FMT and defined-microbial consortia. MTCN will harmonize and standardize the procedures or protocols for microbiome measurement and analysis, microbiome targeted intervention development, and clinical trial design. The NOFO for this initiative is planned for FY 2025.

## CONFERENCES

### NCI Conference on Microbial-Based Cancer Therapeutics (May 25, 2022)

Microbial-based cancer theranostics is a treatment strategy that combines cancer therapeutics with cancer imaging in one multifunctional microbial agent. The purpose of this one-day NCI conference was to discuss the aspects of the field, including the biology of microbial-tumor interaction, microbial-based therapy, microbial-based imaging and diagnosis, microbial-based cancer theranostics, and the potential clinical utility of this strategy.

### Integrative Medicine and COVID-19 Care

Working with NCI's Center for Global Health (CGH) and the HHS Office of Global Affairs, OCCAM applied for and obtained funding from the Asia Pacific Economical Collaboration (APEC) to form the APEC Traditional Medicine and Cancer Network. The goal of this network is to:

- Promote collaborative studies on TM and cancer
- Share information on TM and cancer care
- Establish a TM and Cancer Network website/database
- Propose standards for TM practice and products
- Promote regulations on the safety, quality, and efficacy of TM products

A virtual workshop was held September 20-22, 2023 and explored the use and study of TM for COVID-19 in the APEC member countries. This was the network's first project, and representatives from many APEC member countries attended.

### NCI Integrative Medicine Course

Resulting from an NCI DCTD CAM strategic workshop and needs assessments of NIH fellows, NIH launched the innovative, original NCI-NIH Integrative Medicine (IM) course. It is complementary to an ongoing flagship training curriculum that the NCI Center for Cancer Training (CCT) offers, the Translational Research in Clinical Oncology (TRACO) course.

The IM course is designed for NIH fellows who want to enhance and broaden their knowledge of evidence-based comprehensive integrative healthcare to improve people's lives, including those with cancer. The NCI CCT implements, and the Trans-NIH IM course training committee coordinates the course. The course includes:

- Complementary and integrative medicine topics presented with research evidence, followed by clinical scenarios
- Opportunities to better understand the current state of the science of each subject and introductions to cutting-edge advances in medical research
- Timely topics and FDA regulatory policy

The 2022 topics included traditional Chinese medicine, chronomedicine, exercise and cancer, plus cannabis and cancer research.

## COLLABORATIONS

### NCI Office of Communications and Public Liaison (OCPL)

The director of OCCAM serves as the Editor-in-Chief of the Integrative, Alternative and Complementary Therapies editorial board of the Physicians Data Query (PDQ) program, which OCPL manages. This board produces evidence-based summaries of the literature about various CAM approaches that people with cancer use.

### Cancer Cannabis Research Interest Group (CCRIG)

NCI's CCRIG was established in 2018 with the goals of identifying areas of scientific opportunities and barriers to progress in cannabis- and cannabinoid-related cancer research and proposing initiatives to address them. Program staff from the Division of Cancer Control and Population Sciences (DCCPS), Division of Cancer Prevention, DCB, DCTD, and the Division of Cancer Epidemiology and Genetics identified two projects to further these goals.

- The first was to provide research support for NCI-designated cancer centers by conducting surveys of ambulatory patients with cancer to determine the prevalence and patterns of cannabis use. These funding awards support projects that investigate patterns of cannabis use through surveys of approximately 12,000 patients with cancer from regions with varying laws governing cannabis access.
- The CCRIG's second project was to organize a virtual symposium, the NCI Cannabis, Cannabinoids, and Cancer Research Symposium. This symposium, held December 15-18, 2020, included presentations by 28 international speakers and was attended by more than 450 scientists, clinicians, industry representatives, students, patient advocates, and members of the public. An overview of the presentations and discussions from this meeting was published as a monograph in the *Journal of the National Cancer Institute* (Ellison, 2021). Other CCRIG products include a Notice of Special Interest: Basic Mechanisms of Cannabis and Cannabinoid Action in Cancer and Request for Application (RFA): Cannabis and Cannabinoid Use in Adult Patients During Active Cancer Treatment: Assessing Benefits and Harms.

### DCTD and International Collaborations

*Lifestyle and Past Medical History Survey of Adult Patients Participating in the NCI's Exceptional Responders Initiative (ERI)*

The ERI was a pilot study to investigate the underlying molecular factors associated with exceptional treatment responses to drug therapies in people with cancer. Towards the end of this study, 30 patients participated in a survey designed to assess any changes in their diet, physical activity, or CAM use before, during, or after their exceptional response (Olaku, 2022).

The results of the study included:

- Thirty people completed and returned the survey questionnaire from approximately 88 patients invited to participate.
- Participants ranged in age from 45 to 86 years (mean age = 68.7 years). Approximately 68% were female and 32% were male.
- The most common cancer types among the participants were colorectal (6), breast (4), lung (4), esophagus/gastric (3), pancreas (3), mesothelioma (2), and ovary (2).
- Approximately 93% of the participants had a western diet prior to their cancer diagnosis. Fifty percent changed their diet after their cancer diagnosis.
- Forty percent of the participants changed their level of physical activity after their cancer diagnosis.
- Eighteen patients (60%) reported using a CAM product, practice, or therapy (not including oral vitamins/minerals or spiritual practices) during their exceptional response.
- CAM users generally used multiple CAM approaches (median = 2.5, mean = 4.8).
- The association between CAM use and age was significant with a negative correlation.

*Collaboration with the Central Council for Research in Ayurvedic Sciences in India*

In keeping with the Letter of Intent (LOI) for scientific collaboration between NCI/OCCAM and the Central Council for Research in Ayurvedic Sciences (CCRAS) in India, a series of webinars titled "Thinking Together – A research-based dialog between NCI/OCCAM and CCRAS, India" began on October 7, 2021. These webinars are designed for the two lead organizations to present and discuss issues related to the potential for Ayurvedic and Western medicine physicians and scientists to work together and the research that might develop from such interactions. These discussions were recorded and are archived on the OCCAM website.

## TRAINING

OCCAM continues to educate the next generation of researchers in CAM through two Cancer Research Training Award (CRTA) fellow positions. These fellows generally have a master's degree and are interested in pursuing a higher degree or work in medical research, clinical medicine, or public health. One CRTA fellow studied and published a synthesis of the research literature on the challenges in effective communication between health care practitioners and patients with cancer about CAM (Akeeb, 2022). The other analyzed the quality of online information about the use of CAM interventions to manage cancer-related conditions.

## FUTURE DIRECTIONS

Because industry and academia are not likely to invest heavily in the robust scientific evaluation and development of botanical and dietary supplement compounds that may increase the effectiveness of chemotherapy agents, OCCAM will continue to contribute to this area of research. Planned research activities:

- Follow the successful, APEC-funded conference on Traditional Medicine and COVID-19 care to form the APEC Traditional Medicine and Cancer Network. This network could promote collaborative studies on TM and cancer; share information on TM and cancer care; establish a TM and Cancer Network website/database; propose standards for TM practice and products; and promote regulations on the safety, quality, and efficacy of TM products.
- Explore the effectiveness and efficacy of integration on conventional medicine and alternative medicine. OCCAM and DCCPS plan to work with researchers and practitioners in the US to develop an Integrative Cancer Surveillance System (ICSS). With more variables from alternative medicine added to the current cancer surveillance system, it may provide insight into whether the quality of life (QOL) and overall survival time (OT) can be changed/improved when two medical systems are integrated.

- Work to develop a concept for system biology of nutritional modulation.
- Explore the potential for funding opportunities and initiatives for research to improve OS and QOL for mechanistic studies, drug discovery, clinical trials, adverse effects, health disparity and minority health research, aging/elderly and pediatric cancer patients, databases, and computation modeling of complementary and integrative medicine in the priority areas suggested in the following:
  - Summary report of "The State of the Science: Cancer Complementary and Alternative Medicine Therapeutics Research"
  - 2017 NCI Chronomedicine workshop
  - 2019 NCI Strategic Workshop on Fecal Microbiota Transplant (FMT) and Microbiome Cancer Therapeutics
  - 2020-2030 Strategic Plan for NIH Nutrition Research, FMT, and microbiome-based therapy clinical research, and chronotherapy/chronomedicine
- Collaborate with other NIH programs through the Asian American, Native Hawaiian, and Pacific Islander Health Research Health Science Interest Group (AANHPI-HSIG) to explore the potential for funding initiatives on AANHPI, including never smoker lung cancer, which is over-represented in Asian populations. Complementary and integrative medicine cancer research priority areas will be incorporated.
- The amount and availability of information on CAM and cancer for people with cancer has increased, but tailored education is needed.
- The frequency of CAM use is high (approximately 40-50%) among people with cancer, but studies have shown a significant gap in the disclosure of this use to physicians and infrequent or meager conversations between physicians and people with cancer about this topic. OCCAM will work with other programs at NCI and possibly National Center for Complementary and Integrative Health (NCCIH) to address the following issues: the clinical significance of CAM non-disclosure in the cancer setting, the potential value of improving communication between providers and people with cancer, and legal implications of CAM communication.
- To continue working with the Central Council for Research in Ayurvedic Sciences to better understand the potential for collaborative research between Ayurvedic practitioners and biomedical practitioners to diminish the symptom burden and improve the QOL of people with cancer.
- To promote the exploration of the subjects of whole person cancer care and patient-centered care through research of relevant care models, especially those that incorporate complementary/integrative health approaches.
- Continue to provide education and training for the public, health care practitioners, scientists, grantees, and NIH fellows in CAM research through the OCCAM website and hosting various lectures and discussion groups.

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PROGRAMS AND INITIATIVES (2020-2023)

# DCTD STAFF BIBLIOGRAPHY

# 2020


S. Adhikari *et al.*, A high-stringency blueprint of the human proteome. *Nat Commun* **11**, 5301 (2020).

K. H. Allison *et al.*, Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. *J Clin Oncol* **38**, 1346-1366 (2020).

K. H. Allison *et al.*, Estrogen and Progesterone Receptor Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. *Arch Pathol Lab Med* **144**, 545-563 (2020).

B. P. Alter, A. F. Best, Frequency of heterozygous germline pathogenic variants in genes for Fanconi anemia in patients with non-BRCA1/BRCA2 breast cancer: a meta-analysis. *Breast Cancer Res Treat* **182**, 465-476 (2020).

B. P. Alter, A. F. Best, Correction to: Frequency of heterozygous germline pathogenic variants in genes for Fanconi anemia in patients with non-BRCA1/BRCA2 breast cancer: a meta-analysis. *Breast Cancer Res Treat* **183**, 491 (2020).

A. B. Apolo *et al.*, Phase I Study of Cabozantinib and Nivolumab Alone or With Ipilimumab for Advanced or Metastatic Urothelial Carcinoma and Other Genitourinary Tumors. *J Clin Oncol* **38**, 3672-3684 (2020).

T. S. Armstrong *et al.*, Glioma patient-reported outcome assessment in clinical care and research: a Response Assessment in Neuro-Oncology collaborative report. *Lancet Oncol* **21**, e97-e103 (2020).

S. C. Aruah *et al.*, Overcoming Challenges in Providing Radiation Therapy to Patients With Cancer in Nigeria and Experience in the National Hospital Abuja, Nigeria. *JCO Glob Oncol* **6**, 1232-1236 (2020).

P. A. Ascierto *et al.*, Perspectives in melanoma: meeting report from the "Melanoma Bridge" (December 5th-7th, 2019, Naples, Italy). *J Transl Med* **18**, 346 (2020).

N. S. Azad *et al.*, Nivolumab Is Effective in Mismatch Repair-Deficient Noncolorectal Cancers: Results From Arm Z1D-A Subprotocol of the NCI-MATCH (EAY131) Study. *J Clin Oncol* **38**, 214-222 (2020).

T. Baslan *et al.*, Novel insights into breast cancer copy number genetic heterogeneity revealed by single-cell genome sequencing. *Elife* **9** (2020).

L. Beer *et al.*, Integration of proteomics with CT-based qualitative and radiomic features in high-grade serous ovarian cancer patients: an exploratory analysis. *Eur Radiol* **30**, 4306-4316 (2020).

J. L. Boxerman *et al.*, Consensus recommendations for a dynamic susceptibility contrast MRI protocol for use in high-grade gliomas. *Neuro Oncol* **22**, 1262-1275 (2020).

S. E. Castel, F. Aguet, P. Mohammadi, G. T. Consortium, K. G. Ardlie, T. Lappalainen, A vast resource of allelic expression data spanning human tissues. *Genome Biol* **21**, 234 (2020).

A. Cesano, F. M. Marincola, M. Thurin, Status of Immune Oncology: Challenges and Opportunities. *Methods Mol Biol* **2055**, 3-21 (2020).

B. A. Chabner, N. Coleman, D. Kaufman, A. Lister, R. Rengan, Memorial Tribute to Eli Glatstein. *Oncologist* **25**, 638-640 (2020).

Y. K. Chae *et al.*, Phase II Study of AZD4547 in Patients With Tumors Harboring Aberrations in the FGFR Pathway: Results From the NCI-MATCH Trial (EAY131) Subprotocol W. *J Clin Oncol* **38**, 2407-2417 (2020).

J. Chan *et al.*, Examining geographic accessibility to radiotherapy in Canada and Greenland for indigenous populations: Measuring inequities to inform solutions. *Radiother Oncol* **146**, 1-8 (2020).

L. S. Chang *et al.*, Targeting Protein Translation by Rocaglamide and Didesmethylrocaglamide to Treat MPNST and Other Sarcomas. *Mol Cancer Ther* **19**, 731-741 (2020).

Y. Chen *et al.*, Traditional Cardiovascular Risk Factors and Individual Prediction of Cardiovascular Events in Childhood Cancer Survivors. *J Natl Cancer Inst* **112**, 256-265 (2020).

A. J. Chien *et al.*, MK-2206 and Standard Neoadjuvant Chemotherapy Improves Response in Patients With Human Epidermal Growth Factor Receptor 2-Positive and/or Hormone Receptor-Negative Breast Cancers in the I-SPY 2 Trial. *J Clin Oncol* **38**, 1059-1069 (2020).

K. C. Cho *et al.*, Deep Proteomics Using Two Dimensional Data Independent Acquisition Mass Spectrometry. *Anal Chem* **92**, 4217-4225 (2020).

J. Choi *et al.*, Regulation of B cell receptor-dependent NF-kappaB signaling by the tumor suppressor KLHL14. *Proc Natl Acad Sci U S A* **117**, 6092-6102 (2020).

S. Chopra *et al.*, Gene Expression Profiles from Heart, Lung and Liver Samples of Total-Body-Irradiated Minipigs: Implications for Predicting Radiation-Induced Tissue Toxicity. *Radiat Res* **194**, 411-430 (2020).

D. J. Clark *et al.*, Integrated Proteogenomic Characterization of Clear Cell Renal Cell Carcinoma. *Cell* **180**, 207 (2020).

R. A. Clark *et al.*, Predicting acute ovarian failure in female survivors of childhood cancer: a cohort study in the Childhood Cancer Survivor Study (CCSS) and the St Jude Lifetime Cohort (SJLIFE). *Lancet Oncol* **21**, 436-445 (2020).

C. N. Coleman, Sixteenth Annual Warren K. Sinclair Keynote Address: Frontiers in Medical Radiation Science. *Health Phys* **118**, 349-353 (2020).

C. N. Coleman *et al.*, Radiation-induced Adaptive Response: New Potential for Cancer Treatment. *Clin Cancer Res* **26**, 5781-5790 (2020).

C. N. Coleman, R. T. Hoppe, J. M. Metz, Eli J. Glatstein: A Steward Extraordinaire of Radiation Oncology. *Int J Radiat Oncol Biol Phys* **107**, 1-5 (2020).

C. N. Coleman *et al.*, Achieving flexible competence: bridging the investment dichotomy between infectious diseases and cancer. *BMJ Glob Health* **5** (2020).

C. N. Coleman, J. B. Mitchell, S. M. Hahn, W. G. McKenna, Eli J. Glatstein: Inspiring and Provoking Critical Thinking. *Radiat Res* **193**, 318-321 (2020).

C. N. Coleman *et al.*, Capturing Acquired Wisdom, Enabling Healthful Aging, and Building Multinational Partnerships Through Senior Global Health Mentorship. *Glob Health Sci Pract* **8**, 626-637 (2020).

R. M. Connolly *et al.*, Phase I and Pharmacokinetic Study of Romidepsin in Patients with Cancer and Hepatic Dysfunction: A National Cancer Institute Organ Dysfunction Working Group Study. *Clin Cancer Res* **26**, 5329-5337 (2020).

D. Connors *et al.*, International liquid biopsy standardization alliance white paper. *Crit Rev Oncol Hematol* **156**, 103112 (2020).

G. O. Coyne *et al.*, Phase I trial of TRC102 (methoxyamine HCl) in combination with temozolomide in patients with relapsed solid tumors and lymphomas. *Oncotarget* **11**, 3959-3971 (2020).

G. O. Coyne *et al.*, Intravenous 5-fluoro-2'-deoxycytidine administered with tetrahydrouridine increases the proportion of p16-expressing circulating tumor cells in patients with advanced solid tumors. *Cancer Chemother Pharmacol* **85**, 979-993 (2020).

D. N. Danforth *et al.*, Characteristics of Breast Ducts in Normal-Risk and High-risk Women and Their Relationship to Ductal Cytologic Atypia. *Cancer Prev Res (Phila)* **13**, 1027-1036 (2020).

M. S. Davids *et al.*, A multicenter phase 1 study of nivolumab for relapsed hematologic malignancies after allogeneic transplantation. *Blood* **135**, 2182-2191 (2020).

K. L. Davis *et al.*, Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1-2 trial. *Lancet Oncol* **21**, 541-550 (2020).

K. Demanelis *et al.*, Determinants of telomere length across human tissues. *Science* **369** (2020).

K. T. Do *et al.*, Phase 1 study of the HSP90 inhibitor onalespib in combination with AT7519, a pan-CDK inhibitor, in patients with advanced solid tumors. *Cancer Chemother Pharmacol* **86**, 815-827 (2020).

Y. Dou *et al.*, Proteogenomic Characterization of Endometrial Carcinoma. *Cell* **180**, 729-748 e726 (2020).

S. Dutt, M. M. Ahmed, B. W. Loo, Jr., S. Strober, Novel Radiation Therapy Paradigms and Immunomodulation: Heresies and Hope. *Semin Radiat Oncol* **30**, 194-200 (2020).

J. Eary, L. Shankar, COVID-19 Update from the NCI Cancer Imaging Program. *Radiol Imaging Cancer* **2**, e204017 (2020).

E. F. Edmondson *et al.*, Naturally Acquired Mouse Kidney Parvovirus Infection Produces a Persistent Interstitial Nephritis in Immunocompetent Laboratory Mice. *Vet Pathol* **57**, 915-925 (2020).

I. Eke *et al.*, 53BP1/RIF1 signaling promotes cell survival after multifractionated radiotherapy. *Nucleic Acids Res* **48**, 1314-1326 (2020).

S. Eldridge, L. Guo, J. Hamre, 3rd, A Comparative Review of Chemotherapy-Induced Peripheral Neuropathy in In Vivo and In Vitro Models. *Toxicol Pathol* **48**, 190-201 (2020).

ENCODE Project Consortium *et al.*, Expanded encyclopaedias of DNA elements in the human and mouse genomes. *Nature* **583**, 699-710 (2020).

ENCODE Project *et al.*, Perspectives on ENCODE. *Nature* **583**, 693-698 (2020).

J. Fang, A critical review of five machine learning-based algorithms for predicting protein stability changes upon mutation. *Brief Bioinform* **21**, 1285-1292 (2020).

A. Fedorov *et al.*, DICOM re-encoding of volumetrically annotated Lung Imaging Database Consortium (LIDC) nodules. *Med Phys* **47**, 5953-5965 (2020).

A. Fernandez-Martinez *et al.*, Survival, Pathologic Response, and Genomics in CALGB 40601 (Alliance), a Neoadjuvant Phase III Trial of Paclitaxel-Trastuzumab With or Without Lapatinib in HER2-Positive Breast Cancer. *J Clin Oncol* **38**, 4184-4193 (2020).

N. M. Ferraro *et al.*, Transcriptomic signatures across human tissues identify functional rare genetic variation. *Science* **369** (2020).

K. Fish *et al.*, Rewiring of B cell receptor signaling by Epstein-Barr virus LMP2A. *Proc Natl Acad Sci U S A* **117**, 26318-26327 (2020).

K. T. Flaherty *et al.*, The Molecular Analysis for Therapy Choice (NCI-MATCH) Trial: Lessons for Genomic Trial Design. *J Natl Cancer Inst* **112**, 1021-1029 (2020).

K. T. Flaherty *et al.*, Molecular Landscape and Actionable Alterations in a Genomically Guided Cancer Clinical Trial: National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH). *J Clin Oncol* **38**, 3883-3894 (2020).

J. Foster, B. Freidlin, E. L. Korn, M. Smith, Evaluation of the contribution of randomised cancer clinical trials evaluating agents without documented single-agent activity. *ESMO Open* **5**, e000871 (2020).

J. C. Foster, B. Freidlin, C. A. Kunos, E. L. Korn, Single-Arm Phase II Trials of Combination Therapies: A Review of the CTEP Experience 2008-2017. *J Natl Cancer Inst* **112**, 128-135 (2020).

B. Freidlin, C. J. Allegra, E. L. Korn, Moving Molecular Profiling to Routine Clinical Practice: A Way Forward? *J Natl Cancer Inst* **112**, 773-778 (2020).

B. Freidlin, E. L. Korn, Reply to H. Uno et al and B. Huang et al. *J Clin Oncol* **38**, 2003-2004 (2020).

J. Gill *et al.*, Dose-response effect of eribulin in preclinical models of osteosarcoma by the pediatric preclinical testing consortium. *Pediatr Blood Cancer* **67**, e28606 (2020).

M. A. Gillette *et al.*, Proteogenomic Characterization Reveals Therapeutic Vulnerabilities in Lung Adenocarcinoma. *Cell* **182**, 200-225 e235 (2020).

J. H. Godsey *et al.*, Generic Protocols for the Analytical Validation of Next-Generation Sequencing-Based ctDNA Assays: A Joint Consensus Recommendation of the BloodPAC's Analytical Variables Working Group. *Clin Chem* **66**, 1156-1166 (2020).

M. Good, K. Castro, A. Denicoff, S. Finnigan, L. Parreco, D. S. Germain, National Cancer Institute: Restructuring to Support the Clinical Trials of the Future. *Semin Oncol Nurs* **36**, 151003 (2020).

C. V. Grant *et al.*, CRISPR-Cas9 Genome-Wide Knockout Screen Identifies Mechanism of Selective Activity of Dehydrofalcarinol in Mesenchymal Stem-like Triple-Negative Breast Cancer Cells. *J Nat Prod* **83**, 3080-3092 (2020).

S. R. Greytak *et al.*, Harmonizing Cell-Free DNA Collection and Processing Practices through Evidence-Based Guidance. *Clin Cancer Res* **26**, 3104-3109 (2020).

R. J. Griffin *et al.*, Understanding High-Dose, Ultra-High Dose Rate, and Spatially Fractionated Radiation Therapy. *Int J Radiat Oncol Biol Phys* **107**, 766-778 (2020).

T. Grkovic *et al.*, National Cancer Institute (NCI) Program for Natural Products Discovery: Rapid Isolation and Identification of Biologically Active Natural Products from the NCI Prefractionated Library. *ACS Chem Biol* **15**, 1104-1114 (2020).

A. M. Gross *et al.*, Selumetinib in Children with Inoperable Plexiform Neurofibromas. *N Engl J Med* **382**, 1430-1442 (2020).

D. Grossman *et al.*, Prognostic Gene Expression Profiling in Cutaneous Melanoma: Identifying the Knowledge Gaps and Assessing the Clinical Benefit. *JAMA Dermatol* **156**, 1004-1011 (2020).

GTEx Consortium, The GTEx Consortium atlas of genetic regulatory effects across human tissues. *Science* **369**, 1318-1330 (2020).

C. Happel, A. Ganguly, D. A. Tagle, Extracellular RNAs as potential biomarkers for cancer. *J Cancer Metastasis Treat* **6** (2020).

M. M. Harkenrider *et al.*, Moving Forward in Cervical Cancer: Enhancing Susceptibility to DNA Repair Inhibition and Damage, an NCI Clinical Trials Planning Meeting Report. *J Natl Cancer Inst* **112**, 1081-1088 (2020).

D. J. Harrison *et al.*, Initial in vivo testing of a multitarget kinase inhibitor, regorafenib, by the Pediatric Preclinical Testing Consortium. *Pediatr Blood Cancer* **67**, e28222 (2020).

S. Hayek *et al.*, Prevalence and Predictors of Frailty in Childhood Cancer Survivors and Siblings: A Report From the Childhood Cancer Survivor Study. *J Clin Oncol* **38**, 232-247 (2020).

J. L. Holleran *et al.*, Quantitation of iohexol, a glomerular filtration marker, in human plasma by LC-MS/MS. *J Pharm Biomed Anal* **189**, 113464 (2020).

C. S. Hourigan *et al.*, Impact of Conditioning Intensity of Allogeneic Transplantation for Acute Myeloid Leukemia With Genomic Evidence of Residual Disease. *J Clin Oncol* **38**, 1273-1283 (2020).

Y. Hu *et al.*, Integrated Proteomic and Glycoproteomic Characterization of Human High-Grade Serous Ovarian Carcinoma. *Cell Rep* **33**, 108276 (2020).

S. Hu-Lieskovan *et al.*, SITC cancer immunotherapy resource document: a compass in the land of biomarker discovery. *J Immunother Cancer* **8** (2020).

C. H. Hua *et al.*, Practice patterns and recommendations for pediatric image-guided radiotherapy: A Children's Oncology Group report. *Pediatr Blood Cancer* **67**, e28629 (2020).

A. K. Jain *et al.*, Provider Engagement in Radiation Oncology Data Science: Workshop Report. *JCO Clin Cancer Inform* **4**, 700-710 (2020).

L. Jiang *et al.*, A Quantitative Proteome Map of the Human Body. *Cell* **183**, 269-283 e219 (2020).

D. B. Johnson *et al.*, Trametinib Activity in Patients with Solid Tumors and Lymphomas Harboring BRAF Non-V600 Mutations or Fusions: Results from NCI-MATCH (EAY131). *Clin Cancer Res* **26**, 1812-1819 (2020).

A. Joshi *et al.*, Evaluation of the pharmacokinetic drug-drug interaction potential of iohexol, a renal filtration marker. *Cancer Chemother Pharmacol* **86**, 535-545 (2020).

T. J. Kaufmann *et al.*, Consensus recommendations for a standardized brain tumor imaging protocol for clinical trials in brain metastases. *Neuro Oncol* **22**, 757-772 (2020).

M. S. Khodadoust *et al.*, Pembrolizumab in Relapsed and Refractory Mycosis Fungoides and Sezary Syndrome: A Multicenter Phase II Study. *J Clin Oncol* **38**, 20-28 (2020).

S. Kim-Hellmuth *et al.*, Cell type-specific genetic regulation of gene expression across human tissues. *Science* **369** (2020).

J. Kirby *et al.*, Introduction to special issue on datasets hosted in The Cancer Imaging Archive (TCIA). *Med Phys* **47**, 6026-6028 (2020).

E. A. Kolb *et al.*, Preclinical evaluation of the combination of AZD1775 and irinotecan against selected pediatric solid tumors: A Pediatric Preclinical Testing Consortium report. *Pediatr Blood Cancer* **67**, e28098 (2020).

M. M. Konate, S. Antony, J. H. Doroshow, Inhibiting the Activity of NADPH Oxidase in Cancer. *Antioxid Redox Signal* **33**, 435-454 (2020).

P. A. Konstantinopoulos *et al.*, Berzosertib plus gemcitabine versus gemcitabine alone in platinum-resistant high-grade serous ovarian cancer: a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol* **21**, 957-968 (2020).

P. A. Konstantinopoulos *et al.*, Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. *J Clin Oncol* **38**, 1222-1245 (2020).

K. Krug *et al.*, Proteogenomic Landscape of Breast Cancer Tumorigenesis and Targeted Therapy. *Cell* **183**, 1436-1456 e1431 (2020).

J. Krushkal *et al.*, Epigenome-wide DNA methylation analysis of small cell lung cancer cell lines suggests potential chemotherapy targets. *Clin Epigenetics* **12**, 93 (2020).

C. A. Kunos, J. Capala, Radiopharmaceutical Switch Maintenance for Relapsed Ovarian Carcinoma. *Pharmaceuticals (Basel)* **13** (2020).

C. A. Kunos, L. V. Rubinstein, J. Capala, M. A. McDonald, Phase 0 Radiopharmaceutical-Agent Clinical Development. *Front Oncol* **10**, 1310 (2020).

R. T. Kurmasheva *et al.*, Evaluation of VTP-50469, a menin-MLL1 inhibitor, against Ewing sarcoma xenograft models by the pediatric preclinical testing consortium. *Pediatr Blood Cancer* **67**, e28284 (2020).

M. Lambertini *et al.*, Prognostic role of distant disease-free interval from completion of adjuvant trastuzumab in HER2-positive early breast cancer: analysis from the ALTTO (BIG 2-06) trial. *ESMO Open* **5**, e000979 (2020).

J. M. Lee *et al.*, Phase II trial of bevacizumab and sorafenib in recurrent ovarian cancer patients with or without prior-bevacizumab treatment. *Gynecol Oncol* **159**, 88-94 (2020).

Y. C. Lee *et al.*, Evaluation of toxicities related to novel therapy in clinical trials for women with gynecologic cancer. *Cancer* **126**, 2139-2145 (2020).

E. B. Levy *et al.*, State of the Art: Toward Improving Outcomes of Lung and Liver Tumor Biopsies in Clinical Trials-A Multidisciplinary Approach. *J Clin Oncol* **38**, 1633-1640 (2020).

G. Lopez *et al.*, Somatic structural variation targets neurodevelopmental genes and identifies SHANK2 as a tumor suppressor in neuroblastoma. *Genome Res* **30**, 1228-1242 (2020).

J. Lu *et al.*, NADPH oxidase 1 is highly expressed in human large and small bowel cancers. *PLoS One* **15**, e0233208 (2020).

H. J. Mackay, E. C. Kohn, Intraperitoneal chemotherapy: Hot, timely, and relevant? *Cancer* **126**, 5206-5209 (2020).

M. L. Maitland *et al.*, Enhanced Detection of Treatment Effects on Metastatic Colorectal Cancer with Volumetric CT Measurements for Tumor Burden Growth Rate Evaluation. *Clin Cancer Res* **26**, 6464-6474 (2020).

H. Makhlouf *et al.*, Toward Improving Practices for Submission of Diagnostic Tissue Blocks for National Cancer Institute Clinical Trials. *Am J Clin Pathol* **153**, 149-155 (2020).

J. E. McDermott *et al.*, Correction: Proteogenomic Characterization of Ovarian HGSC Implicates Mitotic Kinases, Replication Stress in Observed Chromosomal Instability. *Cell Rep Med* **1** (2020).

J. E. McDermott *et al.*, Proteogenomic Characterization of Ovarian HGSC Implicates Mitotic Kinases, Replication Stress in Observed Chromosomal Instability. *Cell Rep Med* **1** (2020).

D. M. Merino *et al.*, Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project. *J Immunother Cancer* **8** (2020).

J. L. Mulshine *et al.*, From clinical specimens to human cancer preclinical models-a journey the NCI-cell line database-25 years later. *J Cell Biochem* **121**, 3986-3999 (2020).

P. Narayan *et al.*, State of the Science and Future Directions for Liquid Biopsies in Drug Development. *Oncologist* **25**, 730-732 (2020).

T. Navas *et al.*, Clinical Evolution of Epithelial-Mesenchymal Transition in Human Carcinomas. *Cancer Res* **80**, 304-318 (2020).

D. J. Newman, Modern traditional Chinese medicine: Identifying, defining and usage of TCM components. *Adv Pharmacol* **87**, 113-158 (2020).

D. J. Newman, G. M. Cragg, Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. *J Nat Prod* **83**, 770-803 (2020).

D. J. Newman, G. M. Cragg, Plant Endophytes and Epiphytes: Burgeoning Sources of Known and "Unknown" Cytotoxic and Antibiotic Agents? *Planta Med* **86**, 891-905 (2020).

D. Nguyen, J. Yu, W. C. Reinhold, S. X. Yang, Association of Independent Prognostic Factors and Treatment Modality With Survival and Recurrence Outcomes in Breast Cancer. *JAMA Netw Open* **3**, e207213 (2020).

M. Oliva *et al.*, The impact of sex on gene expression across human tissues. *Science* **369** (2020).

A. Palmisano *et al.*, Bioinformatics Tools and Resources for Cancer Immunotherapy Study. *Methods Mol Biol* **2055**, 649-678 (2020).

A. D. J. Pearson *et al.*, ACCELERATE and European Medicines Agency Paediatric Strategy Forum for medicinal product development of checkpoint inhibitors for use in combination therapy in paediatric patients. *Eur J Cancer* **127**, 52-66 (2020).

A. D. J. Pearson *et al.*, Paediatric Strategy Forum for medicinal product development for acute myeloid leukaemia in children and adolescents: ACCELERATE in collaboration with the European Medicines Agency with participation of the Food and Drug Administration. *Eur J Cancer* **136**, 116-129 (2020).

P. J. Pederson *et al.*, Triple-Negative Breast Cancer Cells Exhibit Differential Sensitivity to Cardenolides from Calotropis gigantea. *J Nat Prod* **83**, 2269-2280 (2020).

F. Petralia *et al.*, Integrated Proteogenomic Characterization across Major Histological Types of Pediatric Brain Cancer. *Cell* **183**, 1962-1985 e1931 (2020).

J. Pidala *et al.*, Randomized multicenter trial of sirolimus vs prednisone as initial therapy for standard-risk acute GVHD: the BMT CTN 1501 trial. *Blood* **135**, 97-107 (2020).

S. Pittaluga *et al.*, Gene Expression Profiling of Mediastinal Gray Zone Lymphoma and Its Relationship to Primary Mediastinal B-cell Lymphoma and Classical Hodgkin Lymphoma. *Blood Cancer Discov* **1**, 155-161 (2020).

E. Z. Polley, Y., *Precision Trials Informatics*, Personalized and Precision Medicine Informatics (2020), pp. 215-222.

D. E. Portal *et al.*, Phase I neoadjuvant study of intravesical recombinant fowlpox-GM-CSF (rF-GM-CSF) or fowlpox-TRICOM (rF-TRICOM) in patients with bladder carcinoma. *Cancer Gene Ther* **27**, 438-447 (2020).

P. G. Prasanna *et al.*, Low-Dose Radiation Therapy (LDRT) for COVID-19: Benefits or Risks? *Radiat Res* **194**, 452-464 (2020).

P. G. S. Prasanna, D. Narayanan, K. Zhang, A. Rahbar, C. N. Coleman, B. Vikram, Radiation Biomarkers: Can Small Businesses Drive Accurate Radiation Precision Medicine? *Radiat Res* **193**, 199-208 (2020).

M. W. Redman *et al.*, Biomarker-driven therapies for previously treated squamous non-small-cell lung cancer (Lung-MAP SWOG S1400): a biomarker-driven master protocol. *Lancet Oncol* **21**, 1589-1601 (2020).

J. E. Reuss *et al.*, Assessment of Cancer Therapy Evaluation Program Advocacy and Inclusion Rates of People Living With HIV in Anti-PD1/PDL1 Clinical Trials. *JAMA Netw Open* **3**, e2027110 (2020).

A. J. Robles *et al.*, Evaluation of Eribulin Combined with Irinotecan for Treatment of Pediatric Cancer Xenografts. *Clin Cancer Res* **26**, 3012-3023 (2020).

M. Roschewski *et al.*, Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. *Sci Immunol* **5** (2020).

O. Rozenblatt-Rosen *et al.*, The Human Tumor Atlas Network: Charting Tumor Transitions across Space and Time at Single-Cell Resolution. *Cell* **181**, 236-249 (2020).

L. M. Russell, C. H. Liu, P. Grodzinski, Nanomaterials innovation as an enabler for effective cancer interventions. *Biomaterials* **242**, 119926 (2020).

A. K. S. Salama *et al.*, Dabrafenib and Trametinib in Patients With Tumors With BRAF(V600E) Mutations: Results of the NCI-MATCH Trial Subprotocol H. *J Clin Oncol* **38**, 3895-3904 (2020).

L. A. Salicrup, M. Ossandon, B. Prickril, A. Rasooly, Bugs as Drugs, potential self-regenerated innovative cancer therapeutics approach for global health. *J Glob Health* **10**, 010311 (2020).

H. Schoder *et al.*, Prognostic value of interim FDG-PET in diffuse large cell lymphoma: results from the CALGB 50303 Clinical Trial. *Blood* **135**, 2224-2234 (2020).

R. Simon, Zhao, Y., *Constructing Software for Cancer Research in Support of Molecular PPM*, Personalized and Precision Medicine Informatics (2020).

K. Somers *et al.*, Effective targeting of NAMPT in patient-derived xenograft models of high-risk pediatric acute lymphoblastic leukemia. *Leukemia* **34**, 1524-1539 (2020).

J. A. Sparano *et al.*, Clinical Outcomes in Early Breast Cancer With a High 21-Gene Recurrence Score of 26 to 100 Assigned to Adjuvant Chemotherapy Plus Endocrine Therapy: A Secondary Analysis of the TAILORx Randomized Clinical Trial. *JAMA Oncol* **6**, 367-374 (2020).

S. Spillane *et al.*, Trends in Alcohol-Induced Deaths in the United States, 2000-2016. *JAMA Netw Open* **3**, e1921451 (2020).

D. St Germain *et al.*, Reporting of health-related quality of life endpoints in National Cancer Institute-supported cancer treatment trials. *Cancer* **126**, 2687-2693 (2020).

J. D. Strope *et al.*, Drug-drug Interactions in Patients with HIV and Cancer in Sub-Saharan Africa. *AIDS Rev* **23**, 13-27 (2020).

G. Suneja *et al.*, Pathways for Recruiting and Retaining Women and Underrepresented Minority Clinicians and Physician Scientists Into the Radiation Oncology Workforce: A Summary of the 2019 ASTRO/NCI Diversity Symposium Session at the ASTRO Annual Meeting. *Adv Radiat Oncol* **5**, 798-803 (2020).

A. A. Tarhini *et al.*, Phase III Study of Adjuvant Ipilimumab (3 or 10 mg/kg) Versus High-Dose Interferon Alfa-2b for Resected High-Risk Melanoma: North American Intergroup E1609. *J Clin Oncol* **38**, 567-575 (2020).

W. P. Tew *et al.*, PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline. *J Clin Oncol* **38**, 3468-3493 (2020).

C. Tlemsani *et al.*, SCLC-CellMiner: A Resource for Small Cell Lung Cancer Cell Line Genomics and Pharmacology Based on Genomic Signatures. *Cell Rep* **33**, 108296 (2020).

L. M. Vasta *et al.*, Nasal chondromesenchymal hamartomas in a cohort with pathogenic germline variation in DICER1. *Rhinol Online* **3**, 15-24 (2020).

K. T. Vo, D. W. Parsons, N. L. Seibel, Precision Medicine in Pediatric Oncology. *Surg Oncol Clin N Am* **29**, 63-72 (2020).

A. H. Wagner *et al.*, A harmonized meta-knowledgebase of clinical interpretations of somatic genomic variants in cancer. *Nat Genet* **52**, 448-457 (2020).

A. G. Waks *et al.*, Reversion and non-reversion mechanisms of resistance to PARP inhibitor or platinum chemotherapy in BRCA1/2-mutant metastatic breast cancer. *Ann Oncol* **31**, 590-598 (2020).

J. Wang *et al.*, HLA-DR15 Molecules Jointly Shape an Autoreactive T Cell Repertoire in Multiple Sclerosis. *Cell* **183**, 1264-1281 e1220 (2020).

J. Wang *et al.*, Colorimetric determination of the activity of alkaline phosphatase by exploiting the oxidase-like activity of palladium cube@CeO(2) core-shell nanoparticles. *Mikrochim Acta* **187**, 115 (2020).

Y. Wang *et al.*, Leukocyte telomere length in patients with myotonic dystrophy type I: a pilot study. *Ann Clin Transl Neurol* **7**, 126-131 (2020).

B. A. P. Wilson, C. C. Thornburg, C. J. Henrich, T. Grkovic, B. R. O'Keefe, Creating and screening natural product libraries. *Nat Prod Rep* **37**, 893-918 (2020).

G. W. Wright *et al.*, A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma with Therapeutic Implications. *Cancer Cell* **37**, 551-568 e514 (2020).

H. Xu *et al.*, ARID5B Influences Antimetabolite Drug Sensitivity and Prognosis of Acute Lymphoblastic Leukemia. *Clin Cancer Res* **26**, 256-264 (2020).

M. Yang *et al.*, Community Assessment of the Predictability of Cancer Protein and Phosphoprotein Levels from Genomics and Transcriptomics. *Cell Syst* **11**, 186-195 e189 (2020).

K. Zakeri, D. Narayanan, P. G. S. Prasanna, B. Vikram, J. C. Buchsbaum, Development of Novel Radiosensitizers through the National Cancer Institute's Small Business Innovation Research Program. *Radiat Res* **193**, 425-434 (2020).

J. F. Zeidner *et al.*, Immunomodulation with pomalidomide at early lymphocyte recovery after induction chemotherapy in newly diagnosed AML and high-risk MDS. *Leukemia* **34**, 1563-1576 (2020).

H. Zhang *et al.*, Photon GRID Radiation Therapy: A Physics and Dosimetry White Paper from the Radiosurgery Society (RSS) GRID/LATTICE, Microbeam and FLASH Radiotherapy Working Group. *Radiat Res* **194**, 665-677 (2020).

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G. Akturk *et al.*, Multiplex Tissue Imaging Harmonization: A Multicenter Experience from CIMAC-CIDC Immuno-Oncology Biomarkers Network. *Clin Cancer Res* **27**, 5072-5083 (2021).

K. S. Albain *et al.*, Race, Ethnicity, and Clinical Outcomes in Hormone Receptor-Positive, HER2-Negative, Node-Negative Breast Cancer in the Randomized TAILORx Trial. *J Natl Cancer Inst* **113**, 390-399 (2021).

K. C. Anderson *et al.*, Minimal Residual Disease in Myeloma: Application for Clinical Care and New Drug Registration. *Clin Cancer Res* **27**, 5195-5212 (2021).

M. J. Aryankalayil *et al.*, Analysis of lncRNA-miRNA-mRNA expression pattern in heart tissue after total body radiation in a mouse model. *J Transl Med* **19**, 336 (2021).

A. Bagchi *et al.*, Impact of Preanalytical Factors on the Measurement of Tumor Tissue Biomarkers Using Immunohistochemistry. *J Histochem Cytochem* **69**, 297-320 (2021).

J. Bayani *et al.*, Evaluation of multiple transcriptomic gene risk signatures in male breast cancer. *NPJ Breast Cancer* **7**, 98 (2021).

S. Bhala, D. R. Stewart, V. Kennerley, V. I. Petkov, P. S. Rosenberg, A. F. Best, Incidence of Benign Meningiomas in the United States: Current and Future Trends. *JNCI Cancer Spectr* **5** (2021).

S. Bhatia *et al.*, A Randomized Phase IIb Study of Low-dose Tamoxifen in Chest-irradiated Cancer Survivors at Risk for Breast Cancer. *Clin Cancer Res* **27**, 967-974 (2021).

A. S. Brohl *et al.*, Immuno-transcriptomic profiling of extracranial pediatric solid malignancies. *Cell Rep* **37**, 110047 (2021).

J. C. Buchsbaum, Comments on "Temporal lobe sparing radiotherapy with photons or protons for cognitive function preservation in paediatric craniopharyngioma" by Toussaint, et al.: Prior Similar Field Arrangement Work and a Need for Variable RBE Use. *Radiother Oncol* **158**, 327-329 (2021).

J. C. Buchsbaum, C. N. Coleman, E. J. Bernhard, M. G. Espey, B. Vikram, Overview and Lessons From the Preclinical Chemoradiotherapy Testing Consortium. *Int J Radiat Oncol Biol Phys* **111**, 1126-1130 (2021).

J. C. Buchsbaum, C. N. Coleman, J. Capala, C. Obcemea, In Reply to Breneman et al. *Int J Radiat Oncol Biol Phys* **110**, 1545-1546 (2021).

J. C. Buchsbaum *et al.*, FLASH Radiation Therapy: New Technology Plus Biology Required. *Int J Radiat Oncol Biol Phys* **110**, 1248-1249 (2021).

J. C. Buchsbaum, B. Vikram, NCI support for pediatric radiation therapy: Past, present, and future. *Pediatr Blood Cancer* **68 Suppl 2**, e28689 (2021).

H. J. Burstein *et al.*, Endocrine Treatment and Targeted Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: ASCO Guideline Update. *J Clin Oncol* **39**, 3959-3977 (2021).

L. Cao *et al.*, Proteogenomic characterization of pancreatic ductal adenocarcinoma. *Cell* **184**, 5031-5052 e5026 (2021).

J. Capala *et al.*, Dosimetry for Radiopharmaceutical Therapy: Current Practices and Commercial Resources. *J Nucl Med* **62**, 3S-11S (2021).

J. Capala, C. A. Kunos, A New Generation of "Magic Bullets" for Molecular Targeting of Cancer. *Clin Cancer Res* **27**, 377-379 (2021).

H. E. Carraway *et al.*, Phase 1 study of the histone deacetylase inhibitor entinostat plus clofarabine for poor-risk Philadelphia chromosome-negative (newly diagnosed older adults or adults with relapsed refractory disease) acute lymphoblastic leukemia or biphenotypic leukemia. *Leuk Res* **110**, 106707 (2021).

M. A. Casal, S. P. Ivy, J. H. Beumer, T. D. Nolin, Effect of removing race from glomerular filtration rate-estimating equations on anticancer drug dosing and eligibility: a retrospective analysis of National Cancer Institute phase 1 clinical trial participants. *Lancet Oncol* **22**, 1333-1340 (2021).

D. Cerna *et al.*, SMAC Mimetic/IAP Inhibitor Birinapant Enhances Radiosensitivity of Glioblastoma Multiforme. *Radiat Res* **195**, 549-560 (2021).

H. J. Chalfin *et al.*, Circulating Tumor Cell Subtypes and T-cell Populations as Prognostic Biomarkers to Combination Immunotherapy in Patients with Metastatic Genitourinary Cancer. *Clin Cancer Res* **27**, 1391-1398 (2021).

A. P. Chen *et al.*, Molecular Profiling-Based Assignment of Cancer Therapy (NCI-MPACT): A Randomized Multicenter Phase II Trial. *JCO Precis Oncol* **5** (2021).

H. X. Chen *et al.*, Network for Biomarker Immunoprofiling for Cancer Immunotherapy: Cancer Immune Monitoring and Analysis Centers and Cancer Immunologic Data Commons (CIMAC-CIDC). *Clin Cancer Res* **27**, 5038-5048 (2021).

G. Chiodin *et al.*, Insertion of atypical glycans into the tumor antigen-binding site identifies DLBCLs with distinct origin and behavior. *Blood* **138**, 1570-1582 (2021).

S. Chopra *et al.*, Whole blood gene expression within days after total-body irradiation predicts long term survival in Gottingen minipigs. *Sci Rep* **11**, 15873 (2021).

J. M. Cleary *et al.*, Differential Outcomes in Codon 12/13 and Codon 61 NRAS-Mutated Cancers in the Phase II NCI-MATCH Trial of Binimetinib in Patients with NRAS-Mutated Tumors. *Clin Cancer Res* **27**, 2996-3004 (2021).

C. N. Coleman *et al.*, Moving Forward in the Next Decade: Radiation Oncology Sciences for Patient-Centered Cancer Care. *JNCI Cancer Spectr* **5** (2021).

B. A. Conley *et al.*, The Exceptional Responders Initiative: Feasibility of a National Cancer Institute Pilot Study. *J Natl Cancer Inst* **113**, 27-37 (2021).

S. Das *et al.*, Comparison of Design, Eligibility, and Outcomes of Neuroendocrine Neoplasm Trials Initiated From 2000 to 2009 vs 2010 to 2020. *JAMA Netw Open* **4**, e2131744 (2021).

K. C. de Andrade *et al.*, Cancer incidence, patterns, and genotype-phenotype associations in individuals with pathogenic or likely pathogenic germline TP53 variants: an observational cohort study. *Lancet Oncol* **22**, 1787-1798 (2021).

O. M. de Goede *et al.*, Population-scale tissue transcriptomics maps long non-coding RNAs to complex disease. *Cell* **184**, 2633-2648 e2619 (2021).

Z. DeFilipp *et al.*, National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: III. The 2020 Treatment of Chronic GVHD Report. *Transplant Cell Ther* **27**, 729-737 (2021).

S. Demaria *et al.*, Radiation dose and fraction in immunotherapy: one-size regimen does not fit all settings, so how does one choose? *J Immunother Cancer* **9** (2021).

D. Dersh *et al.*, Genome-wide Screens Identify Lineage- and Tumor-Specific Genes Modulating MHC-I- and MHC-II-Restricted Immunosurveillance of Human Lymphomas. *Immunity* **54**, 116-131 e110 (2021).

A. L. DiCarlo, M. J. Homer, C. N. Coleman, United States medical preparedness for nuclear and radiological emergencies. *J Radiol Prot* **41** (2021).

C. D. DiNardo, L. A. Korde, M. B. Yurgelun, A Case-Based Approach to Understanding Complex Genetic Information in an Evolving Landscape. *Am Soc Clin Oncol Educ Book* **41**, 1-11 (2021).

L. Dirven *et al.*, Systematic review on the use of patient-reported outcome measures in brain tumor studies: part of the Response Assessment in Neuro-Oncology Patient-Reported Outcome (RANO-PRO) initiative. *Neurooncol Pract* **8**, 417-425 (2021).

L. E. Dodd, B. Freidlin, E. L. Korn, Platform Trials - Beware the Noncomparable Control Group. *N Engl J Med* **384**, 1572-1573 (2021).

J. H. Doroshow, S. Prindiville, W. McCaskill-Stevens, M. Mooney, P. J. Loehrer, COVID-19, Social Justice, and Clinical Cancer Research. *J Natl Cancer Inst* **113**, 1281-1284 (2021).

L. R. Duska *et al.*, A Surgical Window Trial Evaluating Medroxyprogesterone Acetate with or without Entinostat in Patients with Endometrial Cancer and Validation of Biomarkers of Cellular Response. *Clin Cancer Res* **27**, 2734-2741 (2021).

I. Eke *et al.*, The lncRNAs LINC00261 and LINC00665 are upregulated in long-term prostate cancer adaptation after radiotherapy. *Mol Ther Nucleic Acids* **24**, 175-187 (2021).

L. H. El Touny *et al.*, ATR inhibition reverses the resistance of homologous recombination deficient MGMT(low)/MMR(proficient) cancer cells to temozolomide. *Oncotarget* **12**, 2114-2130 (2021).

S. Eldridge, A. Scuteri, E. M. C. Jones, G. Cavaletti, L. Guo, E. Glaze, Considerations for a Reliable In Vitro Model of Chemotherapy-Induced Peripheral Neuropathy. *Toxics* **9** (2021).

G. L. Ellison *et al.*, The National Cancer Institute and Cannabis and Cannabinoids Research. *J Natl Cancer Inst Monogr* **2021**, 35-38 (2021).

J. Fangusaro *et al.*, A phase II trial of selumetinib in children with recurrent optic pathway and hypothalamic low-grade glioma without NF1: a Pediatric Brain Tumor Consortium study. *Neuro Oncol* **23**, 1777-1788 (2021).

L. K. Fogli *et al.*, Challenges and next steps in the advancement of immunotherapy: summary of the 2018 and 2020 National Cancer Institute workshops on cell-based immunotherapy for solid tumors. *J Immunother Cancer* **9** (2021).

B. Freidlin, C. Hu, E. L. Korn, Are restricted mean survival time methods especially useful for noninferiority trials? *Clin Trials* **18**, 188-196 (2021).

B. Freidlin, C. Hu, E. L. Korn, Reply to Quartagno et al. *Clin Trials* **18**, 746 (2021).

P. I. Gonzalez-Ericsson *et al.*, Tumor-Specific Major Histocompatibility-II Expression Predicts Benefit to Anti-PD-1/L1 Therapy in Patients With HER2-Negative Primary Breast Cancer. *Clin Cancer Res* **27**, 5299-5306 (2021).

R. D. Harvey *et al.*, Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Washout Period and Concomitant Medication Work Group. *Clin Cancer Res* **27**, 2400-2407 (2021).

S. B. Hendrix *et al.*, Perspectives on statistical strategies for the regulatory biomarker qualification process. *Biomark Med* **15**, 669-684 (2021).

W. G. Herrick *et al.*, Isoform- and Phosphorylation-specific Multiplexed Quantitative Pharmacodynamics of Drugs Targeting PI3K and MAPK Signaling in Xenograft Models and Clinical Biopsies. *Mol Cancer Ther* **20**, 749-760 (2021).

P. Hingorani *et al.*, ABBV-085, Antibody-Drug Conjugate Targeting LRRC15, Is Effective in Osteosarcoma: A Report by the Pediatric Preclinical Testing Consortium. *Mol Cancer Ther* **20**, 535-540 (2021).

J. A. Hong *et al.*, National Cancer Institute support for targeted alpha-emitter therapy. *Eur J Nucl Med Mol Imaging* **49**, 64-72 (2021).

C. Huang *et al.*, Proteogenomic insights into the biology and treatment of HPV-negative head and neck squamous cell carcinoma. *Cancer Cell* **39**, 361-379 e316 (2021).

E. P. Huang, J. H. Shih, Assigning readers to cases in imaging studies using balanced incomplete block designs. *Stat Methods Med Res* **30**, 2288-2312 (2021).

T. A. Ige *et al.*, Surveying the Challenges to Improve Linear Accelerator-based Radiation Therapy in Africa: a Unique Collaborative Platform of All 28 African Countries Offering Such Treatment. *Clin Oncol (R Coll Radiol)* **33**, e521-e529 (2021).

S. K. Jabbour *et al.*, Potential Molecular Targets in the Setting of Chemoradiation for Esophageal Malignancies. *J Natl Cancer Inst* **113**, 665-679 (2021).

J. D. Kalen *et al.*, Design and Implementation of the Pre-Clinical DICOM Standard in Multi-Cohort Murine Studies. *Tomography* **7**, 1-9 (2021).

K. Kalinsky *et al.*, Effect of Capivasertib in Patients With an AKT1 E17K-Mutated Tumor: NCI-MATCH Subprotocol EAY131-Y Nonrandomized Trial. *JAMA Oncol* **7**, 271-278 (2021).

J. Kang *et al.*, National Cancer Institute Workshop on Artificial Intelligence in Radiation Oncology: Training the Next Generation. *Pract Radiat Oncol* **11**, 74-83 (2021).

N. M. Kendsersky *et al.*, The B7-H3-Targeting Antibody-Drug Conjugate m276-SL-PBD Is Potently Effective Against Pediatric Cancer Preclinical Solid Tumor Models. *Clin Cancer Res* **27**, 2938-2946 (2021).

E. S. Kim *et al.*, Continuing to Broaden Eligibility Criteria to Make Clinical Trials More Representative and Inclusive: ASCO-Friends of Cancer Research Joint Research Statement. *Clin Cancer Res* **27**, 2394-2399 (2021).

J. W. Kim *et al.*, Clinical Activity and Safety of Cediranib and Olaparib Combination in Patients with Metastatic Pancreatic Ductal Adenocarcinoma without BRCA Mutation. *Oncologist* **26**, e1104-e1109 (2021).

P. A. Konstantinopoulos *et al.*, A Replication stress biomarker is associated with response to gemcitabine versus combined gemcitabine and ATR inhibitor therapy in ovarian cancer. *Nat Commun* **12**, 5574 (2021).

L. A. Korde *et al.*, Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline. *J Clin Oncol* **39**, 1485-1505 (2021).

J. Krushkal *et al.*, Molecular genomic features associated with in vitro response of the NCI-60 cancer cell line panel to natural products. *Mol Oncol* **15**, 381-406 (2021).

S. Kummar *et al.*, Combination therapy with pazopanib and tivantinib modulates VEGF and c-MET levels in refractory advanced solid tumors. *Invest New Drugs* **39**, 1577-1586 (2021).

C. A. Kunos *et al.*, Radiopharmaceutical Validation for Clinical Use. *Front Oncol* **11**, 630827 (2021).

R. T. Kurmasheva, S. W. Erickson, E. Earley, M. A. Smith, P. J. Houghton, In vivo evaluation of the EZH2 inhibitor (EPZ011989) alone or in combination with standard of care cytotoxic agents against pediatric malignant rhabdoid tumor preclinical models-A report from the Pediatric Preclinical Testing Consortium. *Pediatr Blood Cancer* **68**, e28772 (2021).

R. T. Kurmasheva *et al.*, In vivo evaluation of the lysine-specific demethylase (KDM1A/LSD1) inhibitor SP-2577 (Seclidemstat) against pediatric sarcoma preclinical models: A report from the Pediatric Preclinical Testing Consortium (PPTC). *Pediatr Blood Cancer* **68**, e29304 (2021).

H. A. Lankes, H. Makhlouf, Biospecimen Collection During the COVID-19 Pandemic. *Am J Clin Pathol* **155**, 55-63 (2021).

D. R. Lewis, E. J. Siembida, N. L. Seibel, A. W. Smith, A. B. Mariotto, Survival outcomes for cancer types with the highest death rates for adolescents and young adults, 1975-2016. *Cancer* **127**, 4277-4286 (2021).

X. Li, J. Luo, X. Jiang, M. Yang, A. Rasooly, Gold nanocluster-europium(III) ratiometric fluorescence assay for dipicolinic acid. *Mikrochim Acta* **188**, 26 (2021).

C. H. Liu, P. Grodzinski, Nanotechnology for Cancer Imaging: Advances, Challenges, and Clinical Opportunities. *Radiol Imaging Cancer* **3**, e200052 (2021).

H. Ma, H. Liang, S. Cai, B. R. O'Keefe, S. L. Mooberry, R. H. Cichewicz, An Integrated Strategy for the Detection, Dereplication, and Identification of DNA-Binding Biomolecules from Complex Natural Product Mixtures. *J Nat Prod* **84**, 750-761 (2021).

S. Martel *et al.*, Body Mass Index and Weight Change in Patients With HER2-Positive Early Breast Cancer: Exploratory Analysis of the ALTTO BIG 2-06 Trial. *J Natl Compr Canc Netw* **19**, 181-189 (2021).

J. M. May, M. Bylicky, S. Chopra, C. N. Coleman, M. J. Aryankalayil, Long and short non-coding RNA and radiation response: a review. *Transl Res* **233**, 162-179 (2021).

U. L. Mirshahi *et al.*, A Genome-First Approach to Characterize DICER1 Pathogenic Variant Prevalence, Penetrance, and Phenotype. *JAMA Netw Open* **4**, e210112 (2021).

A. Mittra *et al.*, Outcomes of Pregnancy During Immunotherapy Treatment for Cancer: Analysis of Clinical Trials Sponsored by the National Cancer Institute. *Oncologist* **26**, e1883-e1886 (2021).

A. Mittra, N. Takebe, V. Florou, A. P. Chen, A. R. Naqash, The emerging landscape of immune checkpoint inhibitor based clinical trials in adults with advanced rare tumors. *Hum Vaccin Immunother* **17**, 1935-1939 (2021).

A. M. Monjazeb *et al.*, Correction: A Randomized Trial of Combined PD-L1 and CTLA-4 Inhibition with Targeted Low-dose or Hypofractionated Radiation for Patients with Metastatic Colorectal Cancer. *Clin Cancer Res* **27**, 4940 (2021).

A. M. Monjazeb *et al.*, A Randomized Trial of Combined PD-L1 and CTLA-4 Inhibition with Targeted Low-Dose or Hypofractionated Radiation for Patients with Metastatic Colorectal Cancer. *Clin Cancer Res* **27**, 2470-2480 (2021).

A. Moreno-Aspitia *et al.*, Updated results from the international phase III ALTTO trial (BIG 2-06/Alliance N063D). *Eur J Cancer* **148**, 287-296 (2021).

J. Morris *et al.*, F-aza-T-dCyd (NSC801845), a Novel Cytidine Analog, in Comparative Cell Culture and Xenograft Studies with the Clinical Candidates T-dCyd, F-T-dCyd, and Aza-T-dCyd. *Mol Cancer Ther* **20**, 625-631 (2021).

S. J. Moschos *et al.*, Targeting the IL-2 inducible kinase in melanoma; a phase 2 study of ibrutinib in systemic treatment-refractory distant metastatic cutaneous melanoma: preclinical rationale, biology, and clinical activity (NCI9922). *Melanoma Res* **31**, 162-172 (2021).

C. S. Moskowitz *et al.*, Development and Validation of a Breast Cancer Risk Prediction Model for Childhood Cancer Survivors Treated With Chest Radiation: A Report From the Childhood Cancer Survivor Study and the Dutch Hodgkin Late Effects and LATER Cohorts. *J Clin Oncol* **39**, 3012-3021 (2021).

D. J. Newman, Natural Product Based Antibody Drug Conjugates: Clinical Status as of November 9, 2020. *J Nat Prod* **84**, 917-931 (2021).

D. J. Newman, Problems that Can Occur when Assaying Extracts to Pure Compounds in Biological Systems. *Curr Ther Res Clin Exp* **95**, 100645 (2021).

T. O. Nielsen *et al.*, Assessment of Ki67 in Breast Cancer: Updated Recommendations From the International Ki67 in Breast Cancer Working Group. *J Natl Cancer Inst* **113**, 808-819 (2021).

G. O'Sullivan Coyne, A. R. Naqash, H. Sankaran, A. P. Chen, Advances in the management of alveolar soft part sarcoma. *Curr Probl Cancer* **45**, 100775 (2021).

A. Palmisano, S. Vural, Y. Zhao, D. Sonkin, MutSpliceDB: A database of splice sites variants with RNA-seq based evidence on effects on splicing. *Hum Mutat* **42**, 342-345 (2021).

N. Pandit-Taskar *et al.*, Dosimetry in Clinical Radiopharmaceutical Therapy of Cancer: Practicality Versus Perfection in Current Practice. *J Nucl Med* **62**, 60S-72S (2021).

V. Parcha *et al.*, Geographic Inequalities in Cardiovascular Mortality in the United States: 1999 to 2018. *Mayo Clin Proc* **96**, 1218-1228 (2021).

R. A. Parise, J. M. Covey, M. G. Hollingshead, A. K. Srivastava, T. W. Synold, J. H. Beumer, Development and validation of an LC-MS/MS generic assay platform for small molecule drug bioanalysis. *J Pharm Biomed Anal* **203**, 114185 (2021).

A. H. Partridge *et al.*, Who are the women who enrolled in the POSITIVE trial: A global study to support young hormone receptor positive breast cancer survivors desiring pregnancy. *Breast* **59**, 327-338 (2021).

S. Patel, J. Vogel, K. Bradley, P. J. Chuba, J. Buchsbaum, M. J. Krasin, Rare tumors: Retinoblastoma, nasopharyngeal cancer, and adrenocorticoid tumors. *Pediatr Blood Cancer* **68 Suppl 2**, e28253 (2021).

A. D. Pearson *et al.*, Bromodomain and extra-terminal inhibitors-A consensus prioritisation after the Paediatric Strategy Forum for medicinal product development of epigenetic modifiers in children-ACCELERATE. *Eur J Cancer* **146**, 115-124 (2021).

A. D. J. Pearson *et al.*, Second Paediatric Strategy Forum for anaplastic lymphoma kinase (ALK) inhibition in paediatric malignancies: ACCELERATE in collaboration with the European Medicines Agency with the participation of the Food and Drug Administration. *Eur J Cancer* **157**, 198-213 (2021).

L. Penter *et al.*, Molecular and cellular features of CTLA-4 blockade for relapsed myeloid malignancies after transplantation. *Blood* **137**, 3212-3217 (2021).

N. Ponde *et al.*, Tolerability and toxicity of trastuzumab or trastuzumab + lapatinib in older patients: a sub-analysis of the ALTTO trial (BIG 2-06; NCCTG (Alliance) N063D). *Breast Cancer Res Treat* **185**, 107-116 (2021).

P. G. Prasanna *et al.*, Therapy-Induced Senescence: Opportunities to Improve Anticancer Therapy. *J Natl Cancer Inst* **113**, 1285-1298 (2021).

P. G. Prasanna, K. Rawojc, C. Guha, J. C. Buchsbaum, J. U. Miszczyk, C. N. Coleman, Normal Tissue Injury Induced by Photon and Proton Therapies: Gaps and Opportunities. *Int J Radiat Oncol Biol Phys* **110**, 1325-1340 (2021).

J. E. Ramis-Zaldivar *et al.*, MAPK and JAK-STAT pathways dysregulation in plasmablastic lymphoma. *Haematologica* **106**, 2682-2693 (2021).

K. A. Rogers *et al.*, Phase 2 study of ibrutinib in classic and variant hairy cell leukemia. *Blood* **137**, 3473-3483 (2021).

J. M. Rohde *et al.*, Discovery and Optimization of 2H-1lambda(2)-Pyridin-2-one Inhibitors of Mutant Isocitrate Dehydrogenase 1 for the Treatment of Cancer. *J Med Chem* **64**, 4913-4946 (2021).

E. Roncali *et al.*, Overview of the First NRG Oncology-National Cancer Institute Workshop on Dosimetry of Systemic Radiopharmaceutical Therapy. *J Nucl Med* **62**, 1133-1139 (2021).

C. J. Roth *et al.*, Multispecialty Enterprise Imaging Workgroup Consensus on Interactive Multimedia Reporting Current State and Road to the Future: HIMSS-SIIM Collaborative White Paper. *J Digit Imaging* **34**, 495-522 (2021).

E. T. Roussos Torres *et al.*, Phase I Study of Entinostat and Nivolumab with or without Ipilimumab in Advanced Solid Tumors (ETCTN-9844). *Clin Cancer Res* **27**, 5828-5837 (2021).

B. Sahaf *et al.*, Immune Profiling Mass Cytometry Assay Harmonization: Multicenter Experience from CIMAC-CIDC. *Clin Cancer Res* **27**, 5062-5071 (2021).

M. E. Sansevere, J. D. White, Quality Assessment of Online Complementary and Alternative Medicine Information Resources Relevant to Cancer. *Integr Cancer Ther* **20**, 15347354211066081 (2021).

S. Satpathy *et al.*, A proteogenomic portrait of lung squamous cell carcinoma. *Cell* **184**, 4348-4371 e4340 (2021).

N. L. Seibel, D. R. Lewis, More Questions Than Answers for Adolescents and Young Adults With Cancer. *JNCI Cancer Spectr* **5** (2021).

A. L. Shaffer, 3rd *et al.*, Overcoming Acquired Epigenetic Resistance to BTK Inhibitors. *Blood Cancer Discov* **2**, 630-647 (2021).

S. St James *et al.*, Current Status of Radiopharmaceutical Therapy. *Int J Radiat Oncol Biol Phys* **109**, 891-901 (2021).

H. Streicher, MHC and the Power of P. *JNCI Cancer Spectr* **5** (2021).

J. J. Sunderland, L. B. Ponto, J. Capala, Radiopharmaceutical Delivery for Theranostics: Pharmacokinetics and Pharmacodynamics. *Semin Radiat Oncol* **31**, 12-19 (2021).

N. Takebe *et al.*, Phase 1 study of Z-endoxifen in patients with advanced gynecologic, desmoid, and hormone receptor-positive solid tumors. *Oncotarget* **12**, 268-277 (2021).

N. Takebe *et al.*, Safety, Antitumor Activity, and Biomarker Analysis in a Phase I Trial of the Once-daily Wee1 Inhibitor Adavosertib (AZD1775) in Patients with Advanced Solid Tumors. *Clin Cancer Res* **27**, 3834-3844 (2021).

P. Tandon *et al.*, Metabolic Regulation of Inflammation and Its Resolution: Current Status, Clinical Needs, Challenges, and Opportunities. *J Immunol* **207**, 2625-2630 (2021).

A. A. Tarhini *et al.*, Immune adverse events (irAEs) with adjuvant ipilimumab in melanoma, use of immunosuppressants and association with outcome: ECOG-ACRIN E1609 study analysis. *J Immunother Cancer* **9** (2021).

B. A. Teicher, TGFbeta-Directed Therapeutics: 2020. *Pharmacol Ther* **217**, 107666 (2021).

M. Thurin, Tumor-Associated Glycans as Targets for Immunotherapy: The Wistar Institute Experience/Legacy. *Monoclon Antib Immunodiagn Immunother* **40**, 89-100 (2021).

S. M. Tolaney *et al.*, Updated Standardized Definitions for Efficacy End Points (STEEP) in Adjuvant Breast Cancer Clinical Trials: STEEP Version 2.0. *J Clin Oncol* **39**, 2720-2731 (2021).

A. N. J. Tutt *et al.*, Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. *N Engl J Med* **384**, 2394-2405 (2021).

V. D. Vanderpuye *et al.*, Assessment of Adult Women With Ovarian Masses and Treatment of Epithelial Ovarian Cancer: ASCO Resource-Stratified Guideline. *JCO Glob Oncol* **7**, 1032-1066 (2021).

G. Vassal *et al.*, International Consensus on Minimum Preclinical Testing Requirements for the Development of Innovative Therapies For Children and Adolescents with Cancer. *Mol Cancer Ther* **20**, 1462-1468 (2021).

D. M. Vega *et al.*, Aligning tumor mutational burden (TMB) quantification across diagnostic platforms: phase II of the Friends of Cancer Research TMB Harmonization Project. *Ann Oncol* **32**, 1626-1636 (2021).

B. P. Venkatesulu *et al.*, Low-Dose Radiation Therapy for COVID-19: Promises and Pitfalls. *JNCI Cancer Spectr* **5**, pkaa103 (2021).

S. Vural, L. C. Chang, L. M. Yee, D. Sonkin, TP53 isoform junction reads based analysis in malignant and normal contexts. *Sci Rep* **11**, 17275 (2021).

S. Vural, A. Palmisano, W. C. Reinhold, Y. Pommier, B. A. Teicher, J. Krushkal, Association of expression of epigenetic molecular factors with DNA methylation and sensitivity to chemotherapeutic agents in cancer cell lines. *Clin Epigenetics* **13**, 49 (2021).

M. J. Wagner *et al.*, Multicenter phase II trial (SWOG S1609, cohort 51) of ipilimumab and nivolumab in metastatic or unresectable angiosarcoma: a substudy of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART). *J Immunother Cancer* **9** (2021).

R. L. Wahl *et al.*, Normal-Tissue Tolerance to Radiopharmaceutical Therapies, the Knowns and the Unknowns. *J Nucl Med* **62**, 23S-35S (2021).

L. B. Wang *et al.*, Proteogenomic and metabolomic characterization of human glioblastoma. *Cancer Cell* **39**, 509-528 e520 (2021).

D. A. Wheeler *et al.*, Molecular Features of Cancers Exhibiting Exceptional Responses to Treatment. *Cancer Cell* **39**, 38-53 e37 (2021).

J. R. Whiteaker *et al.*, Targeted Mass Spectrometry Enables Multiplexed Quantification of Immunomodulatory Proteins in Clinical Biospecimens. *Front Immunol* **12**, 765898 (2021).

J. R. Whiteaker *et al.*, Targeted mass spectrometry-based assays enable multiplex quantification of receptor tyrosine kinase, MAP Kinase, and AKT signaling. *Cell Rep Methods* **1** (2021).

J. R. Whiteaker *et al.*, Targeted Mass Spectrometry Enables Quantification of Novel Pharmacodynamic Biomarkers of ATM Kinase Inhibition. *Cancers (Basel)* **13** (2021).

P. M. Williams *et al.*, Validation of ctDNA Quality Control Materials Through a Precompetitive Collaboration of the Foundation for the National Institutes of Health. *JCO Precis Oncol* **5** (2021).

W. H. Wilson *et al.*, Phase 1b/2 study of ibrutinib and lenalidomide with dose-adjusted EPOCH-R in patients with relapsed/refractory diffuse large B-cell lymphoma. *Leuk Lymphoma* **62**, 2094-2106 (2021).

W. H. Wilson *et al.*, Effect of ibrutinib with R-CHOP chemotherapy in genetic subtypes of DLBCL. *Cancer Cell* **39**, 1643-1653 e1643 (2021).

D. G. Wishka *et al.*, The development of beta-selective glycosylation reactions with benzyl substituted 2-deoxy-1,4-dithio-D-erythro-pentofuranosides: enabling practical multi-gram syntheses of 4'-Thio-2'-deoxycytidine (T-dCyd) and 5-aza-4'-thio-2'-deoxycytidine (aza-T-dCyd) to support clinical development. *Nucleosides Nucleotides Nucleic Acids* **40**, 68-95 (2021).

Y. Xiao *et al.*, Toward Individualized Voxel-Level Dosimetry for Radiopharmaceutical Therapy. *Int J Radiat Oncol Biol Phys* **109**, 902-904 (2021).

S. X. Yang *et al.*, TET2 and DNMT3A mutations and exceptional response to 4'-thio-2'-deoxycytidine in human solid tumor models. *J Hematol Oncol* **14**, 83 (2021).

L. M. Yee, Korn, E.L., Freidlin, B., *Statistical considerations in the development and evaluation of therapeutic biomarkers in cancer*, Handbook of Therapeutic Biomarkers in Cancer (Jenny Stanford Publishing, ed. Second, 2021).

S. Yoo *et al.*, A community effort to identify and correct mislabeled samples in proteogenomic studies. *Patterns (N Y)* **2**, 100245 (2021).

L. Young *et al.*, Ocular adverse events in PD-1 and PD-L1 inhibitors. *J Immunother Cancer* **9** (2021).

Y. Yuan *et al.*, Pathology Laboratory Policies and Procedures for Releasing Diagnostic Tissue for Cancer Research. *Arch Pathol Lab Med* **145**, 222-226 (2021).

Z. Zeng *et al.*, Cross-Site Concordance Evaluation of Tumor DNA and RNA Sequencing Platforms for the CIMAC-CIDC Network. *Clin Cancer Res* **27**, 5049-5061 (2021).

W. Zhang, Z. Zhang, J. Krushkal, A. Liu, Group testing can improve the cost-efficiency of prospective-retrospective biomarker studies. *BMC Med Res Methodol* **21**, 55 (2021).

Y. Zhao *et al.*, TPM, FPKM, or Normalized Counts? A Comparative Study of Quantification Measures for the Analysis of RNA-seq Data from the NCI Patient-Derived Models Repository. *J Transl Med* **19**, 269 (2021).

# 2022


S. Adams *et al.*, A Multicenter Phase II Trial of Ipilimumab and Nivolumab in Unresectable or Metastatic Metaplastic Breast Cancer: Cohort 36 of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART, SWOG S1609). *Clin Cancer Res* **28**, 271-278 (2022).

C. Amador *et al.*, Gene Expression Signatures for the Accurate Diagnosis of Peripheral T-Cell Lymphoma Entities in the Routine Clinical Practice. *J Clin Oncol* **40**, 4261-4275 (2022).

M. Anurag *et al.*, Proteogenomic Markers of Chemotherapy Resistance and Response in Triple-Negative Breast Cancer. *Cancer Discov* **12**, 2586-2605 (2022).

L. R. Avula, P. Grodzinski, Nanotechnology-aided advancement in the combating of cancer metastasis. *Cancer Metastasis Rev* **41**, 383-404 (2022).

P. L. Bedard *et al.*, Phase II Study of Afatinib in Patients With Tumors With Human Epidermal Growth Factor Receptor 2-Activating Mutations: Results From the National Cancer Institute-Molecular Analysis for Therapy Choice ECOG-ACRIN Trial (EAY131) Subprotocol EAY131-B. *JCO Precis Oncol* **6**, e2200165 (2022).

E. R. Bonner *et al.*, Circulating tumor DNA sequencing provides comprehensive mutation profiling for pediatric central nervous system tumors. *NPJ Precis Oncol* **6**, 63 (2022).

C. Braun-Inglis, E. L. Williams, A. Macchiaroli, A. Denicoff, D. E. Gerber, Better Late Than Never: Fully Incorporating Oncology Advanced Practice Providers Into Cancer Clinical Trials. *JCO Oncol Pract* **18**, 729-732 (2022).

K. BrintzenhofeSzoc *et al.*, Through the Lens of Patient Partners: Challenges in Accrual of Older Adults to NCI Clinical Trials. *J Natl Cancer Inst Monogr* **2022**, 125-134 (2022).

J. C. Buchsbaum *et al.*, Tumor Heterogeneity Research and Innovation in Biologically Based Radiation Therapy From the National Cancer Institute Radiation Research Program Portfolio. *J Clin Oncol* **40**, 1861-1869 (2022).

J. C. Buchsbaum *et al.*, Predictive Radiation Oncology - A New NCI-DOE Scientific Space and Community. *Radiat Res* **197**, 434-445 (2022).

C. Chen, Z. Yaari, E. Apfelbaum, P. Grodzinski, Y. Shamay, D. A. Heller, Merging data curation and machine learning to improve nanomedicines. *Adv Drug Deliv Rev* **183**, 114172 (2022).

D. Chihara *et al.*, Trends in Grade 5 Toxicity and Response in Phase I Trials in Hematologic Malignancy: 20-Year Experience From the Cancer Therapy Evaluation Program at the National Cancer Institute. *J Clin Oncol* **40**, 1949-1957 (2022).

D. Chihara *et al.*, Early drug development in solid tumours: analysis of National Cancer Institute-sponsored phase 1 trials. *Lancet* **400**, 512-521 (2022).

S. Chopra *et al.*, Profiling mRNA, miRNA and lncRNA expression changes in endothelial cells in response to increasing doses of ionizing radiation. *Sci Rep* **12**, 19941 (2022).

A. E. Coghill *et al.*, Identifying Epstein-Barr virus peptide sequences associated with differential IgG antibody response. *Int J Infect Dis* **114**, 65-71 (2022).

E. P. Consortium *et al.*, Author Correction: Expanded encyclopaedias of DNA elements in the human and mouse genomes. *Nature* **605**, E3 (2022).

E. P. Consortium *et al.*, Author Correction: Perspectives on ENCODE. *Nature* **605**, E4 (2022).

S. Damodaran *et al.*, Phase II Study of Copanlisib in Patients With Tumors With PIK3CA Mutations: Results From the NCI-MATCH ECOG-ACRIN Trial (EAY131) Subprotocol Z1F. *J Clin Oncol* **40**, 1552-1561 (2022).

K. L. Davis *et al.*, A Phase I/II Trial of Nivolumab plus Ipilimumab in Children and Young Adults with Relapsed/Refractory Solid Tumors: A Children's Oncology Group Study ADVL1412. *Clin Cancer Res* **28**, 5088-5097 (2022).

A. M. Denicoff *et al.*, Implementing Modernized Eligibility Criteria in US National Cancer Institute Clinical Trials. *J Natl Cancer Inst* **114**, 1437-1440 (2022).

A. V. Desai *et al.*, Outcomes Following GD2-Directed Postconsolidation Therapy for Neuroblastoma After Cessation of Random Assignment on ANBL0032: A Report From the Children's Oncology Group. *J Clin Oncol* **40**, 4107-4118 (2022).

A. L. DiCarlo, L. S. Carnell, C. I. Rios, P. G. Prasanna, Interagency perspective: Translating advances in biomarker discovery and medical countermeasures development between terrestrial and space radiation environments. *Life Sci Space Res (Amst)* **35**, 9-19 (2022).

K. K. Dobbin, L. M. McShane, Sample size methods for evaluation of predictive biomarkers. *Stat Med* **41**, 3199-3210 (2022).

I. J. Dunkel *et al.*, Intensive Multimodality Therapy for Extraocular Retinoblastoma: A Children's Oncology Group Trial (ARET0321). *J Clin Oncol* **40**, 3839-3847 (2022).

O. S. Eckstein *et al.*, Phase II Study of Selumetinib in Children and Young Adults With Tumors Harboring Activating Mitogen-Activated Protein Kinase Pathway Genetic Alterations: Arm E of the NCI-COG Pediatric MATCH Trial. *J Clin Oncol* **40**, 2235-2245 (2022).

I. Eke *et al.*, Radiotherapy alters expression of molecular targets in prostate cancer in a fractionation- and time-dependent manner. *Sci Rep* **12**, 3500 (2022).

I. Eke *et al.*, Long-term expression changes of immune-related genes in prostate cancer after radiotherapy. *Cancer Immunol Immunother* **71**, 839-850 (2022).

J. L. Ethier *et al.*, State of the Biomarker Science in Ovarian Cancer: A National Cancer Institute Clinical Trials Planning Meeting Report. *JCO Precis Oncol* **6**, e2200355 (2022).

B. Freidlin, E. L. Korn, A Problematic Biomarker Trial Design. *J Natl Cancer Inst* **114**, 187-190 (2022).

C. E. Geyer, Jr. *et al.*, Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. *Ann Oncol* **33**, 1250-1268 (2022).

L. A. Giddings, D. J. Newman, Extremophilic Fungi from Marine Environments: Underexplored Sources of Antitumor, Anti-Infective and Other Biologically Active Agents. *Mar Drugs* **20** (2022).

D. M. Girardi *et al.*, Cabozantinib plus Nivolumab Phase I Expansion Study in Patients with Metastatic Urothelial Carcinoma Refractory to Immune Checkpoint Inhibitor Therapy. *Clin Cancer Res* **28**, 1353-1362 (2022).

R. Govindan *et al.*, Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of lung cancer and mesothelioma. *J Immunother Cancer* **10** (2022).

A. M. Gross *et al.*, Selumetinib in children with neurofibromatosis type 1 and asymptomatic inoperable plexiform neurofibroma at risk for developing tumor-related morbidity. *Neuro Oncol* **24**, 1978-1988 (2022).

K. F. Grossmann *et al.*, Adjuvant Pembrolizumab versus IFNalpha2b or Ipilimumab in Resected High-Risk Melanoma. *Cancer Discov* **12**, 644-653 (2022).

T. Hassanein *et al.*, Efficacy and Safety of a Botanical Formula Fuzheng Huayu for Hepatic Fibrosis in Patients with CHC: Results of a Phase 2 Clinical Trial. *Evid Based Complement Alternat Med* **2022**, 4494099 (2022).

D. F. Hayes *et al.*, Proceedings From the ASCO/College of American Pathologists Immune Checkpoint Inhibitor Predictive Biomarker Summit. *JCO Precis Oncol* **6**, e2200454 (2022).

N. L. Henry *et al.*, Biomarkers for Systemic Therapy in Metastatic Breast Cancer: ASCO Guideline Update. *J Clin Oncol* **40**, 3205-3221 (2022).

D. L. Hertz, L. M. McShane, D. F. Hayes, Defining Clinical Utility of Germline Indicators of Toxicity Risk: A Perspective. *J Clin Oncol* **40**, 1721-1731 (2022).

P. Hingorani *et al.*, Trastuzumab Deruxtecan, Antibody-Drug Conjugate Targeting HER2, Is Effective in Pediatric Malignancies: A Report by the Pediatric Preclinical Testing Consortium. *Mol Cancer Ther* **21**, 1318-1325 (2022).

M. G. Hollingshead *et al.*, ROADMAPS: An Online Database of Response Data, Dosing Regimens, and Toxicities of Approved Oncology Drugs as Single Agents to Guide Preclinical In Vivo Studies. *Cancer Res* **82**, 2219-2225 (2022).

J. A. Hong *et al.*, The State of Preclinical Modeling for Early Phase Cancer Trials Using Molecularly Targeted Agents with Radiation. *Radiat Res* **198**, 625-631 (2022).

P. Horak *et al.*, Standards for the classification of pathogenicity of somatic variants in cancer (oncogenicity): Joint recommendations of Clinical Genome Resource (ClinGen), Cancer Genomics Consortium (CGC), and Variant Interpretation for Cancer Consortium (VICC). *Genet Med* **24**, 986-998 (2022).

J. M. Hubbard *et al.*, Phase I study of cediranib, an oral VEGFR inhibitor, in combination with selumetinib, an oral MEK inhibitor, in patients with advanced solid malignancies. *Invest New Drugs* **40**, 115-123 (2022).

O. Kantor *et al.*, Expanding the Staging Criteria for T1-2N0 Hormone-Receptor Positive Breast Cancer Patients Enrolled in TAILORx. *Ann Surg Oncol* **29**, 8016-8023 (2022).

O. Kantor *et al.*, ASO Visual Abstract: Expanding Staging Criteria in T1-2N0 Hormone Receptor-Positive Breast Cancer Patients Enrolled in TAILORx. *Ann Surg Oncol* **29**, 8024-8025 (2022).

M. M. Konate, M. C. Li, L. M. McShane, Y. Zhao, Discovery of pathway-independent protein signatures associated with clinical outcome in human cancer cohorts. *Sci Rep* **12**, 19283 (2022).

P. A. Konstantinopoulos *et al.*, Combined PARP and HSP90 inhibition: preclinical and Phase 1 evaluation in patients with advanced solid tumours. *Br J Cancer* **126**, 1027-1036 (2022).

L. A. Korde, M. R. Somerfield, D. L. Hershman, E. T. Neoadjuvant Chemotherapy, P. Targeted Therapy for Breast Cancer Guideline Expert, Use of Immune Checkpoint Inhibitor Pembrolizumab in the Treatment of High-Risk, Early-Stage Triple-Negative Breast Cancer: ASCO Guideline Rapid Recommendation Update. *J Clin Oncol* **40**, 1696-1698 (2022).

E. L. Korn, C. J. Allegra, B. Freidlin, Clinical Benefit Scales and Trial Design: Some Statistical Issues. *J Natl Cancer Inst* **114**, 1222-1227 (2022).

E. L. Korn, B. Freidlin, Time trends with response-adaptive randomization: The inevitability of inefficiency. *Clin Trials* **19**, 158-161 (2022).

I. E. Krop *et al.*, Phase II Study of Taselisib in PIK3CA-Mutated Solid Tumors Other Than Breast and Squamous Lung Cancer: Results From the NCI-MATCH ECOG-ACRIN Trial (EAY131) Subprotocol I. *JCO Precis Oncol* **6**, e2100424 (2022).

J. Krushkal, S. Vural, T. L. Jensen, G. Wright, Y. Zhao, Increased copy number of imprinted genes in the chromosomal region 20q11-q13.32 is associated with resistance to antitumor agents in cancer cell lines. *Clin Epigenetics* **14**, 161 (2022).

K. Krytska *et al.*, Evaluation of the DLL3-targeting antibody-drug conjugate rovalpituzumab tesirine in preclinical models of neuroblastoma. *Cancer Res Commun* **2**, 616-623 (2022).

S. Kumar *et al.*, Gaps and opportunities in the treatment of relapsed-refractory multiple myeloma: Consensus recommendations of the NCI Multiple Myeloma Steering Committee. *Blood Cancer J* **12**, 98 (2022).

J. Le-Rademacher *et al.*, Trial Design Considerations to Increase Older Adult Accrual to National Cancer Institute Clinical Trials. *J Natl Cancer Inst Monogr* **2022**, 135-141 (2022).

S. E. S. Leary *et al.*, Vorinostat and isotretinoin with chemotherapy in young children with embryonal brain tumors: A report from the Pediatric Brain Tumor Consortium (PBTC-026). *Neuro Oncol* **24**, 1178-1190 (2022).

Q. K. Li *et al.*, Neoplastic cell enrichment of tumor tissues using coring and laser microdissection for proteomic and genomic analyses of pancreatic ductal adenocarcinoma. *Clin Proteomics* **19**, 36 (2022).

X. Li, C. Shen, M. Yang, A. Rasooly, DNA-Generated Electric Current Biosensor for Epidermal Growth Factor Receptor 2 (HER2) Analysis. *Methods Mol Biol* **2393**, 437-446 (2022).

J. F. Liu *et al.*, Olaparib With or Without Cediranib Versus Platinum-Based Chemotherapy in Recurrent Platinum-Sensitive Ovarian Cancer (NRG-GY004): A Randomized, Open-Label, Phase III Trial. *J Clin Oncol* **40**, 2138-2147 (2022).

M. R. Lowden *et al.*, Grassroots efforts to end structural racism throughout the US National Institutes of Health. *Nat Med* **28**, 223-224 (2022).

A. S. Mansfield *et al.*, Crizotinib in patients with tumors harboring ALK or ROS1 rearrangements in the NCI-MATCH trial. *NPJ Precis Oncol* **6**, 13 (2022).

J. Manzo *et al.*, A phase 1 and pharmacodynamic study of chronically-dosed, single-agent veliparib (ABT-888) in patients with BRCA1- or BRCA2-mutated cancer or platinum-refractory ovarian or triple-negative breast cancer. *Cancer Chemother Pharmacol* **89**, 721-735 (2022).

J. M. May *et al.*, Serum RNA biomarkers for predicting survival in non-human primates following thoracic radiation. *Sci Rep* **12**, 12333 (2022).

G. E. Mishkin, A. M. Denicoff, A. F. Best, R. F. Little, Update on Enrollment of Older Adults Onto National Cancer Institute National Clinical Trials Network Trials. *J Natl Cancer Inst Monogr* **2022**, 111-116 (2022).

G. E. Mishkin, E. C. Kohn, Biomarker Development: Bedside to Bench. *Clin Cancer Res* **28**, 2722-2724 (2022).

S. Mueller *et al.*, Wee1 kinase inhibitor adavosertib with radiation in newly diagnosed diffuse intrinsic pontine glioma: A Children's Oncology Group phase I consortium study. *Neurooncol Adv* **4**, vdac073 (2022).

G. Nader-Marta *et al.*, Outcomes of patients with small and node-negative HER2-positive early breast cancer treated with adjuvant chemotherapy and anti-HER2 therapy-a sub-analysis of the ALTTO study. *Br J Cancer* **127**, 1799-1807 (2022).

A. R. Naqash *et al.*, Major Adverse Cardiac Events With Immune Checkpoint Inhibitors: A Pooled Analysis of Trials Sponsored by the National Cancer Institute-Cancer Therapy Evaluation Program. *J Clin Oncol* **40**, 3439-3452 (2022).

D. J. Newman, Natural products and drug discovery. *Natl Sci Rev* **9**, nwac206 (2022).

C. Norman Coleman, N. Mayr, Tribulations and Trials: The Implementation of Biologically Dependent Radiation Therapy Technologies. *Int J Radiat Oncol Biol Phys* **113**, 701-704 (2022).

G. O'Sullivan Coyne *et al.*, PARP Inhibitor Applicability: Detailed Assays for Homologous Recombination Repair Pathway Components. *Onco Targets Ther* **15**, 165-180 (2022).

G. O'Sullivan Coyne *et al.*, Clinical Activity of Single-Agent Cabozantinib (XL184), a Multi-receptor Tyrosine Kinase Inhibitor, in Patients with Refractory Soft-Tissue Sarcomas. *Clin Cancer Res* **28**, 279-288 (2022).

L. Oba *et al.*, Utility of interim blood tests for cancer screening in Li-Fraumeni syndrome. *Fam Cancer* **21**, 333-336 (2022).

O. Olaku *et al.*, Survey of Lifestyle, Past Medical History and Complementary and Alternative Medicine Use Among Adult Patients Participating in the National Cancer Institute's Exceptional Responders Initiative. *Transl Oncol* **25**, 101484 (2022).

M. R. Ossandon, B. S. Sorg, D. S. Phatak, K. Kalpakis, Evaluation of Tumor Development Using Hemoglobin Saturation Profile on Rodent Dorsal Window Chamber. *Methods Mol Biol* **2393**, 179-206 (2022).

J. R. Park *et al.*, Early-phase clinical trial eligibility and response evaluation criteria for refractory, relapsed, or progressive neuroblastoma: A consensus statement from the National Cancer Institute Clinical Trials Planning Meeting. *Cancer* **128**, 3775-3783 (2022).

D. W. Parsons *et al.*, Actionable Tumor Alterations and Treatment Protocol Enrollment of Pediatric and Young Adult Patients With Refractory Cancers in the National Cancer Institute-Children's Oncology Group Pediatric MATCH Trial. *J Clin Oncol* **40**, 2224-2234 (2022).

S. Patil *et al.*, Senescence-associated tumor growth is promoted by 12-Lipoxygenase. *Aging (Albany NY)* **14**, 1068-1086 (2022).

N. Ponde *et al.*, Correction to: Tolerability and toxicity of trastuzumab or trastuzumab + lapatinib in older patients: a sub-analysis of the ALTTO trial (BIG 2-06; NCCTG (Alliance) N063D). *Breast Cancer Res Treat* **191**, 225 (2022).

L. Qi *et al.*, Evaluation of an EZH2 inhibitor in patient-derived orthotopic xenograft models of pediatric brain tumors alone and in combination with chemo- and radiation therapies. *Lab Invest* **102**, 185-193 (2022).

O. E. Rahma *et al.*, Phase IB study of ziv-aflibercept plus pembrolizumab in patients with advanced solid tumors. *J Immunother Cancer* **10** (2022).

C. P. Rodriguez *et al.*, Clinical Trial Development in TP53-Mutated Locally Advanced and Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma. *J Natl Cancer Inst* **114**, 1619-1627 (2022).

M. Saad *et al.*, Enhanced immune activation within the tumor microenvironment and circulation of female high-risk melanoma patients and improved survival with adjuvant CTLA4 blockade compared to males. *J Transl Med* **20**, 253 (2022).

C. Salvador-Morales, P. Grodzinski, Nanotechnology Tools Enabling Biological Discovery. *ACS Nano* **16**, 5062-5084 (2022).

H. Sankaran, S. R. Finnigan, L. M. McShane, A. F. Best, N. L. Seibel, Enrollment of adolescent and young adult patients newly diagnosed with cancer in NCI CTEP-sponsored clinical trials before and after launch of the NCI National Clinical Trials Network. *Cancer* **128**, 3843-3849 (2022).

H. Sankaran, S. Negi, L. M. McShane, Y. Zhao, J. Krushkal, Pharmacogenomics of in vitro response of the NCI-60 cancer cell line panel to Indian natural products. *BMC Cancer* **22**, 512 (2022).

H. Schoder *et al.*, Considerations on Integrating Prostate-Specific Membrane Antigen Positron Emission Tomography Imaging Into Clinical Prostate Cancer Trials by National Clinical Trials Network Cooperative Groups. *J Clin Oncol* **40**, 1500-1505 (2022).

J. D. Schoenfeld *et al.*, Durvalumab plus tremelimumab alone or in combination with low-dose or hypofractionated radiotherapy in metastatic non-small-cell lung cancer refractory to previous PD(L)-1 therapy: an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol* **23**, 279-291 (2022).

B. A. Schroeder, J. Jess, H. Sankaran, N. N. Shah, Clinical trials for chimeric antigen receptor T-cell therapy: lessons learned and future directions. *Curr Opin Hematol* **29**, 225-232 (2022).

S. C. Scott *et al.*, Validation of a robust and rapid liquid chromatography tandem mass spectrometric method for the quantitative analysis of navitoclax. *Biomed Chromatogr* **36**, e5289 (2022).

L. Shao *et al.*, Identification of genomic signatures in bone marrow associated with clinical response of CD19 CAR T-cell therapy. *Sci Rep* **12**, 2830 (2022).

L. Shao *et al.*, Genome-wide profiling of retroviral DNA integration and its effect on clinical pre-infusion CAR T-cell products. *J Transl Med* **20**, 514 (2022).

M. P. Smeltzer *et al.*, International Association for the Study of Lung Cancer Study of the Impact of Coronavirus Disease 2019 on International Lung Cancer Clinical Trials. *J Thorac Oncol* **17**, 651-660 (2022).

R. Sridhara *et al.*, Cancer Clinical Trials beyond Pandemic: Report of an American Statistical Association Biopharmaceutical Section Open Forum Discussion. *Journal* 444-449 (2022)

S. Stone, D. J. Newman, S. L. Colletti, D. S. Tan, Cheminformatic analysis of natural product-based drugs and chemical probes. *Nat Prod Rep* **39**, 20-32 (2022).

A. A. Tarhini *et al.*, Improved prognosis and evidence of enhanced immunogenicity in tumor and circulation of high-risk melanoma patients with unknown primary. *J Immunother Cancer* **10** (2022).

P. A. Taylor, J. M. Moran, D. A. Jaffray, J. C. Buchsbaum, A roadmap to clinical trials for FLASH. *Med Phys* **49**, 4099-4108 (2022).

S. M. Temkin *et al.*, Creating work environments where people of all genders in gynecologic oncology can thrive: An SGO evidence-based review. *Gynecol Oncol* **164**, 473-480 (2022).

W. P. Tew, C. Lacchetti, E. C. Kohn, *et al.*, Poly(ADP-Ribose) Polymerase Inhibitors in the Management of Ovarian Cancer: ASCO Guideline Rapid Recommendation Update. *J Clin Oncol* **40**, 3878-3881 (2022).

G. Thanarajasingam *et al.*, Reaching beyond maximum grade: progress and future directions for modernising the assessment and reporting of adverse events in haematological malignancies. *Lancet Haematol* **9**, e374-e384 (2022).

M. Trevino *et al.*, Advancing Research on Medical Image Perception by Strengthening Multidisciplinary Collaboration. *JNCI Cancer Spectr* **6** (2022).

B. Uygur, S. Ferguson, M. Pollack, Hiding in Plain Sight: Surprising Pharma and Biotech Connections to NIH's National Cancer Institute. *J Commer Biotechnol* **27**, 5-13 (2022).

I. Vergote *et al.*, Clinical research in ovarian cancer: consensus recommendations from the Gynecologic Cancer InterGroup. *Lancet Oncol* **23**, e374-e384 (2022).

P. Vikas, L. A. Korde, M. R. Somerfield, D. L. Hershman, Use of Immune Checkpoint Inhibitors in the Treatment of High-Risk, Early-Stage Triple-Negative Breast Cancer: ASCO Guideline Rapid Recommendation Update Q and A. *JCO Oncol Pract* **18**, 649-651 (2022).

P. J. Voon *et al.*, Phase I pharmacokinetic study of single agent trametinib in patients with advanced cancer and hepatic dysfunction. *J Exp Clin Cancer Res* **41**, 51 (2022).

C. L. Wainwright *et al.*, Future directions for the discovery of natural product-derived immunomodulating drugs: an IUPHAR positional review. *Pharmacol Res* **177**, 106076 (2022).

Y. Wang *et al.*, Comprehensive Surfaceome Profiling to Identify and Validate Novel Cell-Surface Targets in Osteosarcoma. *Mol Cancer Ther* **21**, 903-913 (2022).

L. C. Wehmas, C. E. Wood, P. Guan, M. Gosink, S. D. Hester, Organocatalyst treatment improves variant calling and mutant detection in archival clinical samples. *Sci Rep* **12**, 6509 (2022).

S. X. Yang, S. M. Hewitt, J. Yu, Locoregional tumor burden and risk of mortality in metastatic breast cancer. *NPJ Precis Oncol* **6**, 22 (2022).

Y. Yang *et al.*, Oncogenic RAS commandeers amino acid sensing machinery to aberrantly activate mTORC1 in multiple myeloma. *Nat Commun* **13**, 5469 (2022).

Y. Zhang, R. Nordstrom, Celebrating Contributions of Imaging Technology to Fight against Cancer at the 50th NCA Anniversary. *Radiol Imaging Cancer* **4**, e220085 (2022).

I. G. Zubal, J. Capala, Joint NIBIB/NCI/SNMMI Workshop on Directly Imaging Targeted Radionuclide Therapy Isotopes. *J Nucl Med* **63**, 23N-25N (2022).

# 2023


G. A. Abel *et al.*, Health-related quality of life and vulnerability among people with myelodysplastic syndromes: a US national study. *Blood Adv* **7**, 3506-3515 (2023).

A. Acuna-Villaorduna, J. C. Baranda, J. Boehmer, L. Fashoyin-Aje, S. D. Gore, Equitable Access to Clinical Trials: How Do We Achieve It? *Am Soc Clin Oncol Educ Book* **43**, e389838 (2023).

L. M. Adams *et al.*, Mapping the KRAS proteoform landscape in colorectal cancer identifies truncated KRAS4B that decreases MAPK signaling. *J Biol Chem* **299**, 102768 (2023).

A. A. Akeeb, S. M. King, O. Olaku, J. D. White, Communication Between Cancer Patients and Physicians About Complementary and Alternative Medicine: A Systematic Review. *J Integr Complement Med* **29**, 80-98 (2023).

B. Altintas, N. Giri, L. J. McReynolds, A. Best, B. P. Alter, Genotype-phenotype and outcome associations in patients with Fanconi anemia: the National Cancer Institute cohort. *Haematologica* **108**, 69-82 (2023).

D. Araujo *et al.*, Oncology phase I trial design and conduct: time for a change - MDICT Guidelines 2022. *Ann Oncol* **34**, 48-60 (2023).

M. Aryankalayil *et al.*, Biomarkers for biodosimetry and their role in predicting radiation injury. *Cytogenet Genome Res* 10.1159/000531444 (2023).

S. Assouline *et al.*, A randomized phase II/III study of 'novel therapeutics' versus azacitidine in newly diagnosed patients with acute myeloid leukemia (AML), high-risk myelodysplastic syndrome (MDS), or chronic myelomonocytic leukemia (CMML), age 60 or older: a report of the comparison of azacitidine and nivolumab to azacitidine: SWOG S1612. *Leuk Lymphoma* **64**, 473-477 (2023).

M. B. Atkins *et al.*, Combination Dabrafenib and Trametinib Versus Combination Nivolumab and Ipilimumab for Patients With Advanced BRAF-Mutant Melanoma: The DREAMseq Trial-ECOG-ACRIN EA6134. *J Clin Oncol* **41**, 186-197 (2023).

J. C. Baranda *et al.*, Expanding access to early phase trials: the CATCH-UP.2020 experience. *JNCI Cancer Spectr* **7** (2023).

E. Basch *et al.*, Patient-Reported Outcomes During and After Treatment for Locally Advanced Rectal Cancer in the PROSPECT Trial (Alliance N1048). *J Clin Oncol* **41**, 3724-3734 (2023).

D. J. Benedetti *et al.*, Treatment of children with favorable histology Wilms tumor with extrapulmonary metastases: A report from the COG studies AREN0533 and AREN03B2 and NWTSG study NWTS-5. *Cancer* 10.1002/cncr.35099 (2023).

A. F. Best *et al.*, COVID-19 severity by vaccination status in the NCI COVID-19 and Cancer Patients Study (NCCAPS). *J Natl Cancer Inst* **115**, 597-600 (2023).

A. F. Best, Y. Malinovsky, P. S. Albert, The efficient design of Nested Group Testing algorithms for disease identification in clustered data. *J Appl Stat* **50**, 2228-2245 (2023).

J. H. Beumer *et al.*, Evaluating the indotecan-neutropenia relationship in patients with solid tumors by population pharmacokinetic modeling and sigmoidal E(max) regressions. *Cancer Chemother Pharmacol* **91**, 219-230 (2023).

J. P. Bewersdorf *et al.*, Current landscape of translational and clinical research in myelodysplastic syndromes/neoplasms (MDS): Proceedings from the 1(st) International Workshop on MDS (iwMDS) Of the International Consortium for MDS (icMDS). *Blood Rev* **60**, 101072 (2023).

P. Bou-Samra *et al.*, Intraoperative molecular imaging: 3rd biennial clinical trials update. *J Biomed Opt* **28**, 050901 (2023).

P. K. Brastianos *et al.*, BRAF-MEK Inhibition in Newly Diagnosed Papillary Craniopharyngiomas. *N Engl J Med* **389**, 118-126 (2023).

J. J. Burtt, S. Akiba, D. Bazyka, C. N. Coleman, M. Hatch, J. L. Bernstein, Radiation disasters - long term consequences: reflections and summary of a recent symposium. *Int J Radiat Biol* **99**, 561-568 (2023).

A. P. Chen *et al.*, Atezolizumab for Advanced Alveolar Soft Part Sarcoma. *N Engl J Med* **389**, 911-921 (2023).

S. N. Chi *et al.*, Tazemetostat for tumors harboring SMARCB1/SMARCA4 or EZH2 alterations: results from NCI-COG pediatric MATCH APEC1621C. *J Natl Cancer Inst* **115**, 1355-1363 (2023).

S. Chowdhury *et al.*, Proteogenomic analysis of chemo-refractory high-grade serous ovarian cancer. *Cell* **186**, 3476-3498 e3435 (2023).

A. S. Clark *et al.*, Phase II Study of Palbociclib (PD-0332991) in CCND1, 2, or 3 Amplification: Results from the NCI-MATCH ECOG-ACRIN Trial (EAY131) Subprotocol Z1B. *Clin Cancer Res* **29**, 1477-1483 (2023).

K. A. Cole *et al.*, Pediatric phase 2 trial of a WEE1 inhibitor, adavosertib (AZD1775), and irinotecan for relapsed neuroblastoma, medulloblastoma, and rhabdomyosarcoma. *Cancer* **129**, 2245-2255 (2023).

C. N. Coleman *et al.*, The National Cancer Institute's Cancer Disparities Research Partnership Program: a unique funding model 20 years later. *J Natl Cancer Inst* **115**, 1465-1474 (2023).

A. E. DeZern *et al.*, Utility of targeted gene sequencing to differentiate myeloid malignancies from other cytopenic conditions. *Blood Adv* **7**, 3749-3759 (2023).

S. B. Dixon *et al.*, Specific causes of excess late mortality and association with modifiable risk factors among survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort. *Lancet* **401**, 1447-1457 (2023).

Y. Dou *et al.*, Proteogenomic insights suggest druggable pathways in endometrial carcinoma. *Cancer Cell* **41**, 1586-1605 e1515 (2023).

S. G. DuBois *et al.*, Randomized Phase III Trial of Ganitumab With Interval-Compressed Chemotherapy for Patients With Newly Diagnosed Metastatic Ewing Sarcoma: A Report From the Children's Oncology Group. *J Clin Oncol* **41**, 2098-2107 (2023).

A. J. Esbenshade *et al.*, Accumulation of Chronic Disease Among Survivors of Childhood Cancer Predicts Early Mortality. *J Clin Oncol* **41**, 3629-3641 (2023).

J. R. Evans *et al.*, National Cancer Institute (NCI) Program for Natural Product Discovery: Exploring NCI-60 Screening Data of Natural Product Samples with Artificial Neural Networks. *ACS Omega* **8**, 9250-9256 (2023).

J. Fang, The role of data imbalance bias in the prediction of protein stability change upon mutation. *PLoS One* **18**, e0283727 (2023).

J. Fang, Predicting thermostability difference between cellular protein orthologs. *Bioinformatics* **39** (2023).

K. Fanucci *et al.*, Multicenter Phase II Trial of the PARP Inhibitor Olaparib in Recurrent IDH1- and IDH2-mutant Glioma. *Cancer Res Commun* **3**, 192-201 (2023).

S. Forry *et al.*, The NCI Glioblastoma Therapeutics Network (GTN). *Neuro Oncol* **25**, 221-223 (2023).

J. C. Foster, E. L. Korn, B. Freidlin, J. A. Moscow, The potential to backfill in phase I trials: the National Cancer Institute's Cancer Therapy Evaluation Program experience. *JNCI Cancer Spectr* **7** (2023).

B. Freidlin, L. A. Korde, E. L. Korn, Timing and Reporting of Secondary Overall Survival End Points for Phase III Trials in Advanced/Metastatic Disease. *J Clin Oncol* **41**, 4616-4620 (2023).

B. Freidlin, E. L. Korn, Augmenting randomized clinical trial data with historical control data: Precision medicine applications. *J Natl Cancer Inst* **115**, 14-20 (2023).

L. Galluzzi, M. J. Aryankalayil, C. N. Coleman, S. C. Formenti, Emerging evidence for adapting radiotherapy to immunotherapy. *Nat Rev Clin Oncol* **20**, 543-557 (2023).

J. S. Garcia *et al.*, Ipilimumab plus decitabine for patients with MDS or AML in posttransplant or transplant-naive settings. *Blood* **141**, 1884-1888 (2023).

Y. Geffen *et al.*, Pan-cancer analysis of post-translational modifications reveals shared patterns of protein regulation. *Cell* **186**, 3945-3967 e3926 (2023).

E. J. Gorak *et al.*, Discordant pathologic diagnoses of myelodysplastic neoplasms and their implications for registries and therapies. *Blood Adv* **7**, 6120-6129 (2023).

A. M. Gross *et al.*, Long-term safety and efficacy of selumetinib in children with neurofibromatosis type 1 on a phase 1/2 trial for inoperable plexiform neurofibromas. *Neuro Oncol* **25**, 1883-1894 (2023).

L. N. Harris *et al.*, The New NCI Precision Medicine Trials. *Clin Cancer Res* **29**, 4728-4732 (2023).

D. Harrison *et al.*, Evaluation of the pan-class I phosphoinositide 3-kinase (PI3K) inhibitor copanlisib in the Pediatric Preclinical Testing Consortium in vivo models of osteosarcoma. *Pediatr Blood Cancer* **70**, e30017 (2023).

D. F. Hayes, W. Sauerbrei, L. M. McShane, REMARK guidelines for tumour biomarker study reporting: a remarkable history. *Br J Cancer* **128**, 443-445 (2023).

E. P. Huang *et al.*, Criteria for the translation of radiomics into clinically useful tests. *Nat Rev Clin Oncol* **20**, 69-82 (2023).

E. P. Huang *et al.*, Multiparametric Quantitative Imaging in Risk Prediction: Recommendations for Data Acquisition, Technical Performance Assessment, and Model Development and Validation. *Acad Radiol* **30**, 196-214 (2023).

K. Hughes *et al.*, In vivo activity of the dual SYK/FLT3 inhibitor TAK-659 against pediatric acute lymphoblastic leukemia xenografts. *Pediatr Blood Cancer* 10.1002/pbc.30503, e30503 (2023).

T. Ige *et al.*, Understanding the challenges of delivering radiotherapy in low- and middle-income countries in Africa. *J Cancer Policy* **35**, 100372 (2023).

M. Ingham *et al.*, Phase II Study of Olaparib and Temozolomide for Advanced Uterine Leiomyosarcoma (NCI Protocol 10250). *J Clin Oncol* **41**, 4154-4163 (2023).

S. Kaczanowska *et al.*, Immune determinants of CAR-T cell expansion in solid tumor patients receiving GD2 CAR-T cell therapy. *Cancer Cell* 10.1016/j.ccell.2023.11.011 (2023).

O. Kantor *et al.*, Racial and Ethnic Disparities in Locoregional Recurrence Among Patients With Hormone Receptor-Positive, Node-Negative Breast Cancer: A Post Hoc Analysis of the TAILORx Randomized Clinical Trial. *JAMA Surg* **158**, 583-591 (2023).

M. Karkanitsa *et al.*, Dynamics of SARS-CoV-2 Seroprevalence in a Large US population Over a Period of 12 Months. *medRxiv* 10.1101/2023.10.20.23297329 (2023).

C. Keppel *et al.*, The United States Department of Energy and National Institutes of Health Collaboration: Medical Care Advances via Discovery in Physical Sciences. *Med Phys* **50**, e53-e61 (2023).

J. W. Kim *et al.*, Randomized Trial of Olaparib With or Without Cediranib for Metastatic Castration-Resistant Prostate Cancer: The Results From National Cancer Institute 9984. *J Clin Oncol* **41**, 871-880 (2023).

M. M. Kim *et al.*, National Cancer Institute Collaborative Workshop on Shaping the Landscape of Brain Metastases Research: challenges and recommended priorities. *Lancet Oncol* **24**, e344-e354 (2023).

T. K. Kim *et al.*, PD-1H/VISTA mediates immune evasion in acute myeloid leukemia. *J Clin Invest* 10.1172/JCI164325 (2023).

B. Ko, N. Takebe, O. Andrews, M. R. Makena, A. P. Chen, Rethinking Oncologic Treatment Strategies with Interleukin-2. *Cells* **12** (2023).

L. A. Korde, A. F. Best, Response to Song. *J Natl Cancer Inst* **115**, 768 (2023).

E. L. Korn, J. A. Moscow, B. Freidlin, Dose optimization during drug development: whether and when to optimize. *J Natl Cancer Inst* **115**, 492-497 (2023).

A. V. Krauze *et al.*, Revisiting Concurrent Radiation Therapy, Temozolomide, and the Histone Deacetylase Inhibitor Valproic Acid for Patients with Glioblastoma-Proteomic Alteration and Comparison Analysis with the Standard-of-Care Chemoirradiation. *Biomolecules* **13** (2023).

R. Lakhotia *et al.*, Prognostic factors for adult patients with Burkitt lymphoma treated with dose-adjusted EPOCH-R. *Blood Adv* **7**, 5320-5324 (2023).

A. B. A. Laranjeira, M. G. Hollingshead, D. Nguyen, R. J. Kinders, J. H. Doroshow, S. X. Yang, DNA damage, demethylation and anticancer activity of DNA methyltransferase (DNMT) inhibitors. *Sci Rep* **13**, 5964 (2023).

J. Li *et al.*, Formalin Fixation, Delay to Fixation, and Time in Fixative Adversely Impact Copy Number Variation Analysis by aCGH. *Biopreserv Biobank* **21**, 407-416 (2023).

Y. Li *et al.*, Proteogenomic data and resources for pan-cancer analysis. *Cancer Cell* **41**, 1397-1406 (2023).

Y. Li *et al.*, Histopathologic and proteogenomic heterogeneity reveals features of clear cell renal cell carcinoma aggressiveness. *Cancer Cell* **41**, 139-163 e117 (2023).

Y. Li *et al.*, Pan-cancer proteogenomics connects oncogenic drivers to functional states. *Cell* **186**, 3921-3944 e3925 (2023).

W. W. Liang *et al.*, Integrative multi-omic cancer profiling reveals DNA methylation patterns associated with therapeutic vulnerability and cell-of-origin. *Cancer Cell* **41**, 1567-1585 e1567 (2023).

M. P. Little *et al.*, Low-dose radiotherapy for COVID-19 pneumonia and cancer: summary of a recent symposium and future perspectives. *Int J Radiat Biol* **99**, 357-371 (2023).

J. K. Litton *et al.*, Standardized Definitions for Efficacy End Points in Neoadjuvant Breast Cancer Clinical Trials: NeoSTEEP. *J Clin Oncol* **41**, 4433-4442 (2023).

P. M. LoRusso, B. Freidlin, Improving precision oncology through better designs and reporting of biomarker-driven randomized clinical trials. *J Natl Cancer Inst* **115**, 122-124 (2023).

M. A. Lumish, E. C. Kohn, W. P. Tew, Top advances of the year: Ovarian cancer. *Cancer* 10.1002/cncr.35135 (2023).

M. K. Malhotra *et al.*, A phase 1 study of veliparib (ABT-888) plus weekly carboplatin and paclitaxel in advanced solid malignancies, with an expansion cohort in triple negative breast cancer (TNBC) (ETCTN 8620). *Breast Cancer Res Treat* **198**, 487-498 (2023).

L. Martinez-Fructuoso *et al.*, Screen for New Antimicrobial Natural Products from the NCI Program for Natural Product Discovery Prefractionated Extract Library. *ACS Infect Dis* **9**, 1245-1256 (2023).

S. J. McCall *et al.*, The Cooperative Human Tissue Network of the National Cancer Institute: Supporting Cancer Research for 35 Years. *Mol Cancer Ther* **22**, 1144-1153 (2023).

L. M. McShane, M. D. Rothmann, T. R. Fleming, Finding the (biomarker-defined) subgroup of patients who benefit from a novel therapy: No time for a game of hide and seek. *Clin Trials* **20**, 341-350 (2023).

J. H. McVittie *et al.*, Survival Modelling For Data From Combined Cohorts: Opening the Door to Meta Survival Analyses and Survival Analysis using Electronic Health Records. *Int Stat Rev* **91**, 72-87 (2023).

F. Meric-Bernstam *et al.*, National Cancer Institute Combination Therapy Platform Trial with Molecular Analysis for Therapy Choice (ComboMATCH). *Clin Cancer Res* **29**, 1412-1422 (2023).

L. M. Minasian *et al.*, Study design considerations for trials to evaluate multicancer early detection assays for clinical utility. *J Natl Cancer Inst* **115**, 250-257 (2023).

A. Mittra *et al.*, Pharmacodynamic effects of the PARP inhibitor talazoparib (MDV3800, BMN 673) in patients with BRCA-mutated advanced solid tumors. *Cancer Chemother Pharmacol* 10.1007/s00280-023-04600-0 (2023).

J. Mizusawa, H. Sato, L. V. Rubinstein, T. Fujiwara, K. Yonemori, A. Hirakawa, Racial differences in longitudinal toxicities of anticancer agents in early phase cancer clinical trials. *Cancer Med* **12**, 18098-18109 (2023).

A. Modi *et al.*, Integrative Genomic Analyses Identify LncRNA Regulatory Networks across Pediatric Leukemias and Solid Tumors. *Cancer Res* **83**, 3462-3477 (2023).

C. S. Morales, P. Grodzinski, Current landscape of treating different cancers using nanomedicines: Trends and perspectives. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 10.1002/wnan.1927, e1927 (2023).

L. Moreno *et al.*, Combination Early-Phase Trials of Anticancer Agents in Children and Adolescents. *J Clin Oncol* **41**, 3408-3422 (2023).

J. Morris *et al.*, Targeted Investigational Oncology Agents in the NCI-60: A Phenotypic Systems-based Resource. *Mol Cancer Ther* **22**, 1270-1279 (2023).

C. Mpody *et al.*, Current Trends in Mortality Attributable to Racial or Ethnic Disparities in Post-Surgical Population in The United States: A Population-Based Study. *Ann Surg Open* **4**, e342 (2023).

R. Naghavian *et al.*, Microbial peptides activate tumour-infiltrating lymphocytes in glioblastoma. *Nature* **617**, 807-817 (2023).

J. Nguyen *et al.*, Randomized Phase II Trial of Sunitinib or Cediranib in Alveolar Soft Part Sarcoma. *Clin Cancer Res* **29**, 1200-1208 (2023).

P. J. O'Dwyer *et al.*, The NCI-MATCH trial: lessons for precision oncology. *Nat Med* **29**, 1349-1357 (2023).

N. A. Obuchowski *et al.*, A Framework for Evaluating the Technical Performance of Multiparameter Quantitative Imaging Biomarkers (mp-QIBs). *Acad Radiol* **30**, 147-158 (2023).

E. Pan *et al.*, A Phase I Study of Combination Olaparib and Radium-223 in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC) with Bone Metastases (COMRADE). *Mol Cancer Ther* **22**, 511-518 (2023).

A. H. Partridge *et al.*, Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer. *N Engl J Med* **388**, 1645-1656 (2023).

S. P. Patel *et al.*, Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma. *N Engl J Med* **388**, 813-823 (2023).

A. D. J. Pearson *et al.*, Paediatric Strategy Forum for medicinal product development of DNA damage response pathway inhibitors in children and adolescents with cancer: ACCELERATE in collaboration with the European Medicines Agency with participation of the Food and Drug Administration. *Eur J Cancer* **190**, 112950 (2023).

L. Penter *et al.*, Mechanisms of response and resistance to combined decitabine and ipilimumab for advanced myeloid disease. *Blood* **141**, 1817-1830 (2023).

N. S. Phillips *et al.*, Late-onset Cognitive Impairment and Modifiable Risk Factors in Adult Childhood Cancer Survivors. *JAMA Netw Open* **6**, e2316077 (2023).

P. G. S. Prasanna, M. Aryankalayil, D. E. Citrin, C. N. Coleman, Radiation-induced pulmonary fibrosis: roles of therapy-induced senescence and microRNAs. *Int J Radiat Biol* **99**, 1027-1036 (2023).

J. Rahnenfuhrer *et al.*, Statistical analysis of high-dimensional biomedical data: a gentle introduction to analytical goals, common approaches and challenges. *BMC Med* **21**, 182 (2023).

L. Rajdev *et al.*, Assessment of the safety of nivolumab in people living with HIV with advanced cancer on antiretroviral therapy: the AIDS Malignancy Consortium 095 Study. *Cancer* 10.1002/cncr.35110 (2023).

J. Randall *et al.*, In vivo activity of the dual PI3Kdelta and PI3Kgamma inhibitor duvelisib against pediatric acute lymphoblastic leukemia xenografts. *Pediatr Blood Cancer* **70**, e30398 (2023).

Y. Rong *et al.*, NRG Oncology assessment on AI deep-learning based auto-segmentation for radiotherapy: current development, clinical consideration, and future direction. *Int J Radiat Oncol Biol Phys* 10.1016/j.ijrobp.2023.10.033 (2023).

P. S. Rosenberg, A. M. Filho, J. Elrod, A. Arsham, A. F. Best, P. Chernyavskiy, Smoothing Lexis diagrams using kernel functions: A contemporary approach. *Stat Methods Med Res* **32**, 1799-1810 (2023).

S. Scheich *et al.*, Targeting N-linked Glycosylation for the Therapy of Aggressive Lymphomas. *Cancer Discov* **13**, 1862-1883 (2023).

L. K. Shankar *et al.*, Meta-Analysis of the Test-Retest Repeatability of [18F]-Fluorodeoxyglucose Standardized Uptake Values: Implications for Assessment of Tumor Response. *Clin Cancer Res* **29**, 143-153 (2023).

L. K. Shankar *et al.*, Harnessing imaging tools to guide immunotherapy trials: summary from the National Cancer Institute Cancer Imaging Steering Committee workshop. *Lancet Oncol* **24**, e133-e143 (2023).

E. Sharon, J. C. Foster, Design of phase II oncology trials evaluating combinations of experimental agents. *J Natl Cancer Inst* **115**, 613-618 (2023).

S. Singh *et al.*, Consensus report of the 2021 National Cancer Institute neuroendocrine tumor clinical trials planning meeting. *J Natl Cancer Inst* **115**, 1001-1010 (2023).

M. Stahl *et al.*, An agenda to advance research in myelodysplastic syndromes: a TOP 10 priority list from the first international workshop in MDS. *Blood Adv* **7**, 2709-2714 (2023).

M. Stahl *et al.*, Classification, risk stratification and response assessment in myelodysplastic syndromes/neoplasms (MDS): A state-of-the-art report on behalf of the International Consortium for MDS (icMDS). *Blood Rev* **62**, 101128 (2023).

S. M. Sweeney *et al.*, Challenges to Using Big Data in Cancer. *Cancer Res* **83**, 1175-1182 (2023).

S. M. Sweeney *et al.*, Case Studies for Overcoming Challenges in Using Big Data in Cancer. *Cancer Res* **83**, 1183-1190 (2023).

N. Takahashi *et al.*, Berzosertib Plus Topotecan vs Topotecan Alone in Patients With Relapsed Small Cell Lung Cancer: A Randomized Clinical Trial. *JAMA Oncol* **9**, 1669-1677 (2023).

L. P. Taliaferro *et al.*, Sex differences in radiation research. *Int J Radiat Biol* 10.1080/09553002.2023.2283089, 1-20 (2023).

K. Toner *et al.*, Overcoming barriers to drug development and enrollment in clinical trials for adolescents and young adults with lymphoma. *EJHaem* **4**, 921-926 (2023).

P. Torka *et al.*, Is local review of positron emission tomography scans sufficient in diffuse large B-cell lymphoma clinical trials? A CALGB 50303 analysis. *Cancer Med* **12**, 8211-8217 (2023).

J. M. Unger *et al.*, Sponsor Perspectives on the Impact of the COVID-19 Pandemic on Interventional Cancer Clinical Trial Protocols and Data Quality. *JCO Oncol Pract* **19**, 907-916 (2023).

C. L. Vogel *et al.*, Efficacy and Safety of Trastuzumab as a Single Agent in First-Line Treatment of HER2-Overexpressing Metastatic Breast Cancer. *J Clin Oncol* **41**, 1638-1645 (2023).

J. M. Wang *et al.*, Deep learning integrates histopathology and proteogenomics at a pan-cancer level. *Cell Rep Med* **4**, 101173 (2023).

S. L. Wang *et al.*, Exogenous DNA enhances DUOX2 expression and function in human pancreatic cancer cells by activating the cGAS-STING signaling pathway. *Free Radic Biol Med* **205**, 262-274 (2023).

P. Y. Wen *et al.*, RANO 2.0: Update to the Response Assessment in Neuro-Oncology Criteria for High- and Low-Grade Gliomas in Adults. *J Clin Oncol* **41**, 5187-5199 (2023).

K. B. Wisinski *et al.*, Trametinib in Patients With NF1-, GNAQ-, or GNA11-Mutant Tumors: Results From the NCI-MATCH ECOG-ACRIN Trial (EAY131) Subprotocols S1 and S2. *JCO Precis Oncol* **7**, e2200421 (2023).

H. M. Wojcik *et al.*, Exploiting embryonic niche conditions to grow Wilms tumor blastema in culture. *Front Oncol* **13**, 1091274 (2023).

A. C. Wolff *et al.*, Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer. *Arch Pathol Lab Med* **147**, 993-1000 (2023).

A. C. Wolff *et al.*, Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO-College of American Pathologists Guideline Update. *J Clin Oncol* **41**, 3867-3872 (2023).

N. L. Wu *et al.*, Development and Validation of a Prediction Model for Kidney Failure in Long-Term Survivors of Childhood Cancer. *J Clin Oncol* **41**, 2258-2268 (2023).

Y. Wu *et al.*, Epigenetic and transcriptomic characterization reveals progression markers and essential pathways in clear cell renal cell carcinoma. *Nat Commun* **14**, 1681 (2023).

H. Zhang, The National Cancer Institute's Co-Clinical Quantitative Imaging Research Resources for Precision Medicine in Preclinical and Clinical Settings. *Tomography* **9**, 931-941 (2023).

W. Zou *et al.*, Framework for Quality Assurance of Ultrahigh Dose Rate Clinical Trials Investigating FLASH Effects and Current Technology Gaps. *Int J Radiat Oncol Biol Phys* **116**, 1202-1217 (2023).

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