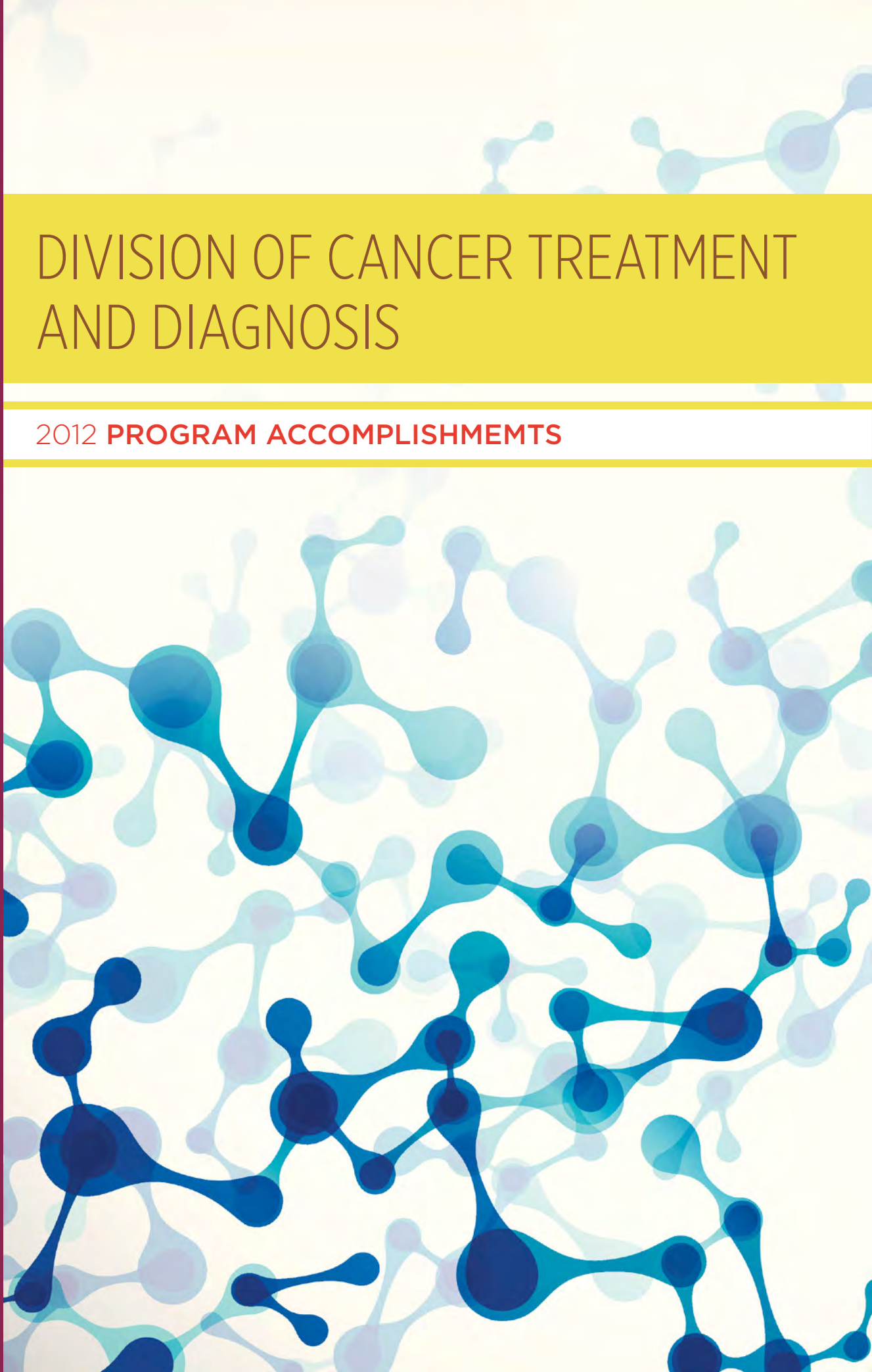


DIVISION OF CANCER TREATMENT AND DIAGNOSIS

2012 **PROGRAM ACCOMPLISHMENTS**



NATIONAL CANCER INSTITUTE

DIVISION OF CANCER TREATMENT AND DIAGNOSIS

2012 **PROGRAM ACCOMPLISHMENTS**

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PREFACE



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

This edition of Program Accomplishments of the Division of Cancer Treatment and Diagnosis (DCTD) offers a multi-year review of the undertakings and achievements of this segment of the National Cancer Institute (NCI). Though not meant to be a complete inventory of the division, this report covers activities and advances from 2011 through 2012 and provides important highlights that have helped advance the diagnosis and treatment of cancer.

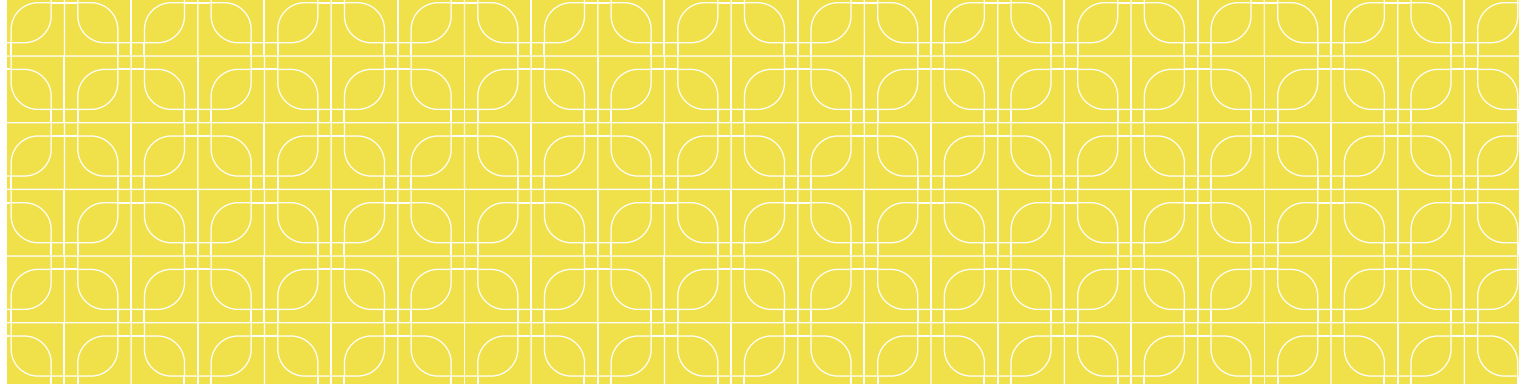
One of our greatest challenges is to increase the speed with which new treatments are brought to the millions of Americans with cancer. DCTD has implemented a number of actions to streamline the drug discovery and development process. The inauguration of the NCI Experimental Therapeutics (NExT) program allows researchers to enter candidate agents into the NCI pipeline at a number of key 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 ongoing

projects are making steady progress toward the initiation of first-in-human clinical studies. Other entry points further along the development pipeline include providing agents for testing in mid-stage clinical trials in our phase 2 clinical trials program.

The evaluation of novel molecularly-targeted therapeutic agents includes development of robust, sensitive assays to demonstrate clinical proof-of-mechanism in tumor tissue. During the current reporting period, supported by the American Recovery and Re-investment Act (ARRA) of 2009, DCTD expanded its pharmacodynamic assay development program so that assays measuring the impact of new drugs could be developed for several important therapeutic areas, including: DNA damage and repair, the epithelial to mesenchymal transition, the MAP kinase pathway, the apoptotic cascade, topoisomerase I, phosphoMET, and HIF-1 α . All of these assays are now in use in NCI-supported clinical trials or are in late-stage preclinical development. The ARRA resources also permitted the development of a molecular characterization facility at our Frederick site that will be used to support national clinical trials matching “actionable” mutations to specific targeted therapeutic agents across disease areas.

During the past two years, the continuing efforts of DCTD to improve its national clinical trials program have continued at a rapid pace. In anticipation of the recompetition of NCI's former Cooperative Group Program into the National Clinical Trials Network (NCTN), consolidation that has yielded four adult network groups (from the prior nine) has occurred, with the concomitant consolidation of statistical offices. In concert with this consolidation, the NCI facilitated the implementation of a uniform clinical trials data management system that will be used for all network trials, as well—in time—for all other clinical trials networks supported by the NCI. Together with the recent, successful implementation of operational efficiency timelines, and a national central institutional review board for all NCI-sponsored network studies, it is expected that when fully configured the NCTN will be able to rapidly develop, accrue, and complete new generations of genomically-based clinical trials carried out across a national clinical research infrastructure with enhanced research capabilities.

In addition to these major DCTD efforts, in these pages readers will find summaries of recently established priorities and scientific advances across a wide variety of diagnostic and therapeutic domains made possible by the many talented and committed staff members throughout the division. It is my privilege to work with these dedicated individuals.



2012 PROGRAM ACCOMPLISHMENTS

DIVISION OF CANCER TREATMENT AND DIAGNOSIS



OVERVIEW

The **Division of Cancer Treatment and Diagnosis (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 patients.

Within DCTD, eight major programs work together to bring unique molecules, diagnostic tests, and therapeutic interventions from the laboratory bench to the patient bedside:

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

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.

The Cancer Therapy Evaluation Program (CTEP) functions as the National Cancer Institute's (NCI's) primary clinical evaluator of new anticancer agents, radiation treatments, and surgical methods. The program administers the 11 cooperative research groups that unite researchers around the nation and the world in the pursuit of distinctive and effective new treatments for cancer.

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 research materials and

manufactures new agents in bulk quantities for use in studies directed toward U.S. Food and Drug Administration (FDA) Investigational New Drug applications.

The Radiation Research Program (RRP) provides expertise to investigators who perform novel radiotherapy research and assists in establishing future directions for radiation research.

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.

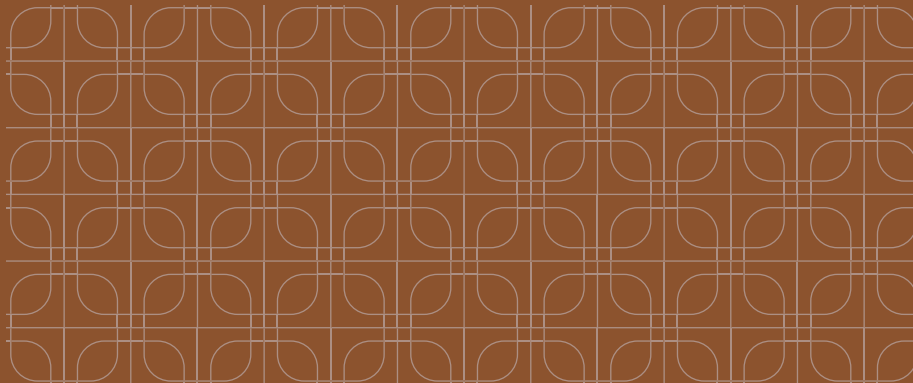
The Biometric Research Branch (BRB) provides state-of-the-art statistical and biomathematical analyses for DCTD and other NCI components.

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.

Additional information about NCI's Division of Cancer Treatment and Diagnosis is available at <http://dctd.cancer.gov> and <http://cancer.gov>.

JAMES H. DOROSHOW

DIRECTOR



James H. Doroshow, MD, FACP, has been the director of DCTD since 2004. He is responsible for integrating the activities of DCTD with the National Cancer Institute's (NCI's) other divisions and offices, as well as extramural scientists and clinicians, patient advocates, and professional cancer organizations. He leads more than 800 DCTD professional staff who represent a wide array of scientific specialties in a multidisciplinary endeavor to discover and develop better diagnostic and therapeutic interventions for cancer. Since coming to NCI, Dr. Doroshow has led the effort to modernize NCI's clinical research infrastructure through the efforts of the Clinical Trials Working Group and has initiated several new programs to reinvigorate early therapeutics discovery and development across the institute. Dr. Doroshow also oversees his own active laboratory program, which focuses on understanding the role of oxidative signals in the development and treatment of solid tumors.

From 1983 to 2004, Dr. Doroshow was the Associate Director for Clinical Research at the City of Hope's (COH) Comprehensive Cancer Center in Duarte, California; the Chairman of the COH Department of Medical Oncology and Therapeutics Research; and the Leader of the COH Cancer Center's Clinical and Experimental Therapeutics Program. While at COH, he founded an early therapeutics consortium of three NCI-designated cancer centers in California funded by NCI's phase 1 and 2 support grants. He was also the principal investigator for COH's membership in the Southwest Oncology Group (SWOG) and the founding Chair of the SWOG Early Therapeutics Committee.

From the time he received his first research grant in 1980, Dr. Doroshow was funded continuously by NCI and the National Institutes of Health (NIH) until moving to NCI in 2004. He is the author of more than 300 full-length publications on the molecular and clinical pharmacology of the anthracycline antibiotics, the role of oxidant stress in signal transduction, and novel therapeutic approaches to breast, gastrointestinal, lung, and gynecologic cancer. Dr. Doroshow is a senior editor of *Clinical Cancer Research* and is a member of the editorial boards of several other journals. Dr. Doroshow served from 1995 to 2001 as a member of the Subspecialty Board on Medical Oncology of the American Board of Internal Medicine, from 1999 to 2000 as Chair of NCI's Scientific Review Group A Cancer Centers, and from 1990 to 1992 as Chair of the NIH Experimental Therapeutics II Study Section. He served as a member of the FDA's Oncologic Drugs Advisory Committee from 2004 to 2007.

Dr. Doroshow received his bachelor's degree, magna cum laude, from Harvard College in 1969 and his medical degree, Alpha Omega Alpha, from Harvard Medical School in 1973. After completing an internship and residency at Massachusetts General Hospital in Boston, he spent three years (1975–1978) as a clinical associate in NCI's Medicine Branch. He is board certified in internal medicine and medical oncology.

DIVISION OF CANCER TREATMENT AND DIAGNOSIS

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Deputy Director

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Director

Biometric Research Branch
Dr. Richard Simon
Chief

Cancer Diagnosis Program

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Dr. Tracy Lively
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Biorepository and Biospecimen Research Branch

Dr. James Vaught
Chief

Diagnostic Biomarkers and Technology Branch

Dr. James Tricoli
Chief

Diagnostics Evaluation Branch

Dr. John Jessup
Chief

Pathology Investigation and Resources Branch

Dr. Irina Lubensky
Chief

Cancer Imaging Program

Dr. Paula Jacobs
Associate Director

Clinical Trials Branch

Dr. Lalitha Shankar
Chief

Molecular Imaging Branch

Dr. Paula Jacobs
Acting Chief

Image-Guided Intervention Branch

Dr. Laurence Clarke
Acting Chief

Imaging Technology Development Branch

Dr. Laurence Clarke
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Associate Director

Clinical Grants and Contracts Branch

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Chief

Clinical Investigations Branch

Dr. Margaret Mooney
Chief

Clinical Trials Monitoring Branch

Gary Smith
Chief

Investigational Drug Branch

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Operations & Informatics Branch

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Pharmaceutical Management Branch

Mr. Charles Hall
Chief

Regulatory Affairs Branch

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Information Technology Branch

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Dr. Bhadransain Vikram
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Clinical Radiation Oncology Branch

Dr. Bhadransain Vikram
Chief

Molecular Radiation Therapeutics Branch

Dr. Stephen S. Yoo
Chief

Radiotherapy Development Branch

Dr. Eric Bernhard
Chief

Molecular Pharmacology Branch

Dr. Beverly Teicher
Chief

MAJOR INITIATIVES AND ACCOMPLISHMENTS

RESEARCH EMPHASIS FOR THE FUTURE

Over the past several years, a review of the DCTD portfolio has identified a number of under-investigated areas of unmet research needs in cancer therapeutics and diagnostics. DCTD continues to make a concerted effort to increase support in these areas through grants, contracts, and the development of new initiatives:

Enhancing tumor response to therapy

- Development of combination targeted therapies in clinically relevant models
- Reducing toxicity by using image-guided interventions to target drug delivery and activation
- Studies on the beneficial or harmful effects of anticancer agents on unintended targets
- Discovery and re-discovery of drugs from natural products

Investigations of the tumor microenvironment

- Designing and testing agents that target the tumor microenvironment by using new in vitro and in vivo models
- Understanding the dynamic relationship between tumors and cells in the microenvironment
- Understanding the role of the tumor microenvironment in tumor transformation and response to treatment through imaging and other noninvasive methods

Development of new methods and technologies

- Development of new imaging technologies, including novel hardware, new research interfaces, refinement of image processing, and further development of virtual imaging
- Development of in vivo imaging-based assays of relevant biomarkers
- Integration of imaging into biomarker development strategies for new therapeutic agents and combinations

Development of new imaging agents

- Development and application of diagnostic devices and technologies that support multi-analyte molecular assays for proof-of-mechanism clinical trials and preclinical studies

- Development of integrated diagnostic devices for real-time analysis of biospecimens
- Methods, mechanisms, and technologies to ensure the availability of appropriately collected clinical specimens for translational research

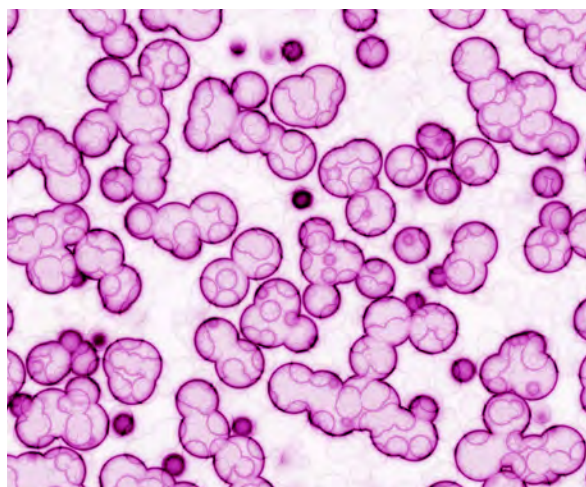
Clinical studies

- Translational and clinical studies in under-investigated diseases—pancreatic cancer, squamous cell carcinoma of the head and neck, bladder cancer, and sarcoma
- Development of pharmacodynamically based proof-of-mechanism clinical trials of investigational targeted agent combinations
- Validation of the clinical utility of molecular profiles
- Clinical studies using imaging approaches to characterize disease anatomy, physiology, and molecular biology
- Validation of the clinical utility of novel and innovative clinical diagnostic devices
- Development of personalized medicine approaches, including the discovery, development, and qualification of biomarkers to define efficacy, toxicity, dosing, and therapeutic schedules

RECOMMENDATIONS DEVELOPED TO RE-ENVISION NCI'S CLINICAL TRIALS SYSTEM

Over the past 7 years, three related working groups have made recommendations to NCI to improve, modernize, and streamline clinical and translational research at the institute. The end results aim to reduce by half the time it takes to open clinical trials. These review groups were:

1. The **Clinical Trials Working Group**, which evaluated the entire range of NCI-supported clinical trials
2. The **Translational Research Working Group**, which focused on research to move basic research discoveries into phase 1 clinical studies
3. The **Operational Efficiency Working Group**, which was formed to make specific recommendations to improve the efficiency of all NCI-sponsored clinical trials



Each of these working groups used an inclusive approach to examine ways to increase the efficiency of cancer clinical trials, decrease redundancy and administrative burdens, and better coordinate activities to enhance the development and delivery of the best therapies to cancer patients. Each of the teams assembled to advise NCI included well-respected translational and clinical research experts as well as patient advocates and practicing physicians from the cancer community, and each group solicited public comments before submitting recommendations to the institute.

The NCI's Clinical Trials Cooperative Group program, administered by DCTD, was created in the 1950s, before the discovery of the genetic underpinnings of cancer that have led to the recent development of targeted cancer therapies and the dawning of personalized cancer treatment. Over time, the process of activating new phase 3 clinical trials conducted by NCI's Cooperative Groups became extraordinarily lengthy, so that on average, opening a phase 3 study required more than 2 years and activation of most phase 1 and 2 studies required more than 500 days. A recent analysis of the activation process for NCI's clinical trials demonstrated that many trials, especially those that took the longest to open, never reached their accrual goals and had to be closed, wasting precious time and resources. Major changes to the NCI clinical trials system are currently being implemented on the basis of these reports.

Clinical Trials Working Group

- Recommendations made in 2005
- Chaired by Dr. James H. Doroshow

- Focused on the entire range of clinical trials supported by NCI
- Recommended 22 strategic initiatives and corresponding implementation plans for revamping the institute's cancer clinical trials system, most of which are nearing completion
- Recommendations addressed six key issues:
 1. Coordination
 2. Scientific prioritization
 3. Standardization
 4. Operational efficiency
 5. Enterprise-wide oversight
 6. Informatics
- Resulted in the creation of nine extramural disease-specific steering committees to develop, evaluate, and prioritize clinical trials at a national level
- Resulted in the creation of a new oversight structure for NCI's clinical trials program:
 - **Coordinating Center for Clinical Trials**, to oversee implementation of the recommendations from the Clinical Trials Working Group
 - **Clinical Trials and Translational Research Advisory Committee (CTAC)**, an external group, to provide strategic advice regarding NCI's clinical trials portfolio and establish the Operational Efficiency Working Group

- Clinical Trials Operating Committee, an internal group, to coordinate and prioritize clinical research across NCI
- Resulted in a systematic review of the steps involved in opening a clinical trial and an implementation plan to decrease by 50% the time required to activate clinical trials
- Resulted in the development of support for biomarker validation clinical trials

Translational Research Working Group

- Recommendations made in 2007
- Co-chaired by Dr. Ernest Hawk, Dr. Lynn Matrisian, and Dr. William Nelson
- Focused on early translational research that is essential to moving basic research discoveries into phase 1 clinical studies
- Examined how NCI could best ensure that the most promising basic research concepts enter developmental pathways and are advanced rapidly and efficiently to either translational success or productive failure
- Developed 15 recommendations and implementation plans in three key categories:
 1. Coordinated management
 2. Tailored funding programs
 3. Operational effectiveness
- Resulted in changes to three existing entities to include translational research in their goals:
 1. The Coordinating Center for Clinical Trials was tasked to oversee implementation of the recommendations from the Clinical Trials Working group and the Translational Research Working Group.
 2. The Clinical Trials Advisory Committee, an external group, became the CTAC.
 3. The Clinical Trials Operating Committee, an internal group, expanded to become the **Clinical and Translational Research Operations Committee**.
- Resulted in the creation of the **Translational Research Program (TRP)**, the chief component of which is the

Specialized Programs of Research Excellence (SPORE) program and the initiation of the first Special Translational Acceleration Project (STRAP) awards

Operational Efficiency Working Group

- Recommendations made in 2010
- Co-chaired by Dr. James H. Doroshow and Dr. Gabriel Hortobagyi
- Established under the auspices of CTAC to advise NCI on strategies to reduce the time required to activate clinical trials
- Resulted in 14 recommendations that were developed into several key initiatives:
 - Cooperative group phase 3 trial process improvements
 - Early drug development trial process improvements
 - Cancer center investigator-initiated trial process improvements
 - Process improvements applicable across trial categories
 - Process improvements to enhance the overall clinical trials program
- Resulted in key activation milestones to decrease by half the time it takes to open clinical trials
- Resulted in the April 2010 implementation by CTEP of an action plan to improve efficiency and speed protocol development

PROJECTS FUNDED BY THE AMERICAN RECOVERY AND REINVESTMENT ACT OF 2009

Under the umbrella of the American Recovery and Reinvestment Act of 2009 (ARRA), DCTD awarded funds for competitive grants and initiated and expanded several cancer diagnostic and therapeutic initiatives. These initiatives concentrate on facilitating the development of new research resources in support of clinical trials, the acceleration of early-stage clinical studies, and enhancement of the NCI Experimental Therapeutics (NExT) drug discovery and development program. Each project underwent multilevel review in NCI before ultimately receiving approval from the White House.

Molecular Characterization Laboratory and Clinical Assay Development Program

The mission of the Molecular Characterization Laboratory and the Clinical Assay Development Program is to improve patient outcomes by translating information from the comprehensive molecular characterization of patients' tumors and associated tissues to their clinical management. Critical to this endeavor is accelerated evaluation of molecular alterations in the tumor and the development and validation of clinical assays assessing these alterations. This initiative provides resources focused on the development, optimization, and validation of molecular profiling procedures and predictive assays that can then be evaluated for clinical utility in well-designed clinical trials.

The initiative consists of two distinct but technologically linked components. The first is the Molecular Characterization Laboratory (MoCha), which performs molecular characterization of patient tumors with one or several genomic analysis platforms. Specific alterations in the genomes and transcriptomes of tumors are poised to become an essential parameter for stratifying patients into different prognostic groups or to make assignments to clinical trials of agents that target the tumor's specific molecular abnormalities. MoCha, initially funded as a pilot program through ARRA, has validated a massively parallel, targeted DNA sequencing panel in a Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratory for use in assigning patients who have exhausted standard treatment options to molecularly targeted investigational treatment. In addition, MoCha will perform whole-exome and whole-genome DNA sequencing and DNA expression analysis on a research basis. The molecular characterization of tumor and normal tissue will be deposited into a searchable database for other researchers to use in hypothesis generation and for comparison with the findings of other laboratories and The Cancer Genome Atlas or other molecular characterization efforts.

The second component of the initiative, the **Clinical Assay Development Program (CADP)**, builds on data generated by MoCha or other laboratories to optimize and validate prognostic and predictive assays that are critical to the individualization of cancer therapy. In this effort, CADP facilitates the validation of assays that are proposed as integral to clinical trials. Investigators with a research-grade assay may submit an application to CADP for support in further assay

development and validation. After evaluation by an external group of experts, the applications are evaluated internally by a multidisciplinary panel. Applications with the highest merit are accepted into the program and provided with resources for assay validation.

MoCha and CADP actively collaborate with various components of NCI that have expertise in areas that are critical for the development of the assays. To accomplish these goals, CADP comprises both MoCha at NCI and the Clinical Assay Development Network, a group of NCI-supported service laboratories (five from academic institutions and three from commercial companies) in the extramural community. Chosen through a competitive Basic Ordering Agreement process, the Clinical Assay Development Network laboratories perform assay validation for those projects that are selected by CADP.

CADP includes tissue resources in addition to laboratory expertise. One of these sources is a health delivery organization with 30 years worth of formalin-fixed, paraffin-embedded tissues from patients in the stable health network and linked to a uniform medical electronic record. Other tissue sources are accessible by CADP under contract for a particular project. Together, these resources and centers create a process to efficiently develop diagnostic tools addressing clinical needs, including co-development of targeted agents and predictive markers. To date, two "companion diagnostic" assays have completed validation and are expected to be used in early-phase trials with a novel agent in 2014. Five other assays are in various stages of project management.

Implementation of Operational Efficiency Working Group Recommendations at NCI's Cooperative Groups and Cancer Centers

Barriers to conducting clinical trials must be overcome to decrease the length of time necessary to evaluate the efficacy of a particular therapeutic agent, to receive FDA approval to treat cancer patients, and to move on more quickly to the development of other potential agents. To the extent that such barriers can be overcome, the overall cost of drug development, as well as the speed with which therapeutic interventions and diagnostic capabilities become available in the clinic, are closely linked with the ability to effectively and efficiently conduct clinical trials.

An initiative is under way to create incentives to implement the NCI Operational Efficiency Working Group recommendation to decrease clinical trial activation times by 50%. Specific project-based milestones and deliverables have been established that, upon achievement, will result in funding to an individual Cancer Center or Cooperative Group. This incentive-based procedure is designed to increase the rate at which efficiency-promoting processes are implemented. A review of progress during the first 2 years of implementation (2010–2012) indicates that trial activation times are about 30% shorter than they were in the period before the Operational Efficiency Working Group was formed.

Clinical Pharmacodynamics

As part of the ARRA initiative, DCTD has been supporting the development of multiplexed assays for pharmacodynamic targets of high priority. These efforts will enable multiple integrated pharmacodynamic readouts from a single tumor biopsy or surrogate tissue specimen. The multiplexed assays will be suitable for the measurement of molecular-level responses to treatment in conjunction with preclinical development of therapeutic agents. These assays will be demonstrated in preclinical models, characterized cell lines, tumor xenograft tissues, and patient plasma samples, and optimized assays will be applied to patient samples in subsequent phase 2 studies. This research will provide valuable tools to evaluate

and validate new anticancer agents in clinical trials and for eventual clinical use to monitor treatment.

Coordination of Clinical/Translational Research Across NCI

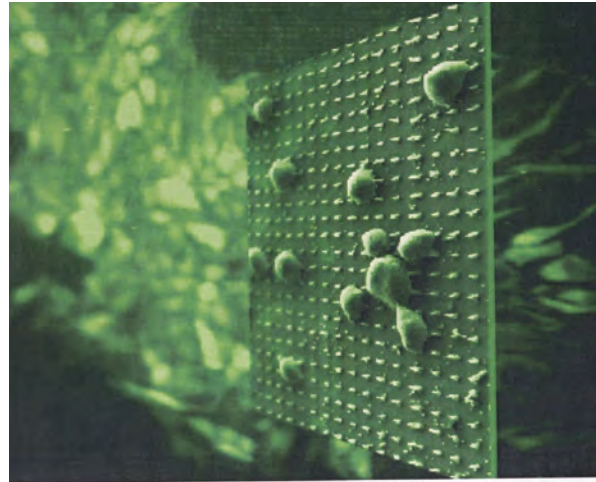
Fostering collaboration among translational cancer researchers supported by various NCI funding mechanisms will lead to the development of a more integrated and efficient and less costly system for moving significant laboratory findings into clinical trials. This collaboration, however, has been difficult to implement. As part of its participation in ARRA, the NCI has been interested in furthering its high-priority goal of accelerating high-impact translational research by encouraging and rewarding collaborative team science. In that spirit, an initiative is being undertaken to provide a unique incentivized opportunity for the creation of a team of investigators with the collective expertise and resources to answer, within 2 years, a hypothesis-driven, mechanism-of-action-oriented scientific question within the context of a clinical trial.

Adoption of New Technologies for Remote Data Capture and Protocol Authoring

ADOPTION of New Technologies for Remote Data Capture and Protocol Authoring (ADOPT) was a multipronged approach to integrate standardized information technology

Projects Approved for Coordination of Clinical/Translational Research Across NCI
Proteasome/HDAC Inhibition in Leukemia/MDS: Phase I Trial & Correlative Studies
Biomarker Prediction of Gleason Upgrade
Predicting Pancreatic Cancer Response for a PARP Inhibitor-Based Clinical Trial
Defining the Importance of Immunity to NY-ESO-1 in Melanoma Therapy and Prognosis
YK-4-279 Specifically Targets ETS Family Fusion Protein Cancers in Clinical Trial

HDAC = histone deacetylase; MDS = myelodysplastic syndrome; PARP = poly(ADP ribose) polymerase.



(IT) tools and processes into the infrastructure of NCI's national clinical trial networks. Standardization and a common infrastructure will improve the efficiency and effectiveness of the networks while providing an opportunity to reduce clinical trial costs and timelines. ARRA funding over 2 years was provided to enable Cooperative Groups, Consortia, and 48 Cancer Centers to adopt new technologies consistent with this initiative. The ADOPT goals and objectives as listed below have been achieved:

- Clinical Data Management System
 - Common remote data capture system for all networks
 - Successfully deployed to 14 NCI-supported multi-center organizations
 - Electronic protocol authoring for rapid development of protocol document requirements
 - Functional and technical requirements finalized
- Project plan for next steps (beyond ADOPT) delivered: Electronic case report forms (eCRF) for rapid, standardized collection of clinical data
 - Standard package of eCRFs identified
 - Policy document for use of eCRFs in the common Clinical Data Management System established

A new initiative to integrate several NCI applications with the Common Clinical Data Management System is currently under way. Deployment of the common Clinical Data Management System, referred to as Medidata Rave, across the NCI Cooperative Groups itself has multiple potential

benefits, and integration with NCI systems will result in additional significant efficiency gains. For example, integration of Medidata Rave with the NCI Safety reporting system (CTEP-AERS) and other routine data reporting tools (CDUS and CTRP) will eliminate duplicative effort, inconsistencies, and reconciliation activities. Finally, the NCI is moving toward integrating selected information contained within Medidata Rave with the Group Biorepository databases, thus providing a link between clinical and genetic/translational research.

Phase 1 and 2 Therapeutic and Imaging Clinical Trials

CTEP and the Cancer Imaging Program are well positioned to coordinate the rapid design and conduct of phase 1/2 and pilot trials with novel agents alone, in combination, or as part of standard therapies. Several categories of early-phase studies are currently being funded through this initiative.

Accelerating Clinical Trials of Novel Oncologic pathWays.

An ARRA-funded, phase 1/2 initiative, called *Accelerating Clinical Trials of Novel Oncologic pathWays* (ACTNOW), is focused on accelerating progress by speeding the development of approximately 37 new clinical treatment trials. These trials test novel agents (alone, in combination, and with other standard therapies) that target new pathways by which cancer cells grow, metastasize, and develop resistance to current treatments. A competitive review of CTEP-solicited nominees for this program from all grantees and contractors involved in this research was conducted to identify the most meritorious proposals. The selected trials have

received enhanced resources to enable rapid development and approval of the treatment protocol such that 90 days from notification of the award, the trial would be either open to enrollment or in review at the local institutional review board. This timeline is significantly shorter than that typically attained by industry-sponsored early clinical trials and is about 9 months shorter than NCI's standard approach to trial development. This accelerated timeline is made possible through the investment of ARRA resources:

- Enabled the hiring of more staff devoted to protocol writing and statistical plans
- Increased the number of personnel available for the development of database and case report forms
- Permitted the use of innovative diagnostic scans, specimen sample collection, assay development, and adequate reimbursement for the research costs associated with data management at local sites

Multicenter Phase 2 Assessment of Tumor Hypoxia in Glioblastoma Using [18F]Fluoromisonidazole with PET and MRI. Also known as ACRIN 6684, this phase 2 trial is part of ACTNOW and is designed to determine the association of baseline fluoromisonidazole (FMISO) positron emission tomography (PET) uptake (tumor-to-blood ratio, hypoxic volume) and magnetic resonance imaging (MRI) parameters with overall survival, time to disease progression, and 6-month progression-free survival in participants with newly diagnosed glioblastoma. FMISO PET is a noninvasive method that can be used to estimate tissue hypoxia. Several studies have validated FMISO uptake as a robust measure of tissue hypoxia, and methodology for FMISO PET imaging has been established in early single-center studies. New advanced MRI methods, such as dynamic contrast enhanced MRI, oxygen breathing during blood oxygenation level-dependent (BOLD) imaging, vessel caliber mapping, or other approaches may also contribute to characterization of tumor physiology and/or prognostic information for patients with glioblastoma multiforme (GBM). Combining such vascular imaging methods with hypoxia data from FMISO uptake recognizes the mechanistic connection between hypoxia and angiogenesis and provides an opportunity to study the association of hypoxia by FMISO PET and tumor vascularity by perfusion MRI. In this study, the researchers used these PET and MRI techniques hand in hand to monitor the standard initial treatment of patients with GBM and to perform pilot work to determine whether FMISO PET may be a useful prognostic marker in patients with GBM. Data gained from

this study will serve as the basis for future clinical trials in which hypoxia imaging could be used for correlative science, patient selection, and response evaluation. This study is currently closed to accrual and is in the follow-up and analysis phase.

Phase 2 Study of 3'-Deoxy-3'[18F]Fluorothymidine in Invasive Breast Cancer. Also known as ACRIN 6688, this ARRA-funded phase 2 study is designed to investigate how noninvasive imaging with fluorothymidine (FLT) can be used to evaluate the effectiveness of neoadjuvant therapy during treatment. While there is some promising evidence that mid-treatment fluorodeoxyglucose PET imaging may be predictive of subsequent tumor response, the tendency of fluorodeoxyglucose to accumulate in inflammatory tissues can complicate the interpretations of mid-therapy images. Preliminary data suggest that early FLT PET is better able to predict response to therapy, as FLT uptake has been shown to correlate with cellular proliferation and not to significantly accumulate in inflammatory tissue. The primary objective of this study is to correlate the percentage change in standardized uptake value between baseline and early-therapy FLT uptake in the primary tumor with pathologic response in patients with locally advanced breast cancer. Additionally, FLT PET parameters were compared with proliferative indices from the initial biopsy and residual tumor surgical samples via Ki67 immunostaining and mitotic index. During this study, potential safety issues and the physiologic effects associated with FLT administration were also evaluated. This study is currently closed to accrual and is in the follow-up and analysis phase.

Monitoring and Predicting Breast Cancer Neoadjuvant Chemotherapy Response with Diffuse Optical Spectroscopic Imaging. Also known as ACRIN 6691, this study's main objective is to use diffuse optical spectroscopic imaging (DOSI) to evaluate response to chemotherapy in women with breast cancer. The primary aim of this clinical trial is to determine whether the baseline to mid-therapy changes in the DOSI measurement of the quantitative tumor tissue optical index can predict final complete pathologic response in breast cancer patients undergoing presurgical neoadjuvant chemotherapy. The secondary aims investigate the correlation between additional DOSI quantitative measurements of tumor biochemical composition obtained at other time points, the full range of pathologic response (i.e., complete, partial, and non-response), and any corresponding imaging measurements. This study is currently open for patient accrual.

Evaluation of [18F]Fluoride PET as a Pharmacodynamic Biomarker for Dasatinib, a Src Kinase Inhibitor, in Men with Castration-Resistant Prostate Cancer and Bone Metastases.

It is estimated that 30–40% of patients with prostate cancer will experience a relapse after local surgery or radiation therapy. Most will develop osteoblastic bony metastasis. Prostate cancer metastases also have a strong constant osteolytic component that correlates to an elevated N-telopeptide of type I collagen excretion into the urine. Current methods of imaging bone cannot detect the therapeutic impact of existing therapies, let alone differentiate the therapeutic effects between various therapies. Standard imaging methods such as computed tomography and MRI scans (measured with Response Evaluation Criteria in Solid Tumors [RECIST]) and bone scintigraphy fall short of enabling the determination of tumor activity and therapeutic response that would assist in treatment selection and prognosis for patients with bone metastasis.

[18F]Fluoride PET in patients undergoing treatment with dasatinib will advance scientific understanding of the effect of the drug (effect of regional bone metabolism [Ki] and fluoride delivery [K1]) on bone metabolism and blood flow as an indirect measure of angiogenesis. Preliminary data in breast cancer patients suggest that fluoride K1 and Ki can be independently and accurately measured for both normal bone and bone metastases. The ability to quantify the changes in fluoride kinetics in response to therapy is critical to better evaluate response to treatment. This study explored the hypothesis that patients with significant changes, as measured by [18F]fluoride in bone metastases, resulting from dasatinib therapy may respond better and have improved progression-free survival. The study is currently in the follow-up and analysis phase, but it is anticipated that this hypothesis-generating project will potentially lead to subsequent trials of [18F]fluoride PET as a prognostic biomarker.

Application of Nanoparticle-Based MRI to Direct Brain Cancer Therapy.

Differentiation between pseudoprogression and true tumor progression is critical in decision making for treatment options in patients with brain tumors so that patients can be maintained on therapies that are effective and can be switched to other therapies if a tumor is progressing. Using standard T2-weighted and gadolinium contrast-enhanced, T1-weighted MRI sequences does not provide a reliable distinction between tumor recurrence or true progression and pseudoprogression. Dynamic susceptibility-weighted, contrast-enhanced (DSC) MRI (sometimes

called perfusion-weighted imaging) measurements of relative cerebral blood volume in regions of interest in the brain may be a useful approach to resolve this dilemma.

Ferumoxytol is an ultrasmall superparamagnetic iron oxide nanoparticle that is gaining use for brain imaging. It has been extensively tested and found to be safe, most importantly, in patients with impaired kidney function, who should not receive gadolinium-based contrast agents. Unlike gadolinium, ferumoxytol is resistant to passage through the leaky capillaries at first-pass bolus and, in the short term (minutes to hours), stays in the intravascular compartment as a blood pool marker. The funded trials (adult and pediatric) are comparing the capability of DSC MRI in combination with ferumoxytol with the gadolinium-based contrast agent gadoteridol to distinguish between true progression and pseudoprogression. The results may show that perfusion MRI with ferumoxytol can facilitate the diagnosis of pseudoprogression of glioblastoma after chemo- and radiation therapy and can predict survival in patients with GBM who appear to have progressive disease.

Chemical Biology Consortium and Overall Therapeutics Program

New Therapeutic Molecules. The NCI Chemical Biology Consortium (CBC) was established to facilitate the discovery and development of new agents to treat cancer. CBC brings together chemical biologists and molecular oncologists from government, industry, and academia to address unmet needs in therapeutic oncology. The immediate goal of CBC's New Therapeutic Molecules initiative is to prevent short-term gaps in the supply of clinical materials to treat patients on NCI-supported clinical studies. Its long-term goal is to develop sufficient efficiencies in production and evaluation of new candidate drugs to make the process more sustainable in supplying patients in clinical studies. This ARRA initiative focuses on all three cornerstones of systemic anticancer treatment: biologics, natural products, and synthetic compounds.

As a new biologic therapy begins to show promise, supply of clinical materials can be the rate-limiting step for expanding access to larger populations. Major delays in expanding production are due to the qualification procedure of facilities and processes for production of biologics at additional sites. When the original site of production is at NCI's Frederick National Laboratory for Cancer Research, NCI is in a unique position to expand capacity to treat a larger set of patients

before commercial facilities can be approved by the FDA. This scenario has been fully substantiated by the recent results of the Children's Oncology Group trial demonstrating a survival advantage by adding the chimeric (ch)14.18 antibody to the therapy of children with neuroblastoma. This antibody, which was made by DTP without commercial support, is illustrative of NCI's commitment to finding treatments for rare cancers that generate commercial interest. Owing to stimulus funding, in late 2010 NCI was able to deliver a sufficient quantity of ch14.18 for ongoing clinical trials studying neuroblastoma. This has enabled NCI to continue to provide this life-saving treatment to patients while simultaneously licensing the agent to a commercial partner and allowing time for that partner time to successfully establish its own production according to Current Good Manufacturing Practice. Similarly, through the newly established Cancer Immunotherapy Network, the extramural immunotherapy community was asked to identify molecules of great interest for further clinical investigation but for which a commercial source is no longer available. With ARRA funding, NCI was able to move directly into the phase 1/2 arena with the production of sufficient clinical material to support three to four peer-reviewed clinical trials each for interleukin-15 and interleukin-7.

Natural products were once the dominant source for new cancer medicines. Because of the de-emphasis of natural products by the commercial sector, there is a unique role for NCI in the investigation of therapies from this source. The NCI collection of natural products is the largest in the world but has yet to be fully explored. Short-term ARRA funding provides a focused opportunity to evaluate new patterns of development for natural products. NCI has been piloting a procedure for more extensive biological testing of natural-product extracts before investing scarce and expensive chemical resources to isolate the active ingredient.

For synthetic anticancer compounds, short-term ARRA funding was utilized by DTP to outsource a 1-year backlog of about 100 in vitro positive synthetic compounds.

Diverse Chemical Libraries for Drug Discovery. Diverse chemical libraries are critical to improving the potential hit rate from screening of new targets by CBC centers. By creating a central library of individual compounds, compound fragments, and fit-for-purpose libraries, NCI and the scientific community will now be able to increase the probability of



identifying target chemical lead compounds in order to support projects aimed at selecting clinical candidates that may have a greater likelihood of showing activity in the clinic.

CBC Small Molecule Repository. NCI has established a state-of-the-art central chemical repository. The facility stores and distributes the institute's recently compiled 115,000-compound screening collection in custom-arrayed formats to be used for early-stage high-throughput screening NExT projects. The facility is also capable of acquiring, storing, and distributing solid synthetic compound samples to NCI and CBC testing centers for preclinical chemical and biological evaluation.

In Vitro/In Vivo Screening of Combination Therapeutic Drugs. Most new anticancer agents are tested singly, but clinical cancer treatments often involve multiple agents and modalities administered in combination over time. To model clinical applications early in the drug development process, DCTD expanded the in vitro screening program for combinations of both approved and investigational therapeutics. DTP also operates an internal program for combinatorial drug screening. One result of this program has been the definition of parameters for study design, cell culture plate layout, and statistical approaches to synergy and/or additivity, throughput rates, and costs. This has provided the basis for the establishment of a network of collaborative in vitro and in vivo screening laboratories.

The in vitro program supports the application of techniques in molecular biology (genomics, small interfering RNA, proteomics, and more), computational and statistical modeling (such as response surface mapping for synergy), and robotics into an applied drug screening effort. Engineering principles and computational models are applied to describe cellular signaling pathway responses to environmental cues leading to cell growth, survival, and death. Investigators can interrogate intracellular responses to drug-induced perturbations at the molecular level in order to prospectively design combinatorial pharmacologic regimens that independently modulate key signaling nodes, cooperatively block redundancy loops, and/or concurrently target epithelial, stromal, and immunologic cells. Although the scientific tools to do this are available, there are relatively few published examples in applied drug development. The model developed through this program will also have applicability for scientists working with non-cancer cells and diseases.

The in vivo program expands and accelerates the ability of DTP to identify promising new combinatorial anticancer regimens and advance them to the clinic. Because the necessary bioassays are technically demanding and time consuming, the in vivo efficacy and toxicity testing of potential cancer therapeutics is a rate-limiting step in applied drug development. Currently, all xenograft testing for DTP is done at the Frederick National Laboratory for Cancer Research. The in vivo study of combinations helps to validate the models developed using in vitro approaches. In follow-up studies to the initial in vivo screen, tumor samples and adjacent normal tissue collected from animals receiving efficacious combinations are assessed by genomic and proteomic technologies, and the in vitro and in vivo data from the same cell lines are compared. Thus, the drug-targeting hypotheses generated in vitro are corroborated in the next higher-level system, the whole organism. All of these data are made available electronically to the entire cancer community.

Comprehensive IT Program for Facilitating Drug Discovery and Development

The discovery and development of new drugs to treat cancer and other diseases increasingly relies on IT to collect and analyze the expanding data sets derived from new technologies. The NCI-60 screen in 96-well plates was state of the art 20 years ago. Today, however, 20,800 data points are generated per week. In comparison, an ultra-high-throughput

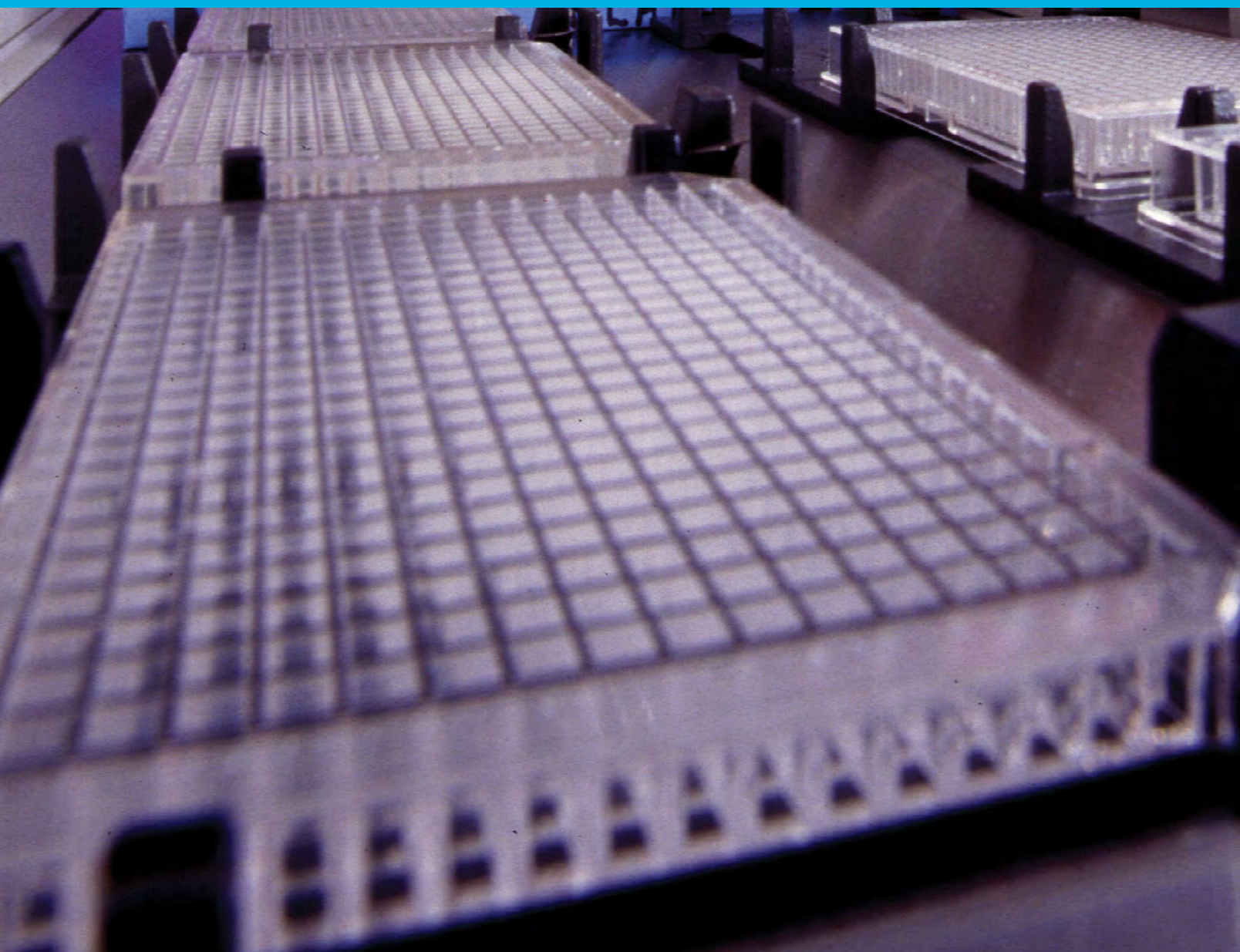
screening assay conducted in 1,536-well plates can generate 2.2 million data points in a week. With the advent of new assays to evaluate pharmacodynamics, an experiment that did not analyze any samples from tumor or normal tissues a few years ago may now generate up to 4,000 samples to be analyzed in multiple assays at multiple sites. This creates data storage and handling issues as well as an analytical bottleneck, since correlations among as many as 10 different endpoints in one experiment is typical. The implementation and integration of new IT software for data acquisition, storage, and evaluation is imperative to drug discovery and development. A software package was selected for primary collection of all data generated by CBC projects. Implementation, however, had been slow due to the limited divisional IT resources to collect the different data streams from DCTD-funded scientists. The goal of this ARRA initiative is to integrate additional software that will facilitate the analysis of data from multiple software companies. These software packages will also be integrated to the extent possible with the current server used to manage projects for the NExT pipeline. This initiative is critical to DCTD's mission to support, in an integrated manner, the various functional components of NExT, including pharmacodynamic assays; in vivo studies including toxicology, pharmacology, and efficacy; in vitro high-throughput screening assays; and microarray data capture.

Recent accomplishments include:

- Establishing organizational processes and procedures to define a data acquisition process to populate the database.
- Integrating various COTS products, including Perkin-Elmer/Spotfire, Accelrys/Pipeline Pilot, and Certara/D360 with the Various DCTD biological, clinical, and chemical data stores.
- Consolidation and centralization of DCTD processing into the infrastructure of the NCI Center for Biomedical Informatics and Information Technology
- Increased use of SharePoint as an internal and external collaboration and workflow management tool

2012 PROGRAM ACCOMPLISHMENTS

CANCER DIAGNOSIS PROGRAM





OVERVIEW

The mission of the **Cancer Diagnosis Program (CDP)** is to improve the diagnosis and assessment of cancer by effectively moving new scientific knowledge 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 evaluate response to treatment. The overarching goals of CDP are to:

- Provide the most effective tools to optimize treatment decision making
- Bring to fruition the promise of biomarkers

CDP's initiatives over the past several years have contributed significantly to progress in the field of biomarker development and clinical application. The program is now building on lessons learned and advances achieved in the science with the Clinical Assay Development Program (CADP). These programs will facilitate the transition of assays based on new molecular insights from the research laboratory to clinical use.

The CADP will provide access to:

- NCI-sponsored service laboratories (the Clinical Assay Development Network) for evaluation of the analytical performance and clinical validity of assays
- Specimens with associated clinical data
- Reference materials and standardized reagents
- Statistical design consultation and regulatory expertise to ensure that assays evaluated in clinical trials are ready for submission to the Food and Drug Administration (FDA) or for clinical use at the conclusion of the trials

The CADP will also support an internal laboratory, the Clinical Assay Development Center, to assist with earlier phases of assay development and transition to clinical laboratory readiness. This laboratory will also provide full genomic characterization of cancer patients in clinical trials sponsored by the Division of Cancer Treatment and Diagnosis (DCTD) and will test the importance of results being generated by The Cancer Genome Atlas project and other large cancer profiling efforts. The results of these characterizations may identify patients who would benefit from trials of new interventions targeted to specific genetic alterations or inform about resistance mechanisms to targeted therapies.

CDP's Program for the Assessment of Clinical Cancer Tests (PACCT) has provided strategic guidance to the translational cancer research community and leveraged NCI-supported programs to achieve significant research goals. These include:

- Launch of the landmark Trial Assigning Individualized Options for Treatment (TAILORx) to evaluate the ability of the OncotypeDX assay to predict benefit from chemotherapy; accrual has been completed, and primary analysis results are expected in 2015
- Publication of the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guidelines for reporting tumor marker studies in biomedical journals
- Development of standards for analytic performance for assays incorporated into clinical trials
- Development of guidelines for validation of omics assays prior to use in a clinical trial
- Discussion and recommendations on how to evaluate the clinical utility of predictive and prognostic assays
- Discussion and recommendations on bringing massively parallel sequencing into clinical use
- Establishment of a major series of international meetings on cancer molecular markers in collaboration with the American Society of Clinical Oncology (ASCO) and the European Organisation for Research and Treatment of Cancer (EORTC)

CDP has designed and implemented Strategic Partnerships to Evaluate Cancer Signatures (SPECS), a cooperative agreement program that has accelerated progress in moving molecular profiles of tumor tissue from the research setting into clinical practice. New diagnostic tools developed by SPECS investigators include:

- An assay for the "intrinsic" subtypes of breast cancer (luminal A and B, HER2, and basal) that can be performed in a clinical laboratory
- A commercially available mass spectroscopic assay to predict response to epidermal growth factor receptor (EGFR) inhibitors
- An improved risk classifier for adult and pediatric patients with acute lymphoblastic leukemia, now incorporated into clinical trials

BARBARA A. CONLEY

ASSOCIATE DIRECTOR



Barbara A. Conley, MD, is Associate Director of the Cancer Diagnosis Program (CDP). An NCI veteran, she participated in several key programs within NCI from 1997 to 2004, including serving as Senior Investigator in the Clinical Investigations Branch of CTEP and Chief of the CDP Diagnostics Research Branch, as well as Head, Aerodigestive Diseases, in the intramural medicine branch. Immediately prior to her current appointment at DCTD, she was Chief, Division of Hematology/Oncology, at Michigan State University (MSU), as well as Scientific Director of the MSU Clinical Translational Science Institute. At MSU and the University of Maryland (1987-1997), Dr. Conley was the principal investigator on several NCI grants and an investigator with the National Surgical Adjuvant Breast and Bowel Project.

Board certified in Internal Medicine and Medical Oncology, Dr. Conley has research interests in diagnostic markers, drug development, and cancers of the aerodigestive tract. She has published extensively in many journals, including the *Journal of Clinical Oncology* and *Nature Medicine*, and is on the editorial board of several professional publications.

Dr. Conley holds an undergraduate degree from the University of Michigan and received her medical degree from MSU.

- A diagnostic signature for rhabdomyosarcoma based on genomic data that predicts outcome more reliably than standard histopathology
- A system for classification of adult non-Hodgkin lymphoma based on gene expression patterns
- A molecular signature for aggressive prostate cancer that can be applied to biopsy specimens with minimal amounts of tissue
- Validation of prognostic signatures for squamous cell lung cancer
- An assay that combines RNA gene expression signatures with gene mutation assessments to identify responders and non-responders to cetuximab therapy in patients with colon cancer

CDP collaborates closely with the Cancer Therapy Evaluation Program (CTEP) to promote the effective integration of biomarker studies into CTEP's cancer therapy trials and to implement recommendations of the Clinical Trials Working Group, especially through the new Biomarker, Imaging, and Quality of Life Studies Funding Program.

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

Research supported by CDP extends to the development of new technologies: the instruments and analytical methods that provide the technical platforms for innovative diagnostics. These development efforts encompass:

- Genomics and next-generation sequencing
- RNA and microRNA expression and sequencing
- DNA methylation and epigenetic regulation
- Proteomics and immunoassays
- Metabolomics and glycomics
- Circulating tumor cells and molecules



Finally, CDP is an essential component of the National Cancer Institute's (NCI's) program to provide cancer tissue specimens for research and to develop the tissue resources of the future. CDP provides ongoing support for two major biospecimen resources, the Cooperative Human Tissue Network and the Cooperative Group Banks, which each year provide thousands of tissue specimens with appropriate pathologic and clinical data to researchers across the country. The new Specimen Resource Locator will enable the CADP to quickly and efficiently gain access to existing tissue resources housed in pathology archives. CDP also generates standards for biorepository infrastructure, pre-analytic specimen standards, and development of procedures to assess and determine whether specimens are fit for purpose in assays that will be used for prognosis and prediction. CDP informs and participates in discussions of ethical issues surrounding tissue procurement, storage, and use, as well as ethical, legal, and social issues surrounding the generation and public availability of omics data.

STRUCTURE AND FUNCTION

Established as a DCTD program in 1996, CDP strives to improve patient outcomes by effectively moving molecular diagnostics into clinical practice. The program stimulates and funds resources and research on diagnostics and improvements in technologies to better characterize cancers in order to develop information that can aid cancer patients and their physicians in clinical decision making.

Numerous barriers have been cited to explain the slow progress in the field of biomarker and assay development. These have included, among others, the lack of appropriate specimens, the lack of a well-defined pathway for development and evaluation of clinical biomarkers, and a lack of standards that assays must meet before being incorporated into trials or clinical practice. PACCT, launched in 2000, has addressed a number of these barriers. The PACCT strategy group prepared a set of standards that assays must meet prior to incorporation into clinical trials and a set of criteria for prioritization of assays for funding through the Biomarker, Imaging and Quality of Life Supplemental Funding Program. CDP staff and members of the PACCT strategy group collaborated with international partners to develop guidelines for reporting studies of prognostic markers. The [Reporting Recommendations for Tumor Marker Prognostic Studies \(REMARK\)](#) guidelines were published in several major scientific journals in 2005 and 2006 and are now used by major journals as criteria for evaluation of submitted articles. To further enhance the understanding and usage of the REMARK guidelines, a comprehensive explanation and elaboration of the REMARK guidelines was published in 2012. A working group of PACCT led the effort to integrate biomarkers into the treatment decision-making process for patients with early-stage breast cancer; the landmark TAILORx program was launched in the spring of 2006 and completed its testing and accrual of more than 11,000 patients in the summer of 2010. This trial is expected to have a major impact on the treatment of women with breast cancer. Other PACCT-directed projects have focused on how to evaluate the clinical utility of predictive and prognostic assays and to ensure that assays being evaluated in clinical trials or being

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.

These achievements, which are beginning to have an impact on medical practice, depend on significant collaboration and coordination among basic and clinical scientists. The “Director’s Challenge: Toward a Molecular Classification of Cancer” (1999–2004; RFA CA-98-027) supported multidisciplinary teams to demonstrate the power of comprehensive molecular technologies in developing profiles of molecular alterations in human tumors. Among the many noteworthy results during this time were the discovery of mutations in the EGFR gene that are associated with response to inhibitors of EGFR signaling, as well as the identification of the “intrinsic” subtypes (luminal A, luminal B, HER2, and basal) of breast cancer. The SPECS program has built on the successes of the Director’s Challenge by establishing the large interdisciplinary teams needed to evaluate the clinical utility of molecular signatures. The SPECS program has successfully brought cancer profiles for pediatric leukemias into clinical trials. Other cancer signatures are being refined and readied for clinical testing, and one is seeking FDA device approval. This initiative requires broad collaboration among clinical trial groups, translational researchers, and technology developers in industry.

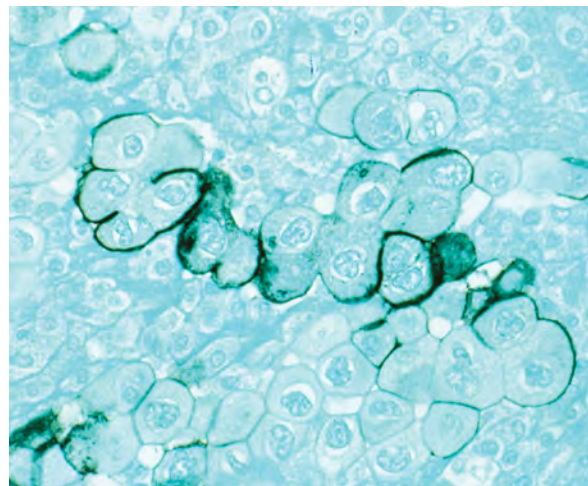
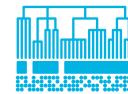
CDP directly supports research projects at all stages of the cancer biomarker development pipeline through an actively managed program of research project grants. The majority of the grants in CDP’s portfolio are solicited for exploratory and developmental projects to encourage the translation of basic discovery research into diagnostic tools.

Although industry and academic researchers are actively developing novel technologies, incentives and guidance are required to encourage these researchers to focus their efforts on technologies and their applications for the benefit of cancer patients. The NCI, with significant input from CDP staff, developed the *Innovative Molecular Analysis Technologies (IMAT)* program. This program supports important research to develop and apply new technologies to cancer diagnosis. CDP staff members continue to play a major role in this ongoing program. The staff also works with the technology research community to advance the development of new tools and platforms for high-throughput analysis of biomarkers and point-of-care analysis systems for clinical

applications. This encompasses the development of genomic, proteomic, metabolomic, and bioinformatic technologies and the engineering of new devices that have the potential to be used for analysis of human tumors. CDP collaborates with programs in the NCI Office of the Director, the National Institute of Biomedical Imaging and Bioengineering, and bioengineering efforts across the National Institutes of Health (NIH). A significant challenge is the great quantity 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 management of patient care.

CDP collaborates with CTEP to promote the effective integration of biomarker studies into DCTD’s cancer therapy trials. CDP staff members review biomarker studies proposed for inclusion in concepts and protocols for CTEP trials and provide recommendations at all stages of trial design, considering both the analytic validity and the clinical utility of novel assays. This effort improves the quality of protocols while also serving CDP’s planning processes by enabling staff to identify obstacles to progress in the field. Trials that include investigational biomarker assays, particularly where assays are integral to the trials, pose special challenges to the implementation of NCI’s operational efficiency initiatives. Members of the CDP staff are actively engaged with CTEP and the investigators of its clinical trials consortia to improve both the efficiency and the scientific output of DCTD trials.

Research must also be supported by provision of critical resources and infrastructure. Biomarker discovery research, assay development, and evaluation of clinical utility of assays all depend on the availability of human tumor specimens with various amounts of associated demographic and clinical data. CDP has a long history of creative approaches to addressing these needs. The Cooperative Human Tissue Network, first funded in 1987, continues to be a mainstay for the community, providing high-quality human specimens to support biomarker discovery and early assay development. The first virtual specimen resource with significant clinical data, the Cooperative Breast Cancer Tissue Resource was recently phased out, but the specimens were used to create statistically designed tissue microarrays that are still in great demand and are being provided to support prognostic marker research. The CDP also supports the specimen banking activities of the National Clinical Trials Network; prior to this stable support, collection of valuable specimens in the



context of randomized trials was haphazard at best. Tissue collection and processing are being standardized, informatics are being implemented, and transparent access procedures are making the specimens more widely available for critical research.

The CADP will require clinical specimens with associated outcome information for assessment of analytical performance of assays. Toward that end, the CDP is developing a Specimen Retrieval System that can provide both required tissues and relevant clinical data in a de-identified fashion.

CDP promotes best practices for biorepositories and conducts research on the effect of pre-analytic variables on assay performance. As part of the mission to transition research assays to the clinic, CDP is involved in national and international deliberations of the ethical, legal, and social implications of this work.

PROGRAM ACCOMPLISHMENTS

The activities of CDP fall into three major categories:

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

DEVELOPMENT AND EVALUATION OF ASSAYS FOR CLINICAL DECISION MAKING

For patients to benefit, biomarkers must move out of the research setting and become the basis for standardized assays that can be performed reliably in clinical laboratories as part of routine medical care. Through its Diagnostics Evaluation Branch, CDP supports both laboratory research and clinical trials to establish both the analytic validity and the clinical utility of emerging biomarkers.

In its Diagnostics Evaluation Branch, CDP:

- Actively manages a portfolio of research grants to support the translation of research biomarkers into clinical assays
- Pursues the effective integration of biomarker research into NCI cancer therapy trials
- Promotes the adoption of community-wide standards for assay performance in both anatomic and molecular pathology

PROGRAM FOR ASSESSMENT OF CLINICAL CANCER TESTS

Many decisions relating to the management of cancer patients depend on information derived from clinical laboratory tests. Significant research and development are involved in producing a test that is reliable enough for routine clinical use. CDP launched the [Program for the Assessment of Clinical Cancer Tests \(PACCT\)](#) in 2000 to develop a process for

moving advances in new technologies and new understanding of cancer biology more efficiently and effectively into clinical practice.

PACCT is not a grants program. Rather, it leverages many NCI-supported activities to accomplish goals identified by the PACCT strategy group. The strategy group comprises scientists from academia, as well as FDA and NCI, with expertise in clinical oncology, pathology, basic cancer biology, diagnostics technology and assay development, clinical trials methodology, and statistics. The strategy group establishes working groups to guide the development of specific projects.

The TAILORx Trial

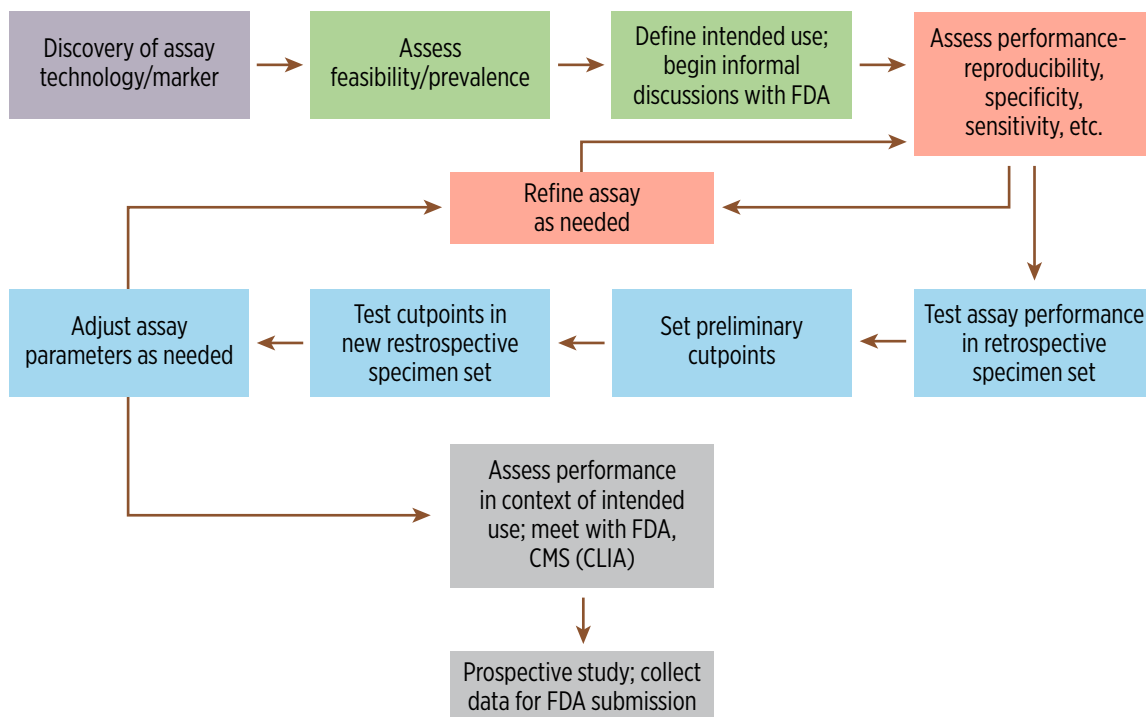
The **Trial Assigning Individualized Options for Treatment (TAILORx)**, the first trial launched by PACCT, is testing whether a set of expressed genes that have been shown to be associated with risk of recurrence in women with node-negative, hormone receptor-positive breast cancer can be used to assign patients to the most appropriate and effective treatment. The signature being tested is the 21-gene Oncotype DX panel developed by Genomic Health, Inc., in collaboration with an NCI cooperative group, the National Surgical Adju-

vant Breast and Bowel Project. 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.

The trial is being carried out as a collaboration of CDP, CTEP, and all of the NCI clinical cooperative groups that perform breast cancer studies. Accrual was completed during 2010, and data collection is ongoing.

Biomarker Evaluation in NCI Cancer Therapy Trials

Members of the CDP staff review biomarker studies proposed for inclusion in CTEP clinical trials, providing critiques and recommendations for both concepts and protocols for phase 1, phase 2, and phase 3 trials. CDP staff members also serve as reviewers on Intergroup Correlative Science Committees for applications to use specimens from the cooperative group tissue banks. Members of CDP provide critical biomarker expertise at clinical trials planning meetings and serve on intergroup task forces. The expertise of the CDP staff has also been critical to the implementation of initiatives of the Clinical Trials Working Group.



THE MARKER DEVELOPMENT PROCESS



The Clinical Trials Working Group report “Restructuring the National Cancer Clinical Trials Enterprise” made a series of recommendations that included the need to provide support for performing assays that are essential to clinical trials. A definition was needed of standards that must be met for any assay being used to make a decision such as eligibility or assignment to a treatment arm. A PACCT working group developed a standards document and a set of criteria for prioritization for funding. These recommendations were approved (July 11, 2007) by the Clinical Trials Advisory Committee and are being implemented in the ongoing Biomarker, Imaging and Quality of Life Supplemental Funding Program.

The CTWG also recommended that the problem of co-development of biomarkers and targeted agents be addressed. PACCT organized a workshop with the FDA and industry to assess the barriers and develop a white paper to address issues to be considered. The workshop, which took place in October 2007, resulted in a commentary published in the *Journal of the National Cancer Institute*.

CDP presented the CADP concept to the public in a workshop with members of industry, academia, and the FDA in May 2009, and participants told CDP and the FDA that 50% of the barriers to assay development now arise from the detrimental effect of patents and licensing. In subsequent discussions with stakeholders, information was presented to demonstrate that as much as 40% of the cost of clinical assays is for royalty and licensing fees. These workshops contributed to the current revision of the CTEP Cooperative Research and Development Agreement intellectual property options. CDP staff continue to collaborate with CTEP and NIH–industry task forces convened under the auspices of the Clinical and Translational Science Awards program to explore additional approaches. The CADP will work to identify ways to help assay developers that are either neutral on the issue of intellectual property or that facilitate negotiations regarding licensing, royalties, or transfer of intellectual property.

REMARK and the EORTC-NCI-ASCO Cancer Molecular Markers Collaboration

CDP has led an NCI collaboration with the European Organisation for Research and Treatment of Cancer (EORTC) to convene a series of meetings on molecular diagnostics. At the first meeting, held in Denmark in 2000, one resulting international working group focused on the development

of guidelines for information that should be included in all publications about tumor markers. The REMARK guidelines were published in several major scientific journals in 2005 and 2006. These guidelines are now being used by journals as standards for the review of manuscripts on markers. To further enhance the understanding and usage of the REMARK guidelines, a comprehensive explanation and elaboration of the REMARK guidelines was published in 2012. ASCO has now joined the NCI–EORTC collaboration on these meetings. With ASCO’s involvement, the Molecular Markers in Cancer meeting, sponsored since November 2007 by EORTC, NCI, and ASCO, is being held annually. The meetings alternate between sites in the United States and Europe. A tutorial for young oncologists and scientists involved in biomarker research occurs each year in conjunction with the meeting. The 2012 meeting took place in Hollywood, Florida, in October and drew more than 300 participants. The tutorial was attended by more than 60 participants, half of whom were awarded highly competitive travel grants to cover their expenses.

Clinical Assay Standardization

Members of the CDP staff are acknowledged experts in the fields of 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.

The CDP, with the PACCT strategy group, has initiated proactive efforts to improve the standardization and reliability of newer assays entering into clinical practice. The use of an assay for 18q loss of heterozygosity, previously shown to be associated with disease progression and poor outcome, to assign adjuvant therapy for patients with stage II colon cancer was approved for use in Eastern Cooperative Oncology Group trial E5202. CDP convened a meeting of the laboratory designated to perform the assay for the trial, as well as the clinical reference laboratories for the other participating clinical trials groups, to perform a laboratory comparability study. Although initial evaluation showed some problems with concordance, pathologists agreed on procedures for dissection and isolation of tumor and normal tissue, and concordance among the laboratories improved.

A second study was organized to address a problem with a quantitative reverse transcriptase–polymerase chain reaction assay for the measurement of BCR-ABL fusion



gene transcripts in blood, used for monitoring the molecular recurrence of chronic myelogenous leukemia after treatment. The assay has produced inconsistent results when performed in different laboratories. CDP formed a consortium of seven major commercial reference and academic clinical laboratories to perform a comparability study. This consortium demonstrated that estimation of actual BCR-ABL gene transcripts and the international scale in a set of clinical samples varied among the laboratories by more than two orders of magnitude when each laboratory used its own test in its CLIA-certified laboratory. Introduction of a calibrator alone did not reduce this disparity in results, but the introduction of a calibrator with a common set of primers, reagents, and standard operating procedures produced comparability among the laboratories that was within an order of magnitude. These studies were presented in fall 2010 at the BCR-ABL Working Group pre-meeting at the annual American Society of Hematology conference, where there was discussion of the implications for the application of these types of sensitive assays for the measurement of gene transcripts. Efforts in the area of measurement of minimal residual disease, using various analytes and platforms, are continuing.

CDP staff members serve on an international subcommittee that was formed to assess the current state of reproducibility of Ki67 assessments across different laboratories. Results from the first phase of the study showed a concerning lack of concordance of Ki67 assessments on a common set of specimens among eight laboratories regarded as experts in assessment of Ki67. These results were presented at the 2012 San Antonio Breast Cancer Symposium, and a manuscript has been drafted for submission for publication. These find-

ings prompted efforts to develop a Web-based training tool to standardize and harmonize Ki67 scoring. CDP statisticians have been involved in developing the training system and analyzing the data. They helped to design a second international reproducibility study, currently ongoing, that will assess whether harmonization efforts were successful.

Strategic Partnering to Evaluate Cancer Signatures

The Strategic Partnerships to Evaluate Cancer Signatures (SPECS) initiative supports large collaborative research groups that are exploring how information derived from comprehensive molecular analyses can be used to guide the care of cancer patients and ultimately improve outcomes. SPECS supports research that bridges the gap between the discovery of molecular signatures and their integration into clinical practice. Investigators are refining and confirming both genomic and proteomic signatures that have already been shown to address clinical needs or questions. They are defining the critical components of the signatures and developing robust assays for measuring those components in the clinical setting. They will confirm that the modified signatures provide reproducible, reliable information that can potentially inform clinical decision making. Several of the signatures developed in the SPECS initiative will be evaluated in prospective clinical trials.

The SPECS program leverages NCI's investment in cancer clinical trials, cancer centers, NCI intramural programs, and the Specialized Programs of Research Excellence (SPORE) program. The projects include collaborations with biotech-



the translation of gene expression signatures, developed by using frozen tumor tissue, into assays that can be performed on samples of formalin-fixed, paraffin-embedded tissue. ARRA support was also used to test the breast cancer gene expression signature developed at Washington University on specimens collected from several large phase 3 clinical trials to support an application for regulatory clearance of this assay by the FDA.

DISCOVERY OF BIOMARKERS AND DEVELOPMENT OF ENABLING TECHNOLOGIES

CDP promotes the discovery of diagnostic, prognostic, and predictive cancer biomarkers and advances the development of new technologies for high-throughput analysis of biomarkers and point-of-care analysis systems for clinical applications. This enterprise encompasses the development of genomic, proteomic, metabolomic, and bioinformatic technologies and the engineering of new devices that have the potential to be used for analysis of human tumors. Through its Diagnostic Biomarkers and Technology Development Branch, CDP:

- Provides grant support for high-risk biomarker discovery projects
- Supports advances in instrumentation and information technology
- Recruits specialists from outside fields into cancer research

CDP's critical role is to develop innovative grant programs supporting investigator-initiated research projects that do not fit into the typical NIH R01 award mechanism and to build collaborations that cross traditional disciplines.

CDP staff has recognized that R21 awards effectively support the initial steps to determine whether a newly identified biomarker has the potential clinical utility to justify further investment. NCI has recently decided to accept unsolicited applications for R21 (exploratory research) grants. CDP staff are available to discuss potential submissions with the research community. CDP also supports a substantial proportion of the R21 and R33 awards funded through NCI's IMAT program, which provides support for investigators from fields not traditionally related to cancer biology or clinical research, including engineers, mathematicians, informatics specialists, and physicists. Investigators supported by

nology companies, community hospitals, national laboratories, and academic institutions in the United States, Canada, and Europe.

The investment in the SPECS projects is being leveraged in the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program developed in collaboration with CTEP and the NCI Office of Cancer Genomics. Gene expression data on more than 200 patients with high-risk pediatric acute lymphoblastic leukemia (ALL), generated in the leukemia SPECS project, are being combined with data being developed by investigators at St. Jude Children's Research Hospital on genomic alterations in the same patients. The combined data are being used to identify genes that are altered in ALL and are candidates for sequencing. Approximately 200 genes are being sequenced to identify mutations that may be potential targets for drug development. A second TARGET project has been initiated to take advantage of the gene expression data being developed on the SPECS pediatric sarcoma project. In 2009, funding from the American Recovery and Reinvestment Act (ARRA) permitted expansion of the TARGET program; its current portfolio of childhood cancers includes high-risk ALL, acute myelogenous leukemia (AML), osteosarcoma, neuroblastoma, and Wilms tumor.

ARRA funds, available in 2009, also significantly accelerated several SPECS projects. Antibodies to components of the proteomic signatures identified in the lung cancer SPECS project were produced with ARRA support to the NCI Clinical Proteomics Center at Vanderbilt University. An ARRA supplement to the lymphoma SPECS project supported

SPECS PROJECTS

A number of SPECS projects are under way to refine and validate molecular signatures in a variety of cancers:

MOLECULAR DIAGNOSIS AND PROGNOSIS IN AGGRESSIVE LYMPHOMA

Lisa M. Rimsza, MD

University of Arizona, Tucson

This program, as a component of the Lymphoma and Leukemia Molecular Profiling Project, will design and validate multi-analyte diagnostic and prognostic assays to differentiate aggressive B-cell non-Hodgkin's lymphoma into prognostic groups. The tissue samples will be formalin fixed and paraffin embedded, and the data generated will be submitted for regulatory review with the intention of establishing a highly accurate standardized diagnostic test with prognostic indicators for widespread clinical use. The ability to distinguish prognostic subgroups will enable the development of therapeutic agents to improve outcomes for patients with the most aggressive forms of this disease.

VALIDATION OF PROGNOSTIC AND PATHWAY SIGNATURES IN LETHAL PROSTATE CANCER

Phillip G. Febbo, MD

University of California, San Francisco

This program will validate established RNA, DNA, and microarray prognostic and pathway signatures in men with high-risk prostate cancer. It will attempt to distinguish causative pathways from those that merely correlate with aggressiveness of disease. The most promising signatures will be adapted to formalin-fixed, paraffin-embedded tissues in order to develop clinically deployable assays. The data generated will be widely shared with the larger investigative community in hopes of accelerating progress toward effective therapies for lethal prostate cancer.

MOLECULAR SIGNATURES FOR OUTCOME PREDICTION AND THERAPEUTIC TARGETING IN ALL

Cheryl L. Willman, MD and Stephen Hunger, co-PI

University of New Mexico, Albuquerque;

Children's Hospital Colorado, Denver, Colorado

This program will expand on the work accomplished under SPECS I, in which microarray-based gene expression signatures that are highly predictive of relapse-free survival in high-risk ALL were developed. The principal investigators (PIs), with collaborators at St. Jude's Hospital and the Children's Oncology Group, have identified a gene expression signature that is similar to that associated with the BCR-ABL fusion gene but without the actual fusion

gene. This Ph1-like kinome syndrome is present in 10% of pediatric cases of ALL and accounts for nearly half of the 20% of children who have bad clinical outcomes. The PIs have developed a CLIA-lab based polymerase chain reaction test to identify these patients and are now testing it in retrospective and prospective trials. Anecdotal cases indicate that the activated kinases identified by this signature may provide new approaches to targeted therapy that would otherwise not have been considered. In addition, preliminary data in adolescents and young adults, as well as older adult populations, suggest that the Ph1 kinome syndrome is present in approximately 25% of adolescents and young adults and nearly 40% of adults. This could provide a major breakthrough in these older populations of ALL patients, who so far have been refractory to treatment.

SQUAMOUS CELL CARCINOMA OF THE LUNG: VALIDATION OF MOLECULAR SIGNATURES FOR PROGNOSIS

Fred R. Hirsch, MD, PhD

University of Colorado, Denver

This program will leverage the resources of the recently established Squamous Lung Cancer Consortium of experienced clinical and biomarker investigators to validate preexisting gene expression signatures for prognosis of squamous cell carcinoma, with the goal of bringing these signatures to a more broadly applicable clinical assay. These validated signatures can be used to identify patients with early-stage squamous cell carcinoma and provide for better selection of candidates for adjuvant therapy. The consortium will also attempt to identify new targets for therapy for patients with squamous cell carcinoma.

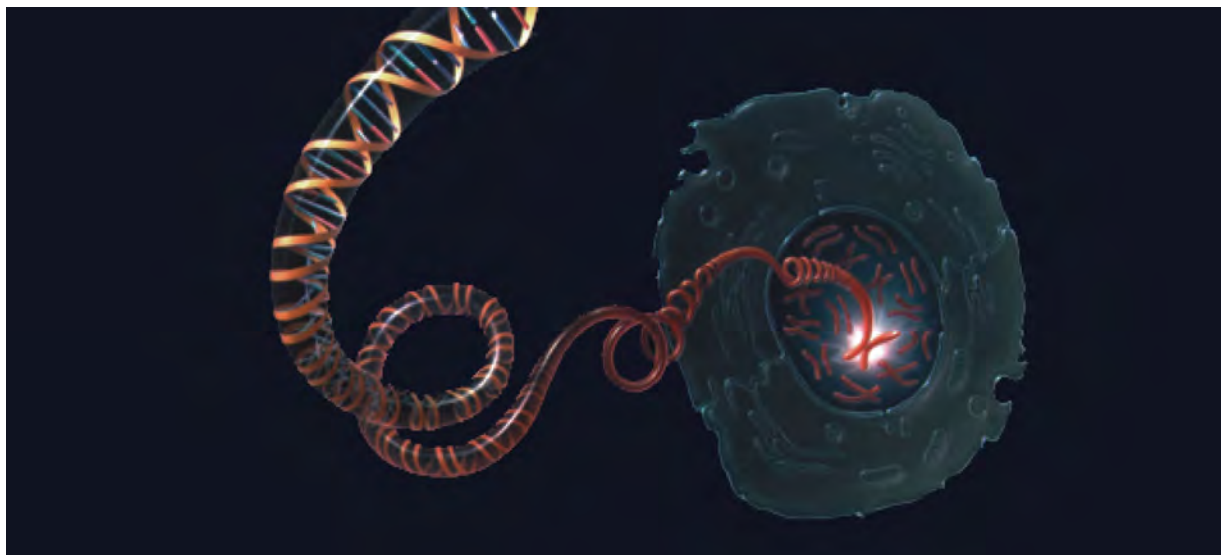
INDIVIDUALIZING COLON CANCER THERAPY USING HYBRID RNA AND DNA MOLECULAR SIGNATURES

Timothy J. Yeatman, MD

H. Lee Moffitt Cancer Center and Research Institute,

Tampa, Florida

This project will use recently developed gene expression signatures, RAS and PI3K, to measure the activation of two of the most important pathways in colon cancer for which there is an increasing availability of pathway-targeted therapeutics. Due to the complex nature of these pathways, simple analysis of single-gene mutations identifies only a proportion of the patients who may respond to these targeted agents. In their SPECS II project, this team will combine RNA gene expression signatures with gene mutation assessments to identify responders and nonresponders to cetuximab therapy.



CDP's IMAT grants are applying increasingly sophisticated analysis technologies to the assessment of gene expression in tumor tissues and are devising methods to analyze increasingly smaller amounts of sample. CDP continues to collaborate with the NCI Small Business Innovation Research Development Center to develop contract solicitations and organize workshops. The effective support of research in this area requires proactive efforts from CDP staff to engage investigators from a multitude of disciplines and guide them toward the most appropriate sources of both NCI grant funds and collaborators. For example, in 2011 CDP organized a public workshop to convene engineers, clinicians, assay developers and experts in medicine for mid and lower income countries to consider low cost point of care diagnostics for cancer in these countries.

Biomarker discovery is just the first in a series of steps toward the implementation of a useful clinical test. Substantial further exploratory and developmental work is required to achieve the necessary analytic performance and to establish the usefulness of a test in its intended setting. CDP has designed and promoted a comprehensive series of Funding Opportunity Announcements that provide appropriate grant mechanisms to support successive stages of developmental biomarker research:

- **Developmental Research in Cancer Prognosis and Prediction** (R21 and R33 awards)
- **Development, Application, and Evaluation of Prediction Models for Cancer Risk and Prognosis** (R21 and R01 awards, in collaboration with NCI's Division of Cancer Control and Population Sciences)

- **Correlative Studies with Specimens from Multisite Trials** (R21 and R01 awards, in collaboration with CTEP)

Support from these grant programs has generated a number of assays now moving into late translation or clinical practice. Examples include:

- A seminal publication to establish a molecular classification system for melanoma
- RNA-based tests for differential diagnosis and prognosis in mesothelioma
- A clinical assay for the internal tandem duplication of the FLT3 oncogene in pediatric AML, now in use in phase 3 trials
- Biomarkers to predict response to chemotherapy for non-small-cell lung cancer

Members of the CDP staff collaborate with staff of other NCI programs and extramural investigators to monitor progress, respond to inquiries from Congress, and develop targeted initiatives in high-priority areas, such as the Community-Oriented Strategic Action Plan for Melanoma Research. CDP staff also played a pivotal role in the process to establish a chartered Cancer Biomarkers Study Section at the NIH Center for Scientific Review.

BIOSPECIMEN RESOURCES AND BIOSPECIMEN SCIENCE

Access to **high-quality tissue specimens** annotated with appropriate clinical and outcome data is critical to continued

scientific progress. Through its Pathology Investigation and Resources Branch, CDP:

- Develops and supports human specimen resources that provide tissue samples to translational cancer researchers
- Assists researchers in locating additional tissue resources and gaining access to the specimens needed for their research
- Supports the development of informatics tools to improve access to human specimens and associated clinical data
- Manages a portfolio of investigator-initiated research grants for the development of emerging technologies in biospecimen science solicited through the IMAT program
- Serves as a source of current information on legal and ethical issues related to the use of human specimens in research for NCI and the extramural community
- Provides expertise related to human tissue specimen resources and advises staff in NCI, NIH, and other federal and nonfederal agencies and institutions, as well as researchers and specimen resource staff throughout the world

The branch monitors changes in scientific needs for tissue specimen resources and ensures that new requirements for specimens can be met in a timely manner.

Cooperative Human Tissue Network. The Cooperative Human Tissue Network (CHTN) provides access to human tissue for basic and translational scientists from academia and industry with the goal of accelerating discoveries in cancer diagnosis and treatment. CHTN offers prospective investigator-defined procurement of malignant, benign, diseased, and uninvolved (normal adjacent) tissues. Network 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. Since its establishment by CDP in 1987, CHTN has provided more than 900,000 high-quality specimens from a wide variety of organ sites to several thousand investigators. CHTN also produces and distributes sections of tissue microarrays constructed from multiple tissue types with several disease-specific designs.

The CHTN consists of six divisions—one that specializes in pediatric biospecimen requests nationwide and five that

serve specific geographic regions in the United States. Its Midwestern Division also serves researchers in Canada. Each division is led by an institution supported by a U01 cooperative agreement award from NCI. Six institutions currently participate in CHTN:

1. Children's Hospital of Columbus—Pediatric Division
2. Ohio State University—Midwestern Division
3. University of Alabama, Birmingham—Southern Division Tissue
4. University of Pennsylvania—Eastern Division
5. University of Virginia—Mid-Atlantic Division
6. Vanderbilt University—Western Division

The CHTN is not a tissue bank; it primarily collects samples prospectively. Limited numbers of certain tumor types (e.g., rare pediatric tumors) are stored to ensure their availability, but specimen storage is not a significant part of CHTN's mission.

Access to the CHTN is provided to any investigator who submits a summary of the project for which the biospecimens are requested and signs the tissue and data use agreements, if appropriate. Priority is given to requests from investigators with peer-reviewed, funded research projects and to new investigators at academic or nonprofit research institutions.

Specimens from CHTN are utilized primarily in basic and early translational cancer research. Recent examples include the identification of a new polyoma virus with suggestive association to human Merkel cell carcinoma, identification of p53 isoforms that regulate cellular senescence in colon cells, and discovery of the role of SATB1, a chromatin organizer, in breast cancer progression.

The CHTN underwent an external review in 2011. The reviewers noted that a vast number of peer-reviewed studies published between 2006 and 2011 were based on analysis of materials provided by the CHTN. During this period, more than 100 grants were obtained using CHTN biospecimens, and a large number of patents were identified that cite the CHTN. The reviewers concluded: "Altogether, the CHTN has had wide-ranging and significant impact on the research community at large. The CHTN's strength lies in the collection and distribution of a wide variety of biospecimens in response to the need of investigators."



NCI Specimen Resource Locator and NCI Tissue Expediter.

CDP provides a specimen resource locator and a tissue expediter to assist individual investigators locate specimens for their research. The NCI Specimen Resource Locator is a searchable Web database that includes resources such as tissue banks and tissue procurement systems with access to normal, benign, precancerous, and/or cancerous human tissue. Researchers can specify types of specimens, number of cases, preservation methods, and associated data. When no match is obtained, the researcher is referred to the NCI Tissue Expediter. The NCI Specimen Locator is currently being updated and improved in collaboration with the Center for Biomedical Informatics and Information Technology.

The role of the NCI Tissue Expediter is to identify sources of human tissue specimens and to help guide researchers to appropriate resources or collaborators. The tissue expediter is a scientist with contacts in the resources community who can rapidly match investigator needs to available resources. The expediter can also help researchers identify potential collaborators when needed.

National Cooperative Clinical Trials Network Banks (Cooperative Oncology Group Banks).

These banks collect and store high-quality, well-annotated human specimens from cancer patients enrolled in NCI-funded phase 3 and large phase 2 clinical treatment trials. These banked specimens are most useful for clinical correlative studies or assay clinical validation studies on uniformly treated patient populations. The Pathology Investigation and Resources Branch has supported these banks since 2005 through U24 awards to each of the Cooperative Oncology Groups, thereby ensuring that the groups implement best practices such as common data structures and standardized collection and storage practices. Currently, each group has a review process for research proposals. If proposals receive favorable reviews, specimens with clinical, treatment, and outcome data can be made available to researchers through collaborative arrangements. The Group Banking Steering Committee was established with representatives from all the cooperative groups and NCI to lead and implement a harmonization of standard operating procedures and a process for fair access to specimens. A public website, an improved Navigator Informatics system, and a common application and review process are being developed to improve access to specimens by the broader research community.

Tissue Microarrays for Breast Carcinoma, Melanoma, and Colorectal Carcinoma.

CDP has developed tissue microarrays (TMAs) to assist investigations in breast cancer, melanoma, and colorectal carcinoma. Application and access procedures are available at <http://cdp.nci.nih.gov/tma.html>.

Breast Cancer Progression and Prognostic TMAs were constructed with tissue and associated pathological and clinical outcome data from the NCI Cooperative Breast Cancer Tissue Resource. The Breast Cancer Progression TMA is designed to permit comparisons of biomarker expression across three stages of disease (node negative, node positive, and metastatic). The Breast Cancer Prognostic TMA is designed for correlation of biomarkers with survival and recurrence outcomes in stage I, II, and III breast cancer. Both TMAs were designed to ensure high statistical power for the intended comparisons.

The **Melanoma Progression TMA** consists of 273 tissue specimens including nevi, primary melanomas, melanomas metastatic to the lymph node, and visceral and dermal metastatic melanomas. This TMA is designed to investigate differences in the expression of markers across various stages of melanoma progression and should be used as a screening array. A new melanoma TMA has been built in collaboration with Rutgers University School of Medicine and is now available to investigators.

The **Colon Cancer Progression–Prognostic TMA** has more than 350 primary colon cancers and 100 control tissues and is designed for examination of associations of markers with tumor stage, clinical outcome, and other clinico-pathological variables in Stage I–IV colon cancer.

Biorepositories and Biospecimen Research Branch.

The Biorepositories and Biospecimen Research Branch, formerly the Office of Biorepositories and Biospecimen Research(OBBR), was incorporated into CDP in 2012. This branch:

- Develops a common, high-quality biorepository infrastructure that promotes resource sharing and team science to facilitate multi-institutional cancer research such as high-throughput genomic and proteomic studies
- Stimulates, coordinates, and funds biobanking as a dedicated area of research and determines the impact of collection and processing variables on the usefulness of biospecimens in research and in development and

validation of in vitro diagnostics for cancer prediction and prognosis

- Facilitates the availability of high-quality biospecimens for precision medicine
- Disseminates NCI Best Practices for Biospecimen Resources and develops future generations of best practices based on data from the Biospecimen Research Network
- Promotes professional oversight of biospecimen standards development by standards organizations
- Coordinates internationally to harmonize biobanking policies and procedures

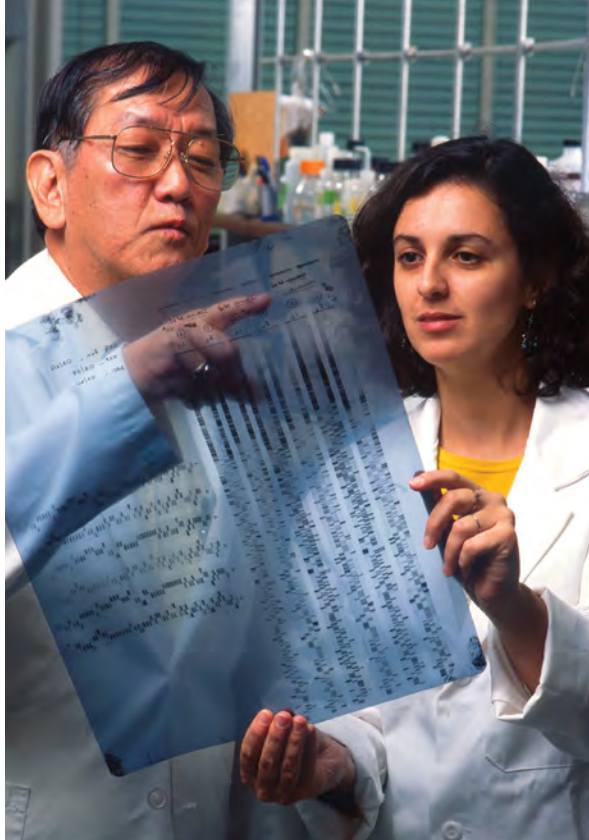
The lack of standardized, high-quality biospecimens has been widely recognized as one of the most significant roadblocks to the progress of cancer research. Over the past decade, NCI has undertaken an intensive due-diligence process to understand the state of its funded biospecimen resources and the quality of biospecimens used in cancer research. This process, which began in 2002 with NCI surveys and community forums, resulted in 2004 and 2005 in the establishment of a trans-divisional Biorepository Coordinating Committee, followed by the creation of OBBR, to lead and coordinate a strategic plan to confront and resolve the issues in a stepwise fashion. These efforts culminated in 2005 with the development of the *First-Generation Guidelines for NCI-Supported Biorepositories*. This first-iteration document was published in the Federal Register on April 28, 2006 (71 FR 25184) and on the OBBR website. The NCI requested public comments on the *Guidelines* both through the *Federal Register* and the OBBR website. The *Guidelines* were subsequently revised on the basis of public comment and input from content experts and renamed the *NCI Best Practices for Biospecimen Resources*. Through this process, NCI has identified 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 current *NCI Best Practices* do not comprise detailed laboratory procedures but rather consist of principles by which such procedures should be developed by biospecimen resources. The recommendations in this document 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, NCI believes that the principles outlined in this document support the goal of optimizing biospecimens for cancer research.

In early 2006, the Biospecimen Research Network (BRN) was initiated to systematically address the impact of specific variables in individual specimen types on molecular data from given analysis platforms. The goal of the BRN is to address these issues by sponsoring, conducting, and collaborating on studies to assess the effects of human specimen pre-analytical variables on the outcome of genomic and proteomic studies conducted for clinical diagnosis and cancer research purposes. By communicating the results of such research to the scientific community, the BRN aims to significantly improve the quality of NCI-funded biospecimen-based research. The results of BRN research will support NCI discovery efforts and contribute to the development of evidence-based best practices for the collection, processing, storage, and analysis of biospecimens, building on the *NCI Best Practices for Biospecimen Resources*.

The activities of the BRN to date include the following:

- A public outreach effort to define issues around human specimen research and identify the most pressing needs for human analyte standardization. Activities include an annual meeting, the [BRN Symposium](#).
- Provision of consultative services on biospecimen issues for programs within the NCI and NIH
- Development of a searchable website of the existing biospecimen literature, the [Biospecimen Research Database](#)

The Biorepositories and Biospecimen Research Branch also serves as the tissue acquisition coordinating center for the NIH Common Fund's Genotype-Tissue Expression (GTEx) Program, which aims to study human gene expression and regulation in multiple normal tissues. The branch has worked in partnership with the Frederick National Laboratory for Cancer Research to develop the infrastructure capable of delivering large quantities of high-quality and annotated tissues from postmortem and organ donor cases for genomic analysis. The program is now transitioning from a pilot study to a fully scaled-up program capable of studying trans expression quantitative trait loci and their potential disease associations.



CURRENT INITIATIVES

CLINICAL ASSAY DEVELOPMENT PROGRAM

The mission of the **Clinical Assay Development Program (CADP)**, established in 2011, is to increase the availability of validated and qualified diagnostic tests for patients and thereby improve access to molecularly guided therapy. This program is designed to identify promising tests, assess the need for further development, and provide services to facilitate optimization of analytical performance and establish clinical validity so that the clinical utility of an assay can be evaluated in well-designed clinical studies. The overall goal of the CADP is to create a process to efficiently develop diagnostic tests that will address clinical needs, including co-development of targeted agents and predictive markers. Projects will meet rigorous performance standards so that they can be applied in clinical decision making. Eight external CLIA-certified laboratories have been competitively identified to assist with assay validation. Six assays are currently in various stages of validation.

SPECIMEN RETRIEVAL SYSTEM FOR ASSAY VALIDATION

The performance characteristics of an assay must be assessed in the same types of specimens as the ones on which the assays will be performed in clinical practice. Therefore, although evidence-based, standardized preparation of specimens is an important goal, assays that are ready for use in current trials must be tested on currently available clinical material.

CDP is establishing a Specimen Retrieval System that will be able to provide sets of appropriate specimens to facilitate evaluation of an assay's analytical performance and initial assessment of clinical validity. These sets of specimens will be associated with clinical and outcome data. The specimen sets will have to be assembled rapidly to meet assay development needs identified during clinical trial concept review. These resources will be supported by performance contracts, and specimens will be obtained in a just-in-time fashion.

SELECTED PUBLICATIONS

Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK): explanation and elaboration, Altman DG, McShane LM, Sauerbrei W, Taube SE. *PLoS Medicine*, 2012;9:e1001216.

<http://www.ncbi.nlm.nih.gov/pubmed/22675273>

- In 2005, Dr. McShane and colleagues published a landmark paper issuing guidance on the reporting of tumor marker studies. Many journals have incorporated these REMARK guidelines as part of their instructions to authors. In 2012, this Explanation and Elaboration was published to further enhance the understanding and usage of the REMARK guidelines.

Biomarker studies: a call for a comprehensive biomarker study registry, Andre F, McShane LM, Michiels S, Ransohoff DF, Altman DG, Reis-Filho JS, Hayes DF, Pusztai L. *Nature Reviews: Clinical Oncology*, 2011;8(3):171–176.

<http://www.ncbi.nlm.nih.gov/pubmed/21364690>

- The article proposes the creation of a registry for biomarker studies, initially focusing on studies that use specimens from randomized trials. Further development could include nonrandomized studies and deposition of raw data, similar to existing genomic data repositories. The benefits of a comprehensive biomarker study registry include more balanced evaluation of proposed markers, fewer false-positive leads in research, and, it is hoped, more rapid identification of promising candidate biomarkers.

Identification of evidence-based biospecimen quality-control tools: a report of the International Society for Biological and Environmental Repositories (ISBER) Biospecimen Science Working Group, Betsou F, Gunter E, Clements J, DeSouza Y, Goddard KA, Guadagni F, Yan W, Skubitz A, Somiari S, Yeadon T, Chuaqui R. *The Journal of Molecular Diagnostics*, 2013;15(1):3–16.

<http://www.ncbi.nlm.nih.gov/pubmed/23195791>

- The quality of RNA preserved in different room-temperature stabilization matrices was investigated at several time points (up to 12 months of storage) was compared with that of RNA stored at -80°C (the current gold standard for RNA preservation). Five participating laboratories applied the samples to the matrices and stored them for the various time points, after which samples were shipped to three testing laboratories, where the samples were rehydrated and analyzed for RNA recovery, purity, and integrity. The results show that RNA integrity is preserved for at least 3.5 months when pure RNA is stored in RNashell or RNastable and shows no decay when compared with storage at -80°C .

Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group, Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J, Ellis M, Henry NL, Hugh JC, Lively T, McShane L, Paik S, Penault-Llorca F, Prudkin L, Regan M, Salter J, Sotiriou C, Smith IE, Viale G, Zujewski JA, Hayes DF; International Ki-67 in Breast Cancer Working Group. *Journal of the National Cancer Institute*, 2011;103(22):1656–1664.

<http://www.ncbi.nlm.nih.gov/pubmed/21960707>

- This paper presents the recommendations of an international group for the use of the Ki67 assay for cell proliferation in clinical trials.

Effects of preanalytical variables on the detection of proteins by immunohistochemistry in formalin-fixed, paraffin-embedded tissue, Engel KB, Moore HM. *Archives of Pathology & Laboratory Medicine*, 2011;135(5):537–543
<http://www.ncbi.nlm.nih.gov/pubmed/21526952>

- This review paper summarizes the published literature on how the results of immunohistochemistry are affected by different biospecimen collection, processing, and storage procedures applied to formalin-fixed, paraffin-embedded tissues. (Summaries of all literature references cited in the paper can be found in the NCI Biospecimen Research Database, an online literature database maintained by BBRB.)

Cancer classification using the Immunoscore: a worldwide task force, Galon J, Pagès F, Marincola FM, Angell HK, Thurin M, Lugli A, Zlobec I, Berger A, Bifulco C, Botti G, Tatangelo F, Britten CM, Kreiter S, Chouchane L, Delrio P, Arndt H, Asslaber M, Maio M, Masucci GV, Mihm M, Vidal-Vanaclocha F, Allison JP, Gnjatic S, Hakansson L, Huber C, Singh-Jasuja H, Ottensmeier C, Zwierzina H, Laghi L, Grizzi F, Ohashi PS, Shaw PA, Clarke BA, Wouters BG, Kawakami Y, Hazama S, Okuno K, Wang E, O'Donnell-Tormey J, Lagorce C, Pawelec G, Nishimura MI, Hawkins R, Lapointe R, Lundqvist A, Khleif SN, Ogino S, Gibbs P, Waring P, Sato N, Torigoe T, Itoh K, Patel PS, Shukla SN, Palmqvist R, Nagtegaal ID, Wang Y, D'Arrigo C, Kopetz S, Sinicropo FA, Trinchieri G, Gajewski TF, Ascierto PA, Fox BA. *Journal of Translational Medicine*, 2012;10:205.

<http://www.ncbi.nlm.nih.gov/pubmed/23034130>

- This publication provides an update of an international group for validation of the tumor immune response profile (“immunoscore”) for prognosis in early stage colon cancer.

The immune score as a new possible approach for the classification of cancer, Galon J, Pagès F, Marincola FM, Thurin M, Trinchieri G, Fox BA, Gajewski TF, Ascierto PA. *Journal of Translational Medicine*, 2012;10:1.

<http://www.ncbi.nlm.nih.gov/pubmed/22214470>

- This publication outlines the international effort to promote the Immunoscore in routine clinical settings for prognosis and prediction of response to cancer treatment.



Best practices for establishing a biobank, Hallmans G, Vaught JB. *Methods in Molecular Biology*, 2011;675:241–260
<http://www.ncbi.nlm.nih.gov/pubmed/20949394>

- This paper provides a general overview of the technical approaches to collecting, processing, and storing biospecimens, as well as related information technology and ethical/regulatory issues that comprise best practices for developing and maintaining a biobank.

American Society of Clinical Oncology Provisional Clinical Opinion: epidermal growth factor receptor (EGFR) mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy, Keedy VL, Temin S, Somerfield MR, Beasley MB, Johnson DH, McShane LM, Milton DT, Strawn JR, Wakelee HA, Giaccone G. *Journal of Clinical Oncology*, 2011;29(15):2121–2127.

<http://www.ncbi.nlm.nih.gov/pubmed/21482992>

- This Provisional Clinical Opinion offers timely clinical direction regarding potentially practice-changing data from major studies.

Standard preanalytical coding for biospecimens: review and implementation of the Sample PREanalytical Code (SPREC), Lehmann S, Guadagni F, Moore H, Ashton G, Barnes M, Benson E, Clements J, Koppandi I, Coppola D, Demiroglu SY, DeSouza Y, De Wilde A, Duker J, Eliason J, Glazer B, Harding K, Jeon JP, Kessler J, Kokkat T, Nanni U, Shea K, Skubitz A, Somiari S, Tybring G, Gunter E, Betsou F (International Society for Biological and Environmental Repositories [ISBER] Working Group on Biospecimen Science). *Biopreservation and Biobanking*, 2012;10(4):366–374
<http://online.liebertpub.com/doi/abs/10.1089/bio.2012.0012>

- This article provides an update on and implementation details for a simple coding system designed to record key information about specific biospecimen collection, processing, and storage procedures.

Short-term stability study of RNA at room temperature, Mathay C, Yan W, Chuaqui R, Skubitz APN, Jeon J-P, Fall N, Betsou F, Barnes M (ISBER Biospecimen Science Working Group). *Biopreservation and Biobanking*, 2012;10(6):532–542.

<http://online.liebertpub.com/doi/abs/10.1089/bio.2012.0030>

- The quality of RNA preserved in different room-temperature stabilization matrices, RNastable (Biomatrix),

GenTegra(IntegenX), and RNashell (Imagene), were compared with that of RNA stored at –80°C (the current gold standard for RNA preservation) in this multicenter study. Five participating laboratories applied the samples to the matrices and stored them for the various time points, after which samples were shipped to three testing laboratories. The results show that RNA integrity is preserved for at least 3.5 months when pure RNA is stored in RNashell or RNastable and shows no decay when compared with storage at –80°C.

Identification of evidence-based biospecimen quality-control tools: a report of the International Society for Biological and Environmental Repositories (ISBER) Biospecimen Science Working Group, Betsou F, Gunter E, Clements J, DeSouza Y, Goddard KA, Guadagni F, Yan W, Skubitz A, Somiari S, Yeadon T, Chuaqui R. *The Journal of Molecular Diagnostics*, 2013;15(1):3–16.

<http://www.ncbi.nlm.nih.gov/pubmed/23195791>

- The goal of this review was to identify quality control (QC) tools for both fluid and solid tissue samples based on a Biospecimen Science literature review of 495 publications from 225 journals. The most readily applicable tools were those where a threshold for the preanalytical variation and a reference interval of the QC analyte were known. Only a few meaningful markers that met these criteria were identified. They included the CD40L for assessing serum exposure at high temperatures, or VEGF for assessing serum freeze-thawing.

Statistical challenges in the development and evaluation of marker-based clinical tests, McShane LM. *BMC Medicine*, 2012;10:52.

<http://www.ncbi.nlm.nih.gov/pubmed/22642713>

- This commentary examines statistical challenges in the development and validation of marker-based tests that have clinical utility for therapeutic decision-making.

Publication of tumor marker research results: the necessity for complete and transparent reporting, McShane LM, Hayes DF. *Journal of Clinical Oncology*, 2012;30(34):4223–4232.

<http://www.ncbi.nlm.nih.gov/pubmed/23071235>

- This review discusses several measures for reporting of marker studies to help assess the adequacy of validation and completeness of evidence to support claims of clinical utility.

Lessons learned from the investigational device exemption review of Children's Oncology Group trial AAML 1031, Meshinchi S, Hunger SP, Aplenc R, Adamson PC, Jessup JM. *Clinical Cancer Research*, 2012;18(6):1547–1554.
<http://www.ncbi.nlm.nih.gov/pubmed/22422407>

- This publication details the process for application for an Investigational device exemption for an integral assay in a clinical trial.

Leveling the playing field: bringing development of biomarkers and molecular diagnostics up to the standards for drug development, Poste G, Carbone DP, Parkinson DR, Verweij J, Hewitt SM, Jessup JM. *Clinical Cancer Research*, 2012;18(6):1515–1523.
<http://www.ncbi.nlm.nih.gov/pubmed/22422403>

- This publication details important steps in assay validation for clinical trials.

Bridging the gap: moving predictive and prognostic assays from research to clinical use, Williams PM, Lively TG, Jessup JM, Conley BA. *Clinical Cancer Research*, 2012;18(6):1531–1539.
<http://www.ncbi.nlm.nih.gov/pubmed/22422405>

- This paper details steps in making a research assay ready for use in a clinical trial as an integral assay.

The NCI Biospecimen Research Network, Moore HM. *Biotechnic & Histochemistry*, 2012;87(1):18–23.
<http://www.ncbi.nlm.nih.gov/pubmed/21745162>

- This article summarizes the development and activities of the NCI Biospecimen Research Network program.

International approaches to advancing biospecimen science, Moore HM, Compton CC, Alper J, Vaught JB. *Cancer Epidemiology, Biomarkers & Prevention*, 2011;20(5):729–732.
<http://www.ncbi.nlm.nih.gov/pubmed/21430299>

- This article summarizes NCI's Biospecimen Research Network and various other international efforts to develop evidence-based approaches for collection, processing, and storage of biospecimens.

Biospecimen reporting for improved study quality (BRISQ), Moore HM, Kelly AB, Jewell SD, McShane LM, Clark DP, Greenspan R, Hayes DF, Hainaut P, Kim P,

Mansfield E, Potapova O, Riegman P, Rubinstein Y, Seijo E, Somiari S, Watson P, Weier HU, Zhu C, Vaught J. *Journal of Proteome Research*, 2011;10(8):3429–3438.
<http://www.ncbi.nlm.nih.gov/pubmed/21574648>

Biospecimen reporting for improved study quality (BRISQ), Moore HM, Kelly AB, Jewell SD, McShane LM, Clark DP, Greenspan R, Hayes DF, Hainaut P, Kim P, Mansfield EA, Potapova O, Riegman P, Rubinstein Y, Seijo E, Somiari S, Watson P, Weier HU, Zhu C, Vaught J. *Cancer Cytopathology*, 2011;119(2):92–101.
<http://www.ncbi.nlm.nih.gov/pubmed/21433001>

Biospecimen reporting for improved study quality, Moore HM, Kelly A, Jewell SD, McShane LM, Clark DP, Greenspan R, Hainaut P, Hayes DF, Kim P, Mansfield E, Potapova O, Riegman P, Rubinstein Y, Seijo E, Somiari S, Watson P, Weier H-U, Zhu C, Vaught J. *Biopreservation and Biobanking*, 2011;9(1):57–70.
<http://online.liebertpub.com/doi/abs/10.1089/bio.2010.0036>

- Published simultaneously in the above three journals, these guidelines are aimed specifically at the reporting of information about biospecimens used in research studies. These guidelines were motivated by increasing evidence that preanalytical factors affecting biospecimens could alter the biomarker profiles and distort research findings generated from them.

Development and use of integral assays in clinical trials, Schilsky RL, Doroshow JH, Leblanc M, Conley BA. *Clinical Cancer Research*, 2012;18(6):1540–1546.
<http://www.ncbi.nlm.nih.gov/pubmed/22422406>

- This paper details recommendations and trial designs for bringing integral assays into clinical trials.

Unique characteristics of adolescent and young adult acute lymphoblastic leukemia, breast cancer, and colon cancer, Tricoli JV, Seibel NL, Blair DG, Albritton K, Hayes-Lattin B. *Journal of the National Cancer Institute*, 2011;103(8):628–635.
<http://www.ncbi.nlm.nih.gov/pubmed/21436065>

- This article relates discussions from a workshop, sponsored by NCI and the Lance Armstrong Foundation, that examined genetic differences in acute lymphoblastic leukemia and breast and colon cancers that might define subtypes prevalent in adolescent and young-adult



populations, as well as other biological features and the epidemiology of these three cancers. Some clinical trials are described that aim to determine whether different therapies might be more effective for this age group.

Biological sample collection, processing, storage and information management, Vaught J, Henderson MK. In: *Molecular Epidemiology: Principles and Practices*, Rothman N, Hainaut P, Schulte P, Smith M, Boffetta P, Perera F (eds). WHO Press, 2011.

- This chapter provides an overview of the technical aspects of managing a biospecimen repository, including collection, processing, and storage approaches, as well as an extensive discussion of informatics needs such as sample tracking, inventory, and analytical data management.

Biospecimens and biorepositories: from afterthought to science, Vaught JB, Henderson MK, Compton CC. *Cancer Epidemiology, Biomarkers & Prevention*, 2012;21(2):253–255.

<http://www.ncbi.nlm.nih.gov/pubmed/22313938>

- This invited editorial summarizes the efforts in recent years at NCI and elsewhere to develop biorepository and biospecimen methods research as a new field of “biospecimen science,” emphasizing the need to develop and publish evidence-based practices.

Sharing individual research results with biospecimen contributors: point, Yassin R, Weil C, Lockhart N. *Cancer Epidemiology, Biomarkers & Prevention*, 2012;21(2):256–259.

<http://www.ncbi.nlm.nih.gov/pubmed/22313939>

- This article presents ethical and policy arguments favoring the return of diagnostic discrepancies, incidental findings, and other types of individual research results to participants in biobanking studies. The paper is published as part of a “point/counterpoint” article in which other authors present ethical and policy arguments against the return of individual research results.

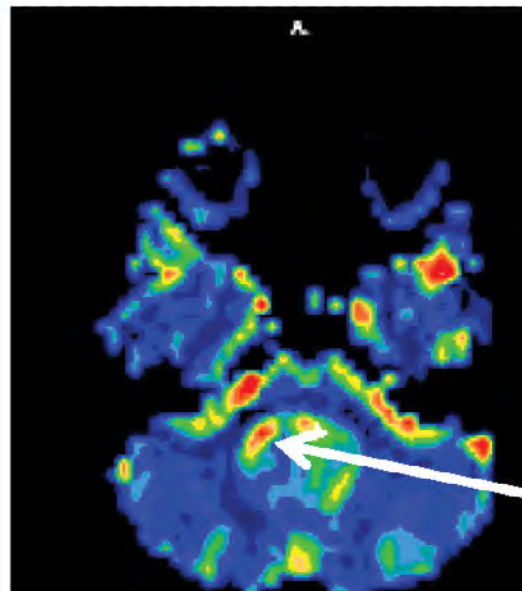
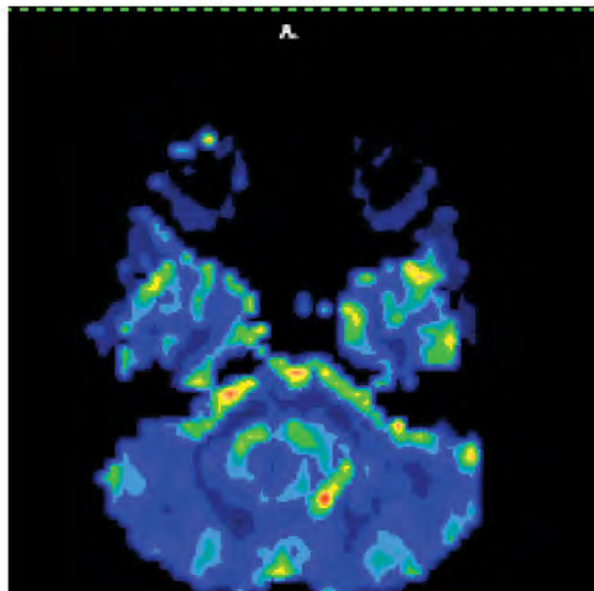
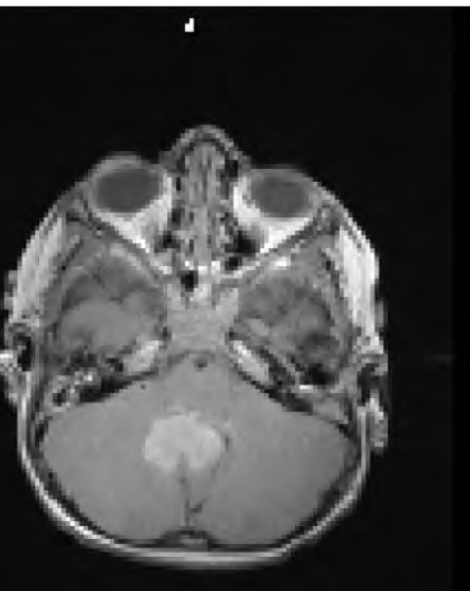
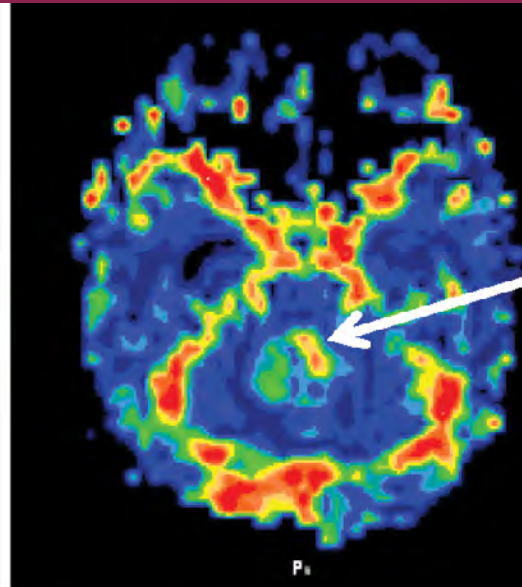
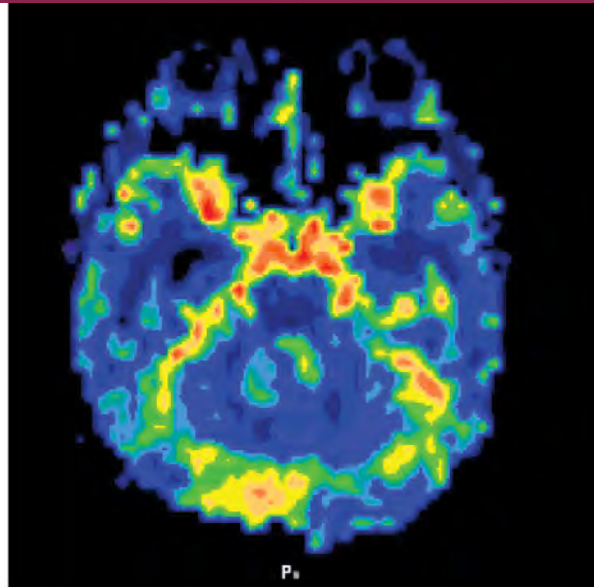
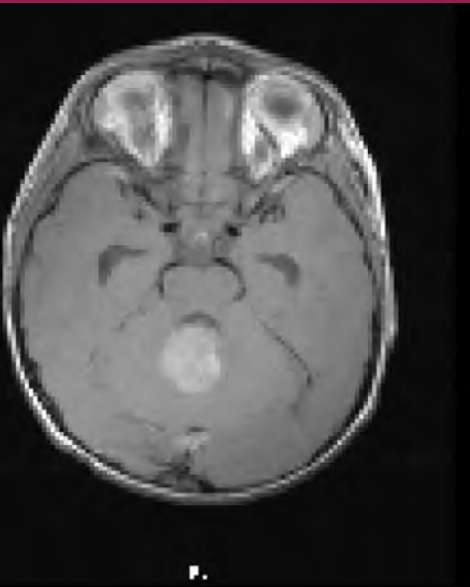
AACR-FDA-NCI Cancer Biomarkers Collaborative consensus report: advancing the use of biomarkers in cancer drug development, Khleif SN, Doroshow JH, Hait WN; AACR-FDA-NCI Cancer Biomarkers Collaborative. *Clinical Cancer Research*, 2010;16(13):3299–3318.

<http://www.ncbi.nlm.nih.gov/pubmed/20501613>

- This paper is a consensus report on best practices for the development and use of markers as drug development tools with participation by many members of CDP and the Biometry Research Branch.

2012 PROGRAM ACCOMPLISHMENTS

CANCER IMAGING PROGRAM





OVERVIEW

The **Cancer Imaging Program (CIP)** of the Division of Cancer Treatment and Diagnosis (DCTD) 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.

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

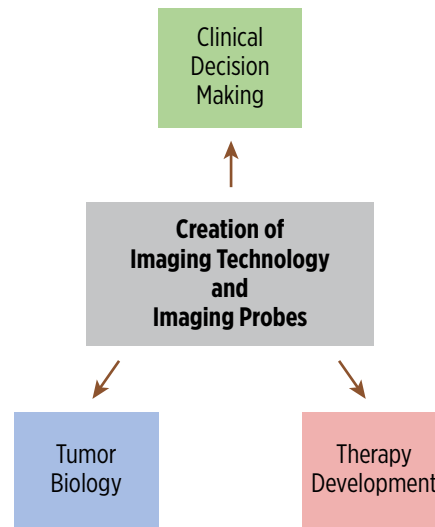
- Enabling discovery
- Directing development
- Personalizing care

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 is an enabling scientific discipline combining advanced technology and complex computational and analytic methods to provide a unique ability to extract spatially and temporally defined information from *in vivo* systems. Imaging allows the interrogation of an intact biologic system across the spectrum from subcellular to macroscopic and from discovery to clinical decision making. In the last decade, major advances have been made in our understanding of tumor systems, in part due to advanced imaging that has not only made strides in spatial and temporal resolution, but has also progressed from anatomical to functional, physiological, genomic, pharmacodynamic, and molecular domains.

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,

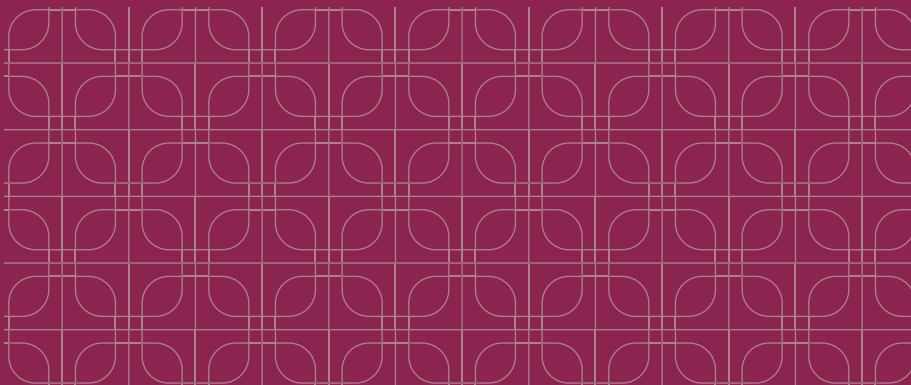


the primary thrust in imaging is functional or molecular imaging to visualize the physiological, pharmacodynamic, cellular, or molecular processes in living tissues as they take place. Advanced imaging is critical for fundamental improvements in the care of cancer patients. As the National Cancer Institute (NCI) continues to discover new molecular signatures of cancer to develop effective therapies with lower morbidity, success can be achieved only by understanding how these targets integrate into complex biological systems. *In vivo* imaging uniquely allows noninvasive visualization of the entire organism in space and over time.

Even more sophisticated and integrated imaging will be required to provide insight into the complex, heterogeneous, and ever-changing biologic system that constitutes cancer. The challenge is to visualize the integrated genomic information needed to understand and manipulate this system through prevention and therapeutic intervention. Imaging will be critical to increasing our understanding of subcellular structural and molecular interactions executed by the proteome-to-cell microenvironment and cell-cell interactions executed by complex signaling and transfer systems. Imaging currently provides information at several places across the genotype-to-phenotype axis, especially at the extremes. At one extreme, imaging is being applied increasingly to evaluate

PAULA M. JACOBS

ASSOCIATE DIRECTOR

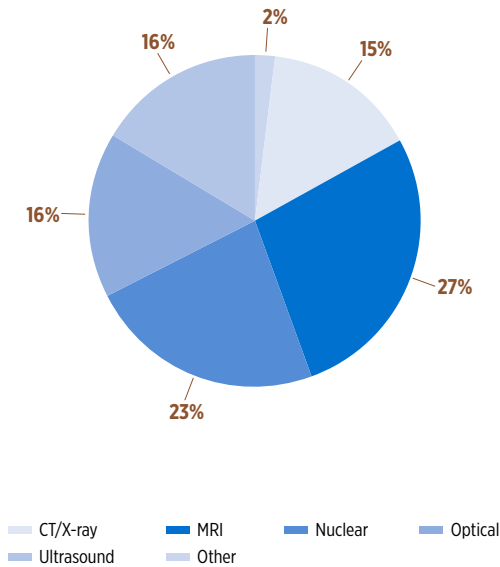


Paula M. Jacobs, PhD, joined NCI after 30 years in the pharmaceutical and medical device industries, where she was a key developer of ultrasmall superparamagnetic iron oxide drugs as magnetic resonance imaging agents and iron replacement therapeutics. She became Deputy Associate Director of DCTD responsible for CIP in 2009 and Acting Associate Director in 2011, and in 2012 she was named Associate Director. Her efforts for NCI have been focused first on lowering the scientific, logistical, and regulatory barriers to investigational use of positron emission tomography radiopharmaceuticals for therapeutic drug development by facilitating access to Investigational New Drug (IND) filings and by overseeing research to develop labeled drugs for clinical and preclinical use. Another effort is focused on wide-ranging aspects of standardization and quantitative imaging techniques, and a third focus is on genome-imaging correlations. Dr. Jacobs serves on three NCI Experimental Therapeutics (NExT) committees to review and manage the projects chosen for development. She oversees a radiochemistry laboratory and radiopharmacy at the Frederick National Laboratory for Cancer Research that provides preclinical and early clinical radiopharmaceuticals in support of therapeutic drug development.

Dr. Jacobs earned her undergraduate degree in chemistry at the Massachusetts Institute of Technology and graduate degrees at Tufts University and Northeastern University. Her postdoctoral training was at Northeastern University, the Massachusetts Institute of Technology, and Peter Bent Brigham Hospital/Harvard Medical School.

Her industrial experience began at Clinical Assays, a division of Baxter Travenol that manufactured in vitro radioimmunoassays, where she was responsible for process improvements in radioactive tracer synthesis, technical product maintenance, product and process improvements, and manufacturing of all reagents used in the company's products. At Seragen, a small biotechnology firm, she was General Manager, with profit and loss responsibility for a division that developed, manufactured, and marketed prostaglandin, leukotriene, and small protein immunoassays. Subsequently she joined Advanced Magnetics as Vice President, Development, to help chart a new course for this small biomedical products company. She was responsible for the development of iron oxide magnetic contrast agents from laboratory synthesis through IND submissions, including design of pharmacology, toxicology, and clinical studies. She served as international liaison for technology transfer to licensees, worked with independent physicians in the United States and abroad to develop physician IND trials in magnetic resonance imaging, and collaborated with academic researchers in a variety of preclinical investigations.

Dr. Jacobs has published papers in the areas of organic chemistry, inorganic chemistry, magnetic resonance imaging, neuro-oncology, and nephrology.



CIP GRANTS BY FUNDING LEVEL ACROSS VARIOUS IMAGING MODALITIES. THE CIP PORTFOLIO INCLUDED 330 FUNDED GRANTS DURING FISCAL YEAR 2012. NEARLY 25% WERE FOR MULTIPLE MODALITIES.



subcellular structure and biology, including protein-protein interactions and compartmentalization within unique intracellular microenvironments. At the other extreme, macro-level imaging is used clinically to evaluate phenotypic changes noninvasively on a daily basis.

In the next decade, CIP-sponsored research will not only contribute to the basic understanding of various cancers but will also enhance the clinical role of imaging in noninvasive diagnosis, help identify disease subsets in patients, improve disease staging and treatment monitoring, and play a pivotal role in the development of new therapies.

As part of its mission, CIP plays a critical role in the activities of the National Institutes of Health (NIH) and NCI, contributing to the integration of imaging with emerging technologies such as nanotechnology, cancer genomics, proteomics, and high-throughput screening. 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.

STRUCTURE AND FUNCTION

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. 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.

Extracting relevant information from imaging is a major goal of CIP. More advanced imaging, as well as quantitative and directed approaches, will need to be developed through extensive collaborations that include not only biologists but also 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 “omic” space. Similar approaches employing complex cell systems have already revealed unanticipated network connectivity when these systems are perturbed with drugs. This information has led to refined models that can be used in drug development for predicting not only target response but also toxicity. Recent work using optical imaging in a preclinical model has demonstrated that imaging allows this powerful approach to be used in a preclinical setting with the potential for clinical translation. It is anticipated that such translation will depend heavily on collaboration with ongoing research in nanotechnology.

CIP STRATEGIC GOALS

- Encourage investigators to design and apply imaging to better understand tumor networks and systems.
- 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 the development of clinically relevant imaging techniques that do not require the intravenous injection of exogenous contrast agents.
- Expand and improve the correlation of imaging phenotype extraction data with genomic and expression data in parallel with the expansion of The Cancer Genome Atlas to map additional cancers.
- Translate imaging-derived knowledge and techniques to help realize the potential of personalized medicine.

HISTORICAL NOTE

NCI established the Diagnostic Imaging Program in October 1996. The name of the program has changed twice since that time—to the Biomedical Imaging Program in 2001 and to the Cancer Imaging Program in 2003—to more clearly reflect the role of the program to both NCI and the public.

CIP unites researchers from disciplines as diverse as radiology, nuclear medicine, bioengineering, biology, genomics, chemistry, computer science, informatics, and physics in a team science approach. The program encourages extramural researchers to integrate and apply new imaging discoveries and developments to drug discovery, monitoring of therapies, and understanding cancer biology—all directly aimed at the clinical management of cancer and cancer risk.

CIP activities and responsibilities can be divided into five broad areas:

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

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

MOLECULAR IMAGING BRANCH

The ultimate goal of in vivo cancer molecular imaging by the Molecular Imaging Branch is to provide a definitive, minimally 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, pharmacodynamics, and physiological processes in cancer



- Imaging technologies capable of detecting rare events at highest resolution in vivo
- Advanced image reconstruction and processing capabilities
- Highly multidisciplinary approaches

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

- Filing Investigational New Drug (IND) applications and encouraging suppliers for noncommercial positron emission tomography (PET) molecular imaging agents
- Supporting small-animal imaging to evaluate novel molecular probes and their utility to evaluate therapeutic agents
- Collaboration with the Molecular Imaging Program of the Center for Cancer Research and the Molecular Imaging Clinic in the NIH Clinical Center

CLINICAL TRIALS BRANCH

CIP supports clinical trials in several ways:

- Awarding grants and contracts to extramural investigators for exploratory trials
- Providing guidance through imaging review of protocols sponsored by the Cancer Therapy Evaluation Program (CTEP)
- Supporting trials performed with an imaging trial-specific Cooperative Group, the American College of Radiology Imaging Network (ACRIN)
- Overseeing the Phase 1 and 2 Clinical Trials Contract Program
- Developing trial-related informatics

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

IMAGE-GUIDED INTERVENTION BRANCH

The CIP Image-Guided Intervention Branch promotes the integration of imaging, informatics, and interventional methods to address diverse challenges such as directed biopsy, image-guided tumor ablations, dimensionality of scale, and targeted drug delivery. The branch is heavily involved in nanotechnology and supports the development of nano-based probes and delivery vectors where imaging plays a significant role in development or application.

IMAGING TECHNOLOGY DEVELOPMENT BRANCH

The Imaging Technology Development Branch supports the development and validation of biomedical imaging technology and methods to enable basic research and clinical investigations of cancer biology and treatment responses. Its strategy is characterized by a balanced emphasis on both current-generation (commercially supported) imaging platforms and the next generation of imaging platforms. This includes an emphasis on multimodality imaging and methods of quantitative imaging on resolution scales from the molecular level to the organ level.

IMAGING INFORMATICS

The informatics activities of CIP address major challenges to the acceleration of cancer imaging research. CIP established and supports [The Cancer Imaging Archive \(TCIA\)](#) to address both the lack of readily accessible, large, curated clinical image collections and the barriers to interinstitutional sharing of image data.

TCIA provides access to more than 12 terabytes of curated image data in 26 purpose-built collections driven by NCI program agendas. CIP is also actively involved in the important area of imaging genomics and has acquired for analysis medical images associated with tissues analyzed by [The Cancer Genome Atlas \(TCGA\)](#) activities. The TCGA imaging activities address the need to accelerate and facilitate the incorporation of genomics science in cancer imaging research.

PROGRAM ACCOMPLISHMENTS

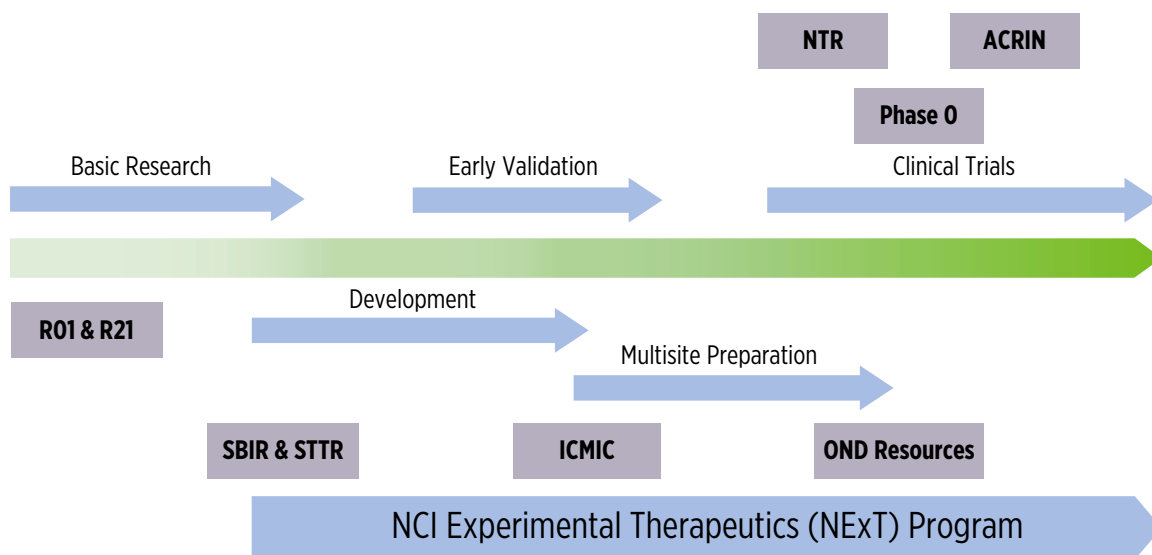
MAJOR ONGOING INITIATIVES

CIP initiatives cover the full spectrum of research efforts, from basic research to clinical trials. These programs serve a variety of needs in the cancer imaging community. In addition to many investigator-initiated basic research efforts, several key program announcements use the R01 and R21 grant mechanisms to foster needed research. The In Vivo Cellular and Molecular Imaging Centers, the Network for Translational Research: Optical Imaging in Multimodality Platforms, and ACRIN each use specialized grant mechanisms suited for their positions in the research pipeline.

CIP also works in close collaboration with intramural NCI scientists in the development of new imaging probes. A number of these probes are PET agents for molecular imaging directed at important targets such as angiogenesis and proliferation. This collaboration is bidirectional, forming a novel development pipeline with the Center for Cancer Research, which is providing the infrastructure for early clinical trials of imaging probes, and DCTD, which is providing expertise in drug development.

Imaging Drug Group and the NCI Experimental Therapeutics Program

Molecular imaging has an enormous impact on the entire 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 Development of Clinical Imaging Drugs and Enhancers (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, this imaging drug development program became the foundation for the Imaging Drug Group, which integrated the activities of several cross-institute imaging drug activities into one decision-making committee. In



IMAGING RESEARCH SPECTRUM AND KEY CIP PROGRAMS

ICMIC = In Vivo Cellular and Molecular Imaging Centers;
 NTR = Network for Translational Research; SBIR = Small Business Innovation Research; STTR = Small Business Technology Transfer
 ACRIN = American College of Radiology Imaging Network.



doing so, the Imaging Drug Group subsumed the DCIDE program and formed bridges to other important programs in the Center for Cancer Research and DCTD. Going forward, the **NCI Experimental Therapeutics (NExT)** initiative has taken on the activities that the DCIDE program performed. The Imaging Drug Group has also acted in an advisory role with the Center for Cancer Research's Molecular Imaging Program and the Small Animal Imaging Program (at the Frederick National Laboratory for Cancer Research), as well as the Nanotechnology Characterization Laboratory.

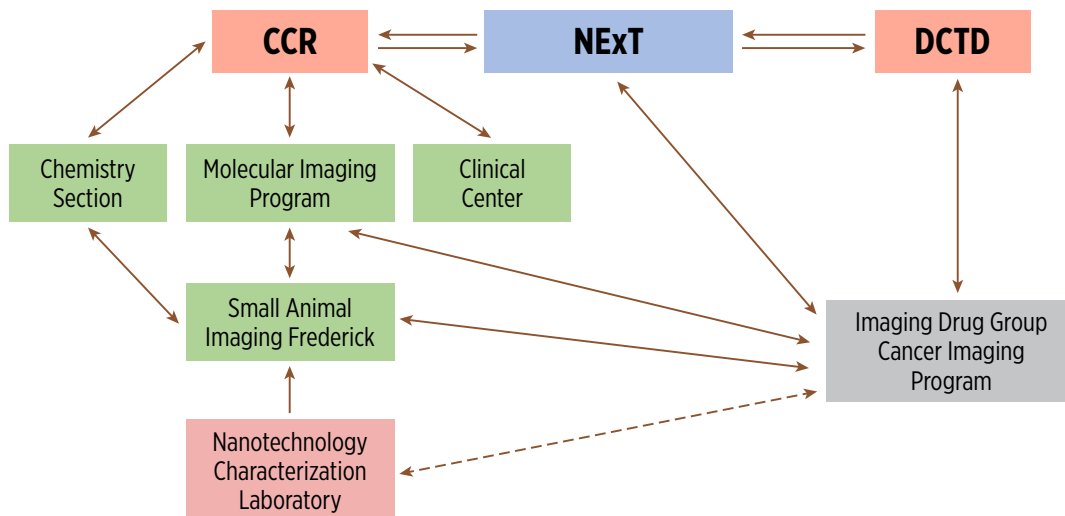
The Imaging Drug Group was essential for facilitating the development of novel imaging agents, because very few alternative sources of funds exist for such studies. For most academic investigators who discover interesting new lead compounds for imaging agents, the regulatory process is unfamiliar and daunting terrain. Most commercial entities and universities correctly view the development of such discoveries as high risk (high cost, low potential revenue) that often cannot be justified in an environment of limited resources. Pre-investigational new drug application and early feasibility studies generally cannot be funded through the typical grant mechanisms because they are considered neither original nor novel research.

The NExT program has now integrated the ideas 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 cancer patients.

Clinical Trials and CIP

Although phase 0 and imaging feasibility studies can be performed at the NIH Clinical Center, this venue is not sufficient to perform many studies due to a number of factors, including lack of PET radiochemistry capabilities and limited access to imaging time. CIP is working with academic centers and commercial vendors that have capabilities and patient populations that complement the Clinical Center's capabilities. Using this mechanism, CIP has been able to support extramural efforts to develop imaging drugs.

Later-phase clinical trials, both of imaging drugs and of imaging for the evaluation of therapy, are handled through ACRIN, a Cooperative Group managed by CIP. Another mechanism for inclusion of imaging in therapy trials is by supplements to trials being funded through other Cooperative Groups.



IMAGING DRUG DEVELOPMENT AT NCI

[18F]SODIUM FLUORIDE NEW DRUG APPLICATION

Fluoride ions accumulate in areas of increased osteogenic activity, which occur in both benign and malignant skeletal conditions. **[18F]Sodium fluoride** has been used as a skeletal imaging agent to delineate areas of abnormal osteogenesis, but it is not yet reimbursed by the Centers for Medicare and Medicaid Services (CMS). It can be used for bone scans with PET to diagnose skeletal metastases from primary cancers elsewhere, as well as for many nonmalignant skeletal conditions. Skeletal metastases are a serious issue for many cancers, particularly breast and prostate. In 2007, 2.6 million bone scans were performed, the vast majority of them with a technetium agent. However, in the last several years there have been extended widespread shortages of these radiopharmaceuticals because of serious problems with the few aging nuclear reactors that manufacture the precursor isotope, and these outages are expected to continue for several more years. Without bone scans, appropriate treatment for metastatic cancer may be delayed, or patients may be treated with systemic therapies in the absence of definitive diagnosis. This can lead to unnecessary side effects and inappropriate expense.

In view of the public health impact of these shortages on cancer patient care, CIP filed NCI's first New Drug Application for [18F]sodium fluoride in December 2008 so that the drug, which has a short half-life (2 hours), could be supplied by commercial firms with Drug Master Files for manufacturing the agent. FDA approval was received in January 2011. This approval enabled multiple entities to file Abbreviated New Drug Applications (for "generic" drugs) and facilitated both availability to patients and reimbursement by insurance companies. The drug is now reimbursed by CMS under a "coverage with evidence development" process.

Molecular Imaging Clinic

As noted, exploratory and imaging feasibility trials had been performed outside of the NCI intramural program, in part because of the NCI intramural program's limited access to the radiochemistry and imaging platform resources required to perform such studies. Four years ago, the intramural Molecular Imaging Clinic was established to provide a dedicated research infrastructure for such trials. This facility is engaged in performing multiple phase 0 and 1 imaging studies, including some with radiopharmaceuticals supplied by the radiopharmacy at the Frederick National Laboratory for Cancer Research that was developed in collaboration by CIP during the same period.

Synthesis of Agents

As part of the imaging drug development pipeline, the acquisition of trial-acceptable agents and precursors is a pivotal step to clinical trials. For imaging agents, the commercial interest in production is tempered by limited potential markets. Although there are a few examples of small biotechnology products, most imaging agents of interest are currently downstream markers of nucleic acid, amino acid, or lipid synthesis or labeled species of existing drugs through a process of chelation or by synthesis of labeled species from precursor compounds. CIP has developed mechanisms to secure these materials for both preclinical and early clinical investigations.



SYNTHESIS OF RADIOPHARMACEUTICALS FOR PRECLINICAL INVESTIGATIONS.



Institution	Principal Investigator
Emory University	Carolyn Meltzer
Johns Hopkins University	Zaver Bhujwalla
Massachusetts General Hospital	Ralph Weissleder
Memorial Sloan-Kettering Cancer Center	Steven Larson
Stanford University	Sanjiv Gambhir
University of California, Los Angeles	Harvey Herschman
University of California, San Diego	Robert Mattrey
University of Michigan	Brian Ross
Vanderbilt University	John Gore
Washington University	David Piwnica-Worms



CURRENTLY FUNDED IN VIVO CELLULAR AND MOLECULAR IMAGING CENTERS

Molecular Imaging Radiopharmaceutical Resources

CIP has filed INDs for some **molecular imaging radiopharmaceuticals** to perform multicenter clinical trials and to facilitate access by the wider research community. CIP holds the following active INDs:

- [18F]Fluorothymidine, targeted to areas of increased proliferation
- [18F]Fluoromisonidazole, targeted to hypoxic tissues
- 16 α -[18F]Fluoro-17 β -estradiol, targeted to estrogen receptors
- [18F]Sodium fluoride, accumulating in areas of increased osteogenic activity
- [111In]Trastuzumab, targeted to HER2-expressing cancers
- [89Zr]Panitumumab, targeted to cancers expressing epidermal growth factor receptor (HER1)
- Ferumoxytol, an iron oxide nanoparticle for magnetic resonance imaging (MRI)
- [18F]Fluorodeoxycytidine

NCI's IND for [18F]fluorothymidine was filed in 2004, those for the other agents subsequently. To facilitate further clinical research on the radiopharmaceuticals by the research community, a subset of the documents filed in several of these INDs is freely available to 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. Food and Drug Administration (FDA). CIP will provide a letter to cross-reference the NCI IND file at the FDA for pharmacology, toxicology, dosimetry, and previous human experience.

In addition, CIP has contracted with commercial firms that have filed Drug Master Files for the manufacturing and distribution of [18F]fluorothymidine, [18F]sodium fluoride, and [18F]fluoromisonidazole. This effort has made it possible for clinical investigators without radiochemistry facilities to study these agents.

MOLECULAR IMAGING

Molecular Imaging Program

The In Vivo Cellular and Molecular Imaging Centers (ICMICs), established in 1999, are 5-year P50 grants that support interdisciplinary scientific teams conducting cutting-edge cancer molecular imaging research. Nearly 700 ICMIC-supported papers have been published since 2008. ICMIC projects are designed to:

- Support innovative cancer molecular imaging research projects
- Support unique core facilities
- Enable awardees to initiate pilot research in promising new directions
- Provide interdisciplinary career development opportunities for investigators who are new to the field of molecular cancer imaging

Research supported through the ICMICs has had high impact in a number of areas:

- Enabling technologies:
 - Advances in optical imaging technology, particularly in tomographic imaging
 - Split luciferase constructs for studying protein–protein interactions
- Fundamental discoveries related to cancer biology:
 - Investigation of the relationship of hypoxia to breast tumor invasiveness and metastasis
- Direct clinical applications:
 - Combined virus and cell biotherapy
 - Use of the HSV1-sr39tk PET reporter to monitor the treatment of melanoma by genetically modified T-cells
 - Development of a PET probe for imaging T-cell activation
 - Development of magnetic nanoparticles as a clinical product

NCI Cancer Research Imaging Camp. The NCI Cancer Research Imaging Camp is a collaboration between DCTD and the Division of Cancer Biology. This intensive, annual, 6-day, hands-on workshop for early-career, basic cancer biologists focuses on in vivo imaging techniques. Through lectures and hands-on laboratory sessions, 25 students and 25 faculty gain experience with a wide range of imaging modalities, including advanced optical imaging, magnetic resonance imaging (MRI), PET, single-photon emission computed tomography, computed tomography (CT), and ultrasound. Upon completion of this course, participants are able to select and apply the appropriate in vivo imaging technique necessary to investigate a biological hypothesis and to interpret the resulting imaging data.

Molecular Imaging and Contrast Agent Database. The Molecular Imaging and Contrast Agent Database, established in 2004, was generated through the NIH Common Fund, which was formerly the NIH Roadmap. It is a collaboration among NCI, the National Library of Medicine, and the NIH Office of the Director. This freely accessible database catalogues, in a comprehensive and easily accessible manner, key research data on in vivo molecular imaging and contrast agents. More than 1,380 of approximately 5,400 molecular imaging agents have been catalogued.

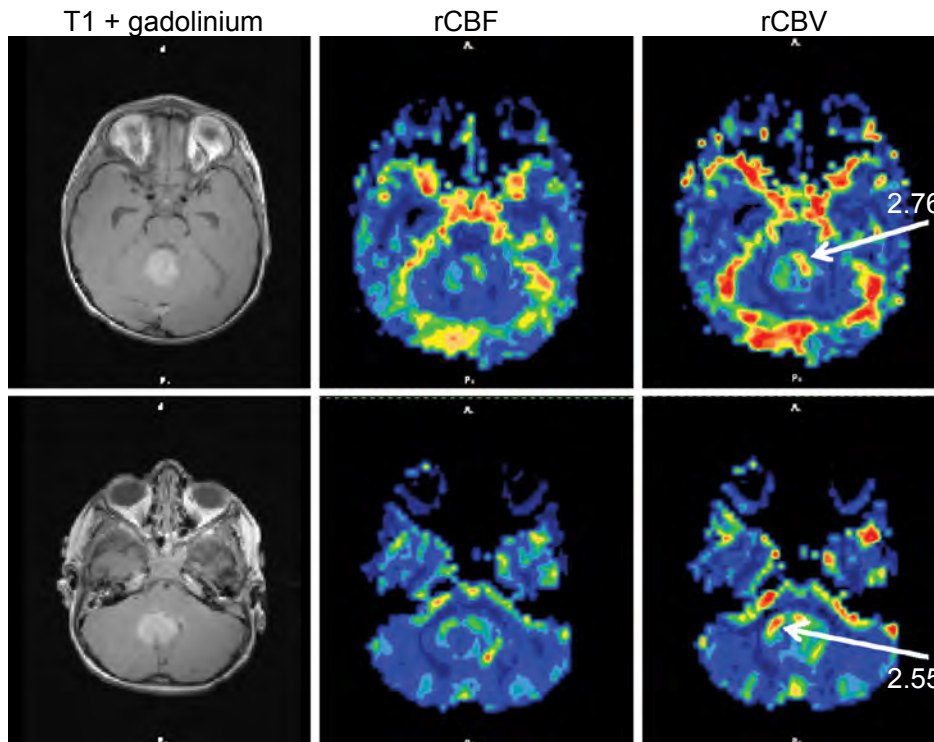
Other Molecular Imaging Initiatives

Additional research is needed for molecular imaging to realize its full potential of integrating data from disparate biological sources. It is necessary to discover and develop agents and technologies to acquire high-resolution in vivo imaging data and to expand computational systems approaches to integrate imaging data with biological and omics data.

In 2011, CIP and the Division of Cancer Biology issued an interdivisional Request for Applications (RFA) entitled “Advanced In Vivo Imaging to Understand Cancer Systems (R01).” The purpose of the RFA was to promote and support new collaborative projects focusing on the integration of advanced in vivo imaging technologies with systems biology approaches to understand complex cancer phenomena at highest resolution.

Six R01 grants were awarded:

1. David Dingli, PI: Mayo Clinic, Rochester, Minnesota
2. Paul Kinahan, PI: University of Washington, Seattle
3. Ralph Weissleder, PI: Massachusetts General Hospital–Harvard University, Boston



IMAGES FROM A PATIENT IN THE PEDIATRIC IRON OXIDE STUDY UNDER ARRA

Dynamic susceptibility-weighted, contrast-enhanced MRI with ferumoxytol contrast in a 5-year-old patient with medulloblastoma prior to surgery. The image shows heterogeneously increased vascularity and a relative cerebral blood volume (rCBV) of 2.55–2.76 in the tumor, despite homogenous gadolinium enhancement. Tumor was confirmed at resection. rCBF = relative cerebral blood flow.

4. Vladislav Verkusha, PI: Albert Einstein College of Medicine, New York
5. Hank Kung, PI: University of Pennsylvania, Philadelphia
6. Steven Kron, PI: University of Chicago

- Single-center evaluations of the role of iron oxide nanoparticle (ferumoxytol) magnetic resonance to direct brain cancer therapy in both adult and pediatric populations

CLINICAL TRIALS

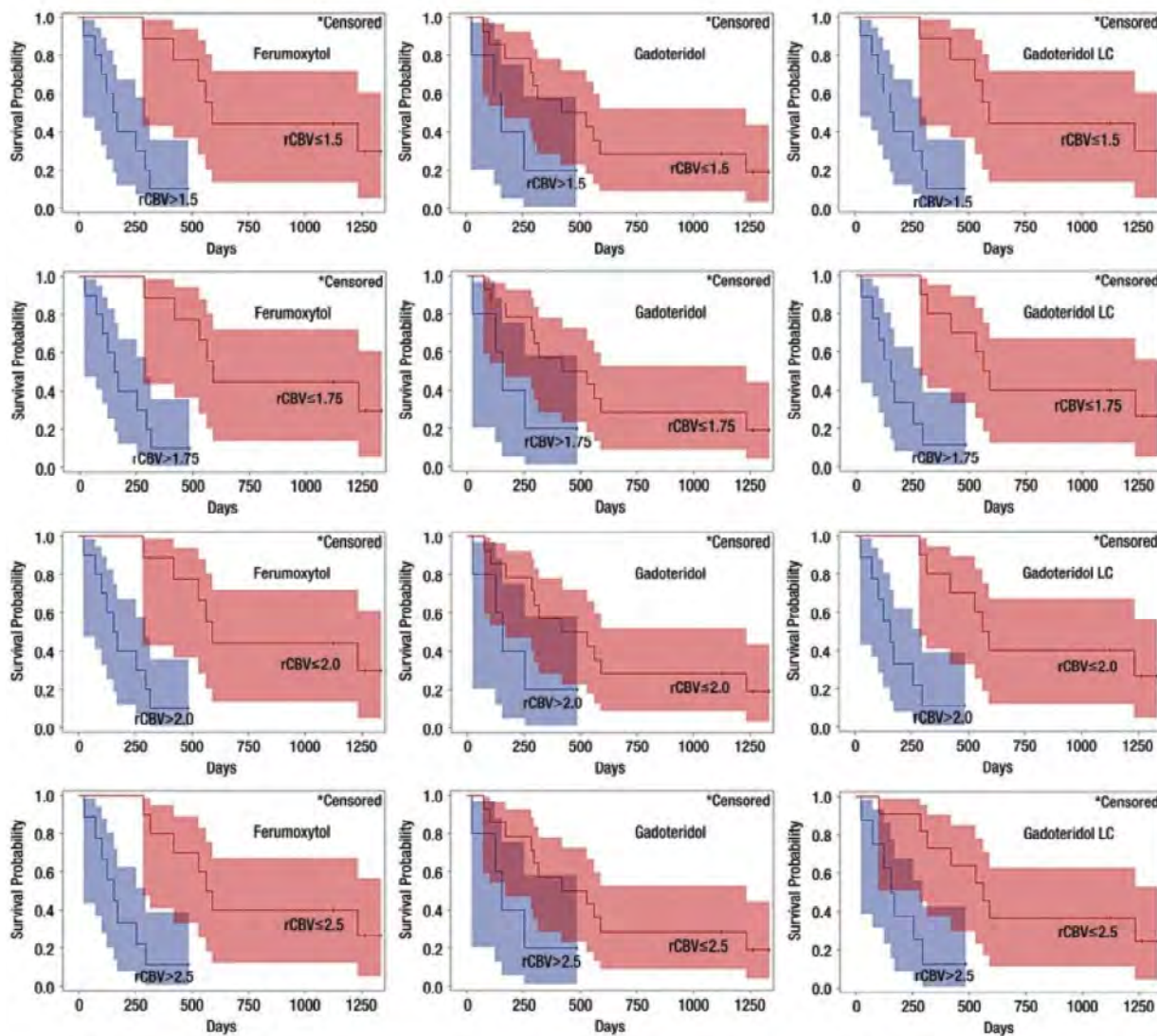
American Recovery and Reinvestment Act

As part of NCI's efforts under the American Recovery and Reinvestment Act (ARRA), CIP provided additional resources over 2 years for the most promising early-phase trials. The studies that received funding from this initiative are:

- Three multicenter studies evaluating [18F]fluorothymidine-PET as a predictive marker in cancer therapy of solid tumors (non-small-cell lung cancer, breast cancer, and glioblastoma multiforme [GBM])
- A multicenter study evaluating [18F]sodium fluoride-PET as a pharmacodynamic biomarker

The standard-of-care imaging is a T1-weighted MRI with gadolinium-based contrast agent. Experimental imaging with ferumoxytol is a dynamic susceptibility-weighted, contrast-enhanced MRI technique that allows determination of relative cerebral blood flow and relative cerebral blood volume in selected areas of the image. Increased flow and volume indicate increased vascularity and may correlate with malignancy.

The researchers also showed that perfusion MRI with ferumoxytol may facilitate the diagnosis of pseudoprogression of GBM after chemotherapy and radiation therapy and can predict survival in GBM patients who appear to have progressive disease.

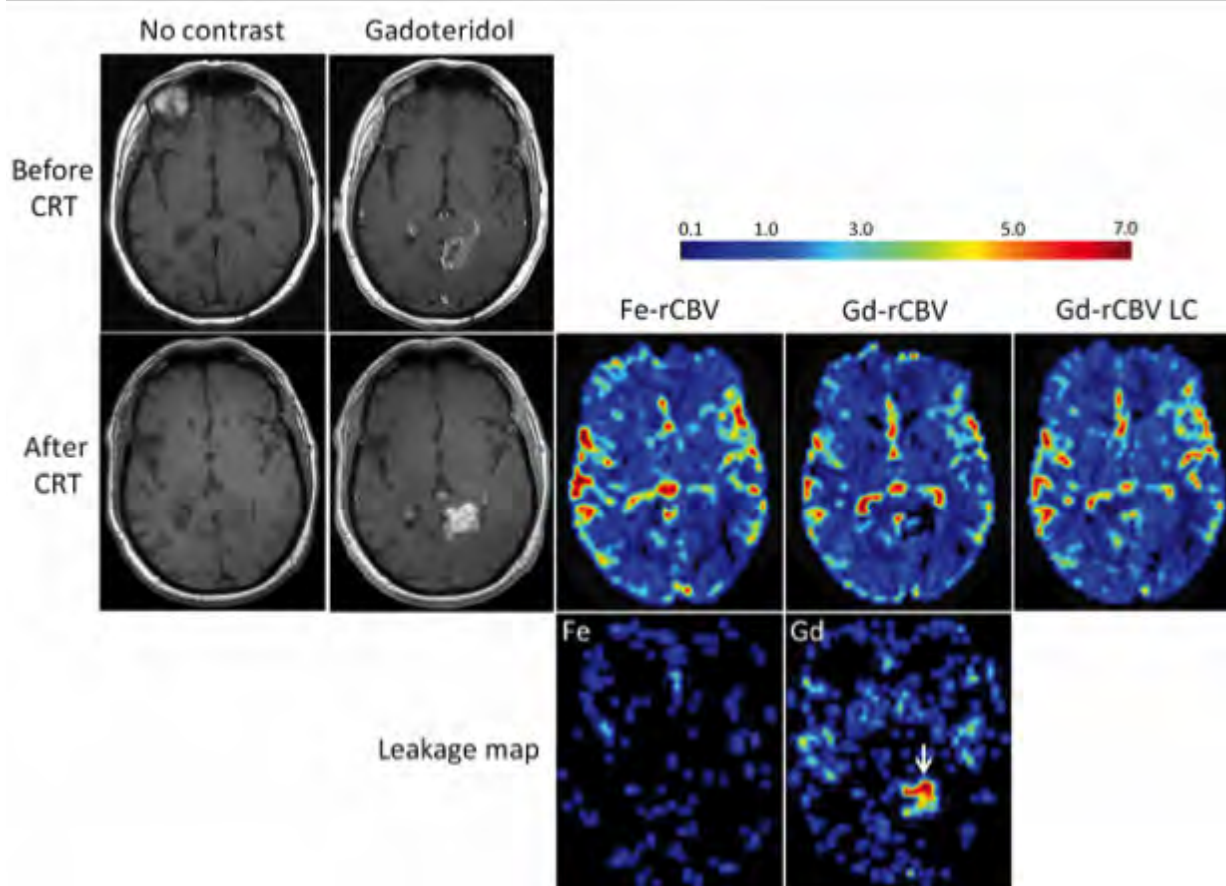


KAPLAN-MEIER ESTIMATES OF SURVIVAL FOR PATIENTS WITH HIGH AND LOW RELATIVE CEREBRAL BLOOD VOLUME (rCBV) VALUES

Charts show survival of GBM patients according to rCBV by using four cutoff values. Tumor rCBV was measured by using ferumoxytol versus gadoteridol and gadoteridol with leakage correction (LC). Kaplan-Meier survival curves show best survival prediction by using rCBV values obtained with ferumoxytol ($P < 0.001$) when cutoff range is between 1.5 and 2.0.



Based on the findings of this study, perfusion MRI with ferumoxytol can assist clinicians in establishing which patients have active GBM after chemoradiation therapy and should begin second-line or experimental therapy without delay, and which patients have a better prognosis and would benefit from continuation of adjuvant treatment.



AXIAL IMAGES OF 73-YEAR-OLD MAN WITH GBM SHOW PSEUDOPROGRESSION OF DISEASE

CRT = Chemoradiation therapy; LC = leakage correction; rCBV = relative cerebral blood volume.

ACRIN LUNG CANCER TRIAL RESULTS SHOW MORTALITY BENEFIT WITH LOW-DOSE CT

Initial results from the **National Lung Screening Trial (NLST)**, released in November 2010, show that current or former heavy smokers between the ages of 55 and 74 who underwent screening with low-dose helical CT at 33 participating sites experienced 20% fewer deaths from lung cancer than a group of peers who received screening with standard chest x-rays.

NLST is a collaboration between ACRIN and the Lung Screening Study group in NCI's Division of Cancer Prevention. Over 53,000 participants were recruited, more than 3,400 over its initial goal and more than 6 months earlier than expected. The study was designed to have 90% statistical power to detect progressively smaller mortality effects. With a large number of participants in a randomized, controlled trial, NLST provides clear evidence that a screening procedure can be effective in reducing mortality from lung cancer.

Starting in August 2002, NLST enrolled about 53,500 men and women at 33 trial sites nationwide over 20 months. Participants were required to have a smoking history of at least 30 pack-years and were either current or former smokers without signs, symptoms, or history of lung cancer. Pack-years are calculated by multiplying the average number of packs of cigarettes smoked per day by the number of years a person has smoked.

An ancillary finding of the study, which was not the main endpoint of the trial's design, showed that all-cause mortality (deaths due to any factor, including lung cancer) was 7% lower in those screened with low-dose helical CT than in those screened with chest x-ray. Approximately 25% of deaths in the NLST were due to lung cancer; other deaths were due to factors such as cardiovascular disease.

The ACRIN-NLST participating sites contributed to a biorepository (blood, sputum, urine), a tissue bank for future biomarker research, and the evaluation of quality-of-life issues, cost-effectiveness assessments, and the impact of screening with low-dose helical CT versus chest x-ray on smoking cessation.

Further analysis and research will be required to fully understand the implications of these results and those of the secondary aims. Analysis of the full data set related to the primary aim is ongoing.

The Cancer Intervention and Surveillance Modeling Network (CISNET) is a consortium of NCI-sponsored investigators who use statistical modeling to improve understanding of cancer control interventions in prevention, screening, and treatment. This modeling approach, which has been validated in several previous studies, can be used to guide public health research and priorities. The network is working on a project to study the efficacy of lung cancer screening for smokers in different age and exposure-level groups, based on the results of benefit for spiral CT screening found in the NLST for heavy smokers.

The results are based on six different models developed by members of the CISNET network. The centers that created these models are:

- Erasmus Medical Center, The Netherlands
- Fred Hutchinson Cancer Research Center, Seattle, Washington
- Pacific Institute for Research and Evaluation, Calverton, Maryland
- Rice University–MD Anderson Cancer Center, Houston, Texas
- Massachusetts General Hospital–Harvard Medical School, Boston
- Yale University, New Haven, Connecticut



American College of Radiology Imaging Network—A Cooperative Group for Multicenter Imaging Clinical Trials

ACRIN is a clinical trials network made up of affiliated investigators at more than 100 academic and community-based facilities in the United States and internationally. ACRIN's research encompasses the full range of medical imaging investigation, from landmark cancer screening trials to early-phase trials evaluating imaging biomarkers and novel imaging technologies. NCI established ACRIN to provide a flexible, responsive Cooperative Group for the systematic study of novel and maturing imaging technologies in clinical trials. Funded continually for more than a decade, ACRIN has established and instituted a formal, well-integrated clinical trials infrastructure that represents an exemplary, well-leveraged resource poised to provide significant contributions in the field of research on the comparative effectiveness of advanced imaging techniques.

ACRIN is addressing the special issues of imaging clinical trials (e.g., fast-developing technologies, quality control, operator dependence) while providing multidisciplinary, multi-institutional, interorganizational clinical research with a level of pertinence, validity, reliability, and generalizability that is not possible with single-institution observational studies.

In the face of several significant challenges (absence of a preexisting culture of prospective, controlled clinical trials in radiology; lack of control of patient referrals; and the expectation that radiology be service-oriented centers rather than

primary research units), ACRIN has established an intrinsically collaborative imaging clinical trials pipeline with ideas emerging from key scientific committees. It conducts clinical trials that have changed or influenced clinical practice and has established an information technology infrastructure sufficient to provide core services to other NCI- and NIH-sponsored groups. ACRIN serves as a primary source for the dissemination of imaging standards, qualification of sites, and core laboratories for PET and CT/MRI, as well as a National PET Registry and National Coverage Determinations for the Centers for Medicare and Medicaid Services.

Three primary scientific objectives frame the work of ACRIN:

1. Strategies for imaging surveillance of populations at high risk for cancer
2. Imaging approaches to the characterization of disease to guide targeted therapy
3. Biomarkers of therapeutic response from implementation in clinical trials and clinical care

Currently, there are significant delays in the time required to open a clinical trial with advanced imaging as an essential component. To shorten the process, NCI and its partners, ACRIN and the American College of Radiology, plan to develop standard operating procedures and a corresponding guideline for qualifying the 58 clinically focused NCI-designated Cancer Centers as Centers of Quantitative Imaging Excellence.

In May 2012, ACRIN merged its oncology research program with the Eastern Cooperative Oncology Group (ECOG), a membership-based research organization whose large-scale cancer treatment clinical trials for major diseases have changed the standard of care for cancer patients. The new ECOG-ACRIN Cancer Research Group designs and conducts clinical research along the cancer care continuum, with a focus on diagnostic, therapeutic, preventive, and biomarker-driven trials.

ACRIN and cancer imaging research have experienced groundbreaking developments within the last decade. Several ACRIN trials are now among the highest-profile clinical trials in NCI's portfolio, and a majority of trials involve collaboration with therapy cooperative groups or industries, as detailed in the following paragraphs.

MRI Predicts Overall Survival of Patients with Recurrent GBM Early on in Treatment Regimen with Bevacizumab.

Results of an ACRIN study demonstrate that changes in tumor enhancement on post-gadolinium T1-weighted MRI are highly predictive of which patients with recurrent GBM brain tumors will benefit from second-line therapy that includes the antiangiogenic drug bevacizumab.

An Open-Source and Automated Lesion Tracking Tool Significantly Increases Efficiency of Quantitative Image Interpretation. A pilot study evaluating radiologists' use of the electronic Physician Annotation Device (ePAD), a research project of ACRIN's Biomedical Informatics Committee, demonstrates a 23% increase in reader efficiency. ePAD is an image-viewing workstation that summarizes previous cancer lesion measurements and centralizes the process of recording and reporting them. One key advantage of this open-source tool is the ability to reduce the time spent by radiologists in this process.

Collaboration with CTEP

As a member of the CTEP Protocol Review Committee, CIP helps to identify opportunities for the evaluation of 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 for molecular and functional imaging endpoints. They also ensure that NCI consensus guidelines for acquisition and interpretation of various imaging modalities are implemented.

Phase 1 and 2 Program for the Evaluation of Molecular and Functional Imaging Agents

A contract-supported infrastructure supports phase 1 (safety) and phase 2 (preliminary efficacy) clinical trials of promising imaging agents. This mechanism is evaluating the use of molecularly targeted and functional imaging agents to assess therapeutic anticancer agents. The goal of the program is to provide a mechanism to expedite the development of promising molecular probes from the laboratory to IND status as well as early clinical trials. Established because its projects are not competitive in the regular grant pool, the program focuses on studying imaging agents in a standardized setting to evaluate reproducibility and translatability

across different histologies, which is necessary for assay development. The program is evaluating nine methodologies in tumors including non-small-cell lung cancer, breast, cervical, prostate, and glioma.

Phase 2 N01 Program

The Phase 2 N01 Program is a collaboration between CIP and CTEP that provides advanced imaging support for seven contractors comprised mostly of multi-institutional consortia, including a total of 22 NCI-designated Cancer Centers. Reflecting the need to incorporate novel imaging endpoints in the development of investigational agents, the re-competed Phase 2 N01 Program includes the integration of molecular imaging with investigational drug development in early clinical trials carried out with CIP- and CTEP-held IND agents. Participation in this program requires the inclusion of sites that have undergone qualification for advanced imaging and have identified nuclear medicine physicians and radiologists to be an integral part of the drug development team. This contract supports, in selective phase 2 treatment trials, the evaluation of molecular and functional imaging agents in a standardized, prospective fashion to enable evaluation of the core issues of preliminary efficacy and technical performance (reproducibility and quantitative vs. semiquantitative analysis) that are often lacking in current trials. The imaging agents and methods that prove successful in these early clinical trials can then be validated in larger studies through clinical trials in Cancer Centers or Cooperative Groups.

Early-Phase Clinical Trials in Imaging and Image-Guided Interventions

CIP sponsors an R21 Program Announcement, PAR-11-216, which opened in June 2011 and is designed to support clinical trials conducting preliminary evaluation of the safety and efficacy of imaging agents and imaging-guided interventions, among other indications. Compared with its predecessor, the Quick Trials PAR-08-147, the Early-Phase Clinical Trials Program Announcement has refined its purpose and primarily provides funding for the immediate conduct of phase 0, 1, or small phase 2 clinical trials that are designed and developed to facilitate completion within the 2-year funding period. This Program Announcement is designed to fill the gap for projects that seek to obtain early information about an imaging agent or imaging-guided intervention but do not yet have sufficient supporting data to compete successfully



for R01 funding. The imaging and imaging-guided intervention studies that prove successful in these early clinical trials can then be validated in larger studies through competitive R01 mechanisms or clinical trials in Specialized Programs of Research Excellence (SPoREs), Cancer Centers, or Cooperative Groups.

National NCI Steering Committees

CIP has active representation in the national disease-specific and investigational drugs steering committees that were developed based on the recommendations of the [Clinical Trials Working Group](#). Members of CIP's Clinical Trials Branch bring perspective to the trial planning process regarding available and developing imaging tools that can help evaluate cancer patients and inform their consequent management.

In 2010, the formation of a Clinical Imaging Steering Committee (CISC) was approved. A component of the network of committees recommended by CTWG, the Clinical Imaging Steering Committee is a forum for the extramural imaging and oncology communities to provide strategic input to NCI regarding the significant investment in imaging activities in clinical trials. The committee is charged with providing analyses of proposed clinical trial imaging concepts and imaging components of concepts and facilitating the sharing of ideas among a broad range of investigators, including radiologists and nuclear medicine physicians specializing in anatomic, molecular, and functional imaging; basic and translational scientists; NCI staff; community oncologists; community imagers; and patient advocates.

Biomarker Evaluation

CIP works with a variety of groups and task forces on guidelines defining the standards appropriate for adding biomarkers to therapeutic trials and for evaluating biomarkers alone. These guidelines will form the basis for funding opportunities for clinical trials in both early and late drug development. There are multiple collaborations with:

- Biomarker task force and clinical trial design task forces of the Investigational Drug Steering Committee

- Program for the Assessment of Clinical Cancer Tests
- Oncology Biomarker Qualification Initiative—two demonstration projects evaluating fluorodeoxyglucose PET as a biomarker in lymphoma and lung cancer
- Interagency Oncology Task Force

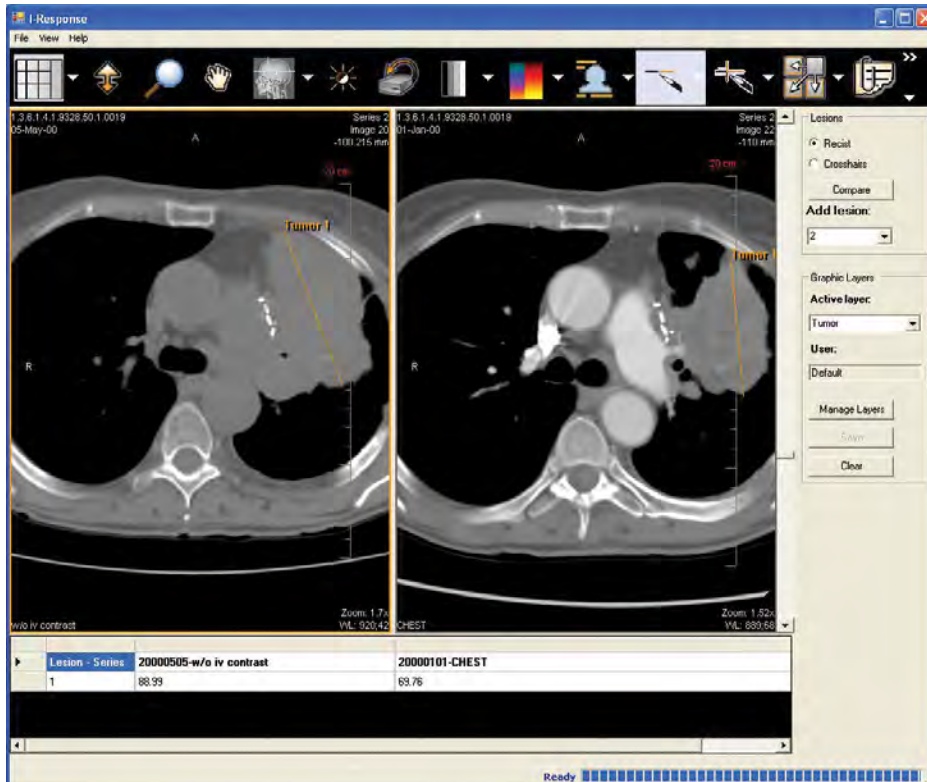
Response Assessment Evaluation

In association with the European Organisation for Research and Treatment of Cancer, NCI's Response Evaluation Criteria in Solid Tumors (RECIST) committee has developed updated guidelines for the assessment of response to therapy by anatomic imaging. These organizations are also formulating a joint guideline for the use of quantitative fluorodeoxyglucose PET in the assessment of tumor response in clinical trials. CIP is also supporting the development of a proposal for an infrastructure for the implementation of RECIST—an FDA-acknowledged imaging methodology for clinical trial endpoints where noninvasive imaging is required to track tumor change over time.

For the Agency for Healthcare Research and Quality, CIP staff members have served as reviewers for CMS-related evaluation of the application for Medicare reimbursement for fluorodeoxyglucose PET in glioma, pancreatic, ovarian, cervical, testicular, and small-cell lung cancer.

An NCI-CMS task force has successfully implemented strategies to extend CMS reimbursement for fluorodeoxyglucose PET studies in all NCI-sponsored phase 2 and 3 therapeutic clinical trials.

As part of the trans-NCI International Trials Collaboration Group, CIP has been working on identifying both barriers to and opportunities for enhanced participation in international trials.



RECIST MEASUREMENTS
TAKEN ON A LUNG TUMOR AT
TWO DIFFERENT TIMES

Clinical Trial Information Technology Infrastructure

As the underlying information technology infrastructure is critical to the successful conduct of clinical trials, CIP's Clinical Trials Branch has been collaborating with several entities to ensure that the information technology needs of conducting imaging clinical trials are met. For example, there is ongoing work with the Clinical Trials Reporting Program to ensure that imaging metadata are properly abstracted into that program's database, thus enabling accurate cross-portfolio analysis of the current use of advanced imaging in clinical trials. In addition, the Clinical Trials Branch has been working with the Cancer Data Standards Registry as partners in creating standardized Imaging Case Report Forms for use in all NCI-sponsored clinical trials. CIP will also be working closely with the newly formed National Cancer Informatics Program through its Imaging Working Group and Semantics Infrastructure Working Group to ensure that imaging needs are properly represented at the vocabulary and data element level.

Because of the efforts of CIP's Clinical Trials Branch, NCI has successfully launched the revised Adverse Event Expedited Reporting System, an electronic mechanism that will for the first time capture severe adverse events in imaging and imaging-guided intervention studies. In addition, a customizable clinical metadata system—C3D—has been successfully adopted in six imaging protocols at phase 1/2 contract sites and is being piloted in an ACRIN trial. Simultaneously, the common data element directory for imaging trials has been growing and is being shared across ACRIN and other Cooperative Groups trials.

CIP Website Usability Evaluation Project

In June 2012, CIP successfully competed for \$46,519 in NIH Evaluation Set-Aside funding from the Office of Program Evaluation and Performance to support the CIP Website Usability Evaluation Project. Working with a third-party contractor, CIP is using the funds to perform a comprehensive usability evaluation of the CIP website, which was redesigned in early 2011. The evaluation assesses the CIP website on a



number of different levels, including site traffic analysis, heuristic assessment, compliance with Section 508 requirements, and a number of monitored and scripted recordings of actual website users. Results from this evaluation project will be used to further enhance and refine the CIP website.

NCI Workshops Related to Clinical Imaging

- **NCI Diffusion-Weighted MRI Workshop—Current Status and Feasibility for Multicenter Clinical Evaluations, January 24–25, 2011:** This 2-day workshop brought together clinical and basic science experts in diffusion-weighted MRI with the intent of developing cross-communication and recommendations on incorporating diffusion-weighted MRI in multicenter clinical trials. The workshop has resulted in two proposed multicenter trial concepts evaluating diffusion-weighted MRI (ACRIN 6701 and ACRIN 6702) that were submitted by workshop participants to NCI and subsequently approved, as well as a white paper on clinical diffusion-weighted MR that is being readied for submission for publication.
- **NCI Cooperative Groups Radiotherapy–Imaging Workshop, May 19, 2011:** This workshop brought together representatives from the NCI Cooperative Groups and related consortia to assess the current imaging and information technological needs of these groups. DCTD used information gathered from this workshop to assess the current and near-future needs for the support of advanced imaging and radiotherapy in NCI cooperative group studies. As a result, the funding announcement for the restructured cooperative groups included an imaging and radiotherapy core services component.

IMAGE-GUIDED INTERVENTIONS

Extramural funding of research related to imaging-guided interventions at NCI includes traditional P01, R01, R21, R33, Small Business Technology Transfer (STTR) (R41/R42), and Small Business Innovation Research (SBIR) (R43/R44) grants, as well as a one-time issuance of four 2-year administrative supplements for SPOREs in 2005. Since 2002, there have been several IGI-related Program Announcements at NCI. These programs continue and include SBIR/ STTR, exploratory R21, and R01 initiatives:

- **Image-Guided Interventions (SBIR) PA-10-079 and (STTR) PA-10-080:** The overall goals of the IGI initiative are to provide support for the development and optimization of fully integrated cancer imaging, monitoring,

and therapy systems and the validation of integrated IGI systems through clinical evaluations. These initiatives were adopted by the NCI SBIR Development Center and were recently reissued.

- **Image-Guided Drug Delivery in Cancer (R01), PA-09-253:** The Imaging-Guided Drug Delivery initiative encourages innovative translational research in the development of quantitative in vivo imaging characterization of imaging-guided drug delivery in cancer, including characterizations of the target, delivery validation, and therapy response. This initiative supports research in the development of integrated imaging-based platforms for multifunctional and multiplexed drug delivery systems in cancer. Validation studies in nonhuman primates or large animal models and first-in-human studies directed toward translation of imaging-guided drug delivery technology into the clinic are appropriate for this initiative. A goal of this research is the development of minimally invasive or noninvasive “theranostic” (combined therapeutic and diagnostic) approaches to cancer in order to optimize the therapeutic ratio and to provide quantitative imaging evaluation of therapy. These grants also support the development of techniques to identify and modulate features of the tumor microenvironment for selective drug targeting and release. Imaging will not only play a major role in the development of such techniques but may well guide their delivery and release. The first application receipt date for this initiative was February 5, 2010, and resulted in 12 pending applications. This initiative was developed in collaboration with the NCI Alliance for Nanotechnology in Cancer.

Previous IGI Program Announcements include the Academic–Industrial Partnerships for the Development and Validation of In Vivo Imaging Systems and Methods for Cancer Investigators (R01) and Quantitative Imaging for Evaluation of Response to Cancer Therapies (U01).

For the future, the challenge for IGI is to apply image-guided techniques in unique applications to address tumor complexity and heterogeneity. Major emphasis will be placed on improved methods for rational and directed biospecimen identification and collection. It is critical to address the issue of co-correlation at vastly different physical scales and the integration of such 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 not trivial but essential to advancing the understanding of human cancer.

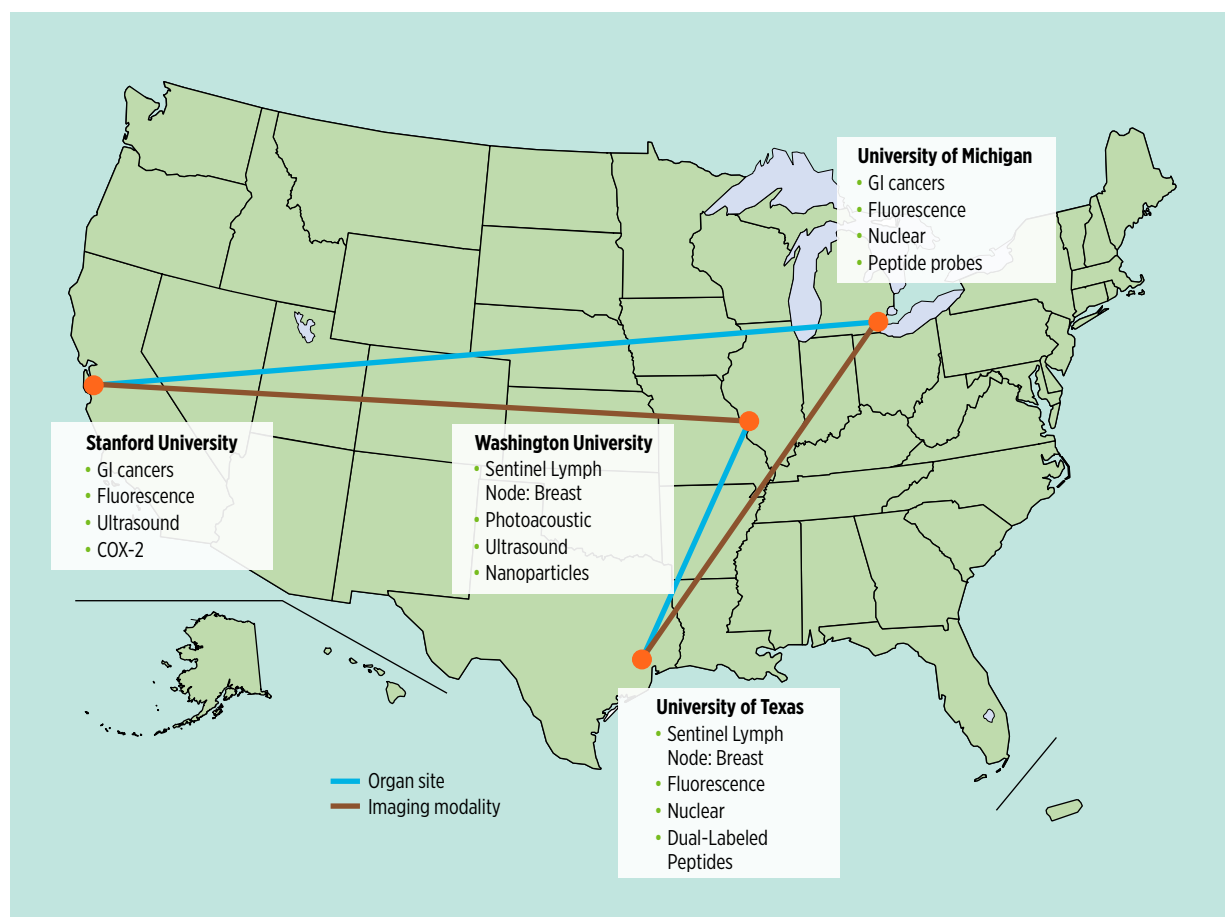
IMAGING TECHNOLOGY

Image Database Consortia

The creation of image database consortia has stimulated the development of more standardized methods for quantitative imaging by not only the academic research community but also professional imaging societies, such as the Radiological Society of North America, the Society of Nuclear Medicine, the American Association of Physicists in Medicine, and the International Society of Magnetic Resonance in Medicine. In addition, the FDA is reviewing how to incorporate these resources in the process of accelerating FDA approval of clinical decision tools.

Network for Translational Research for Optical and Multimodal Imaging Platforms

The Network for Translational Research will conclude in September 2013. The four teams that have participated in this cooperative agreement are now performing clinical trials with devices developed and optimized during the previous years of the program. The rationale behind this program has been to advance optical imaging methods toward clinical application by connecting them to imaging technologies that already have clinical recognition. Two teams are combining optical methods to ultrasound imaging, and the other two are combining optical methods to traditional nuclear imaging.



THE FOUR NETWORK FOR TRANSLATIONAL RESEARCH CENTERS AND METHODS OF INTERCONNECTIVITY



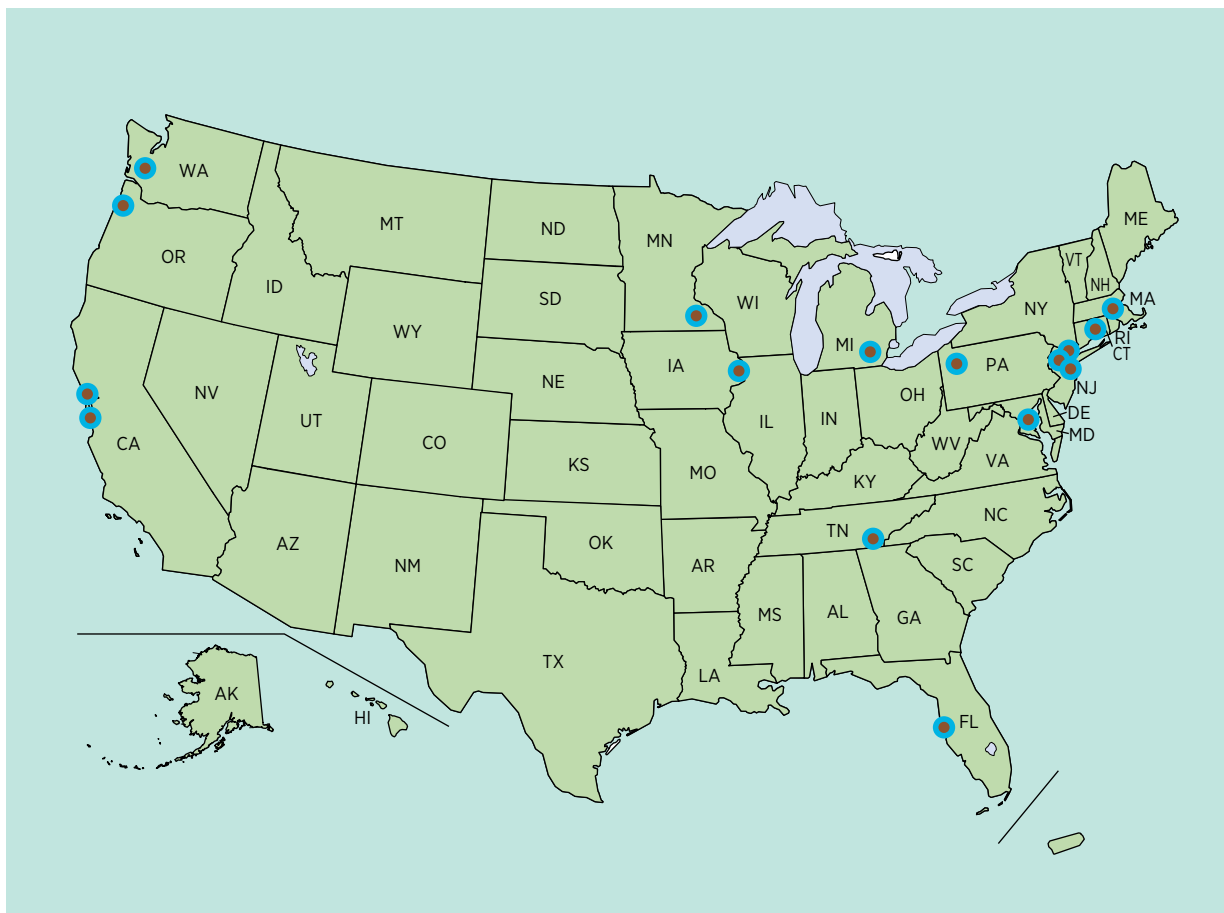
State-of-the-art optical technologies have been developed and optimized during the course of this program. Photoacoustic tomography, catheter-based fluorescence and confocal imaging, and high-sensitivity lymphatic imaging have advanced significantly as a result. The network members continue to be engaged in consensus-based decision making to develop ways for validating their various imaging techniques. The use of common tools such as the Siemens Sciport software package has facilitated this consensus process.

An important networking concept that was shown to be successful with the network was the use of working groups or cores that brought focus to common issues such as information technology, standards and validation methods, chemical probes, and instrumentation. These groups worked across the

technical teams, bringing avenues of communication across the network. Each group has published at least one article in peer-reviewed journals during the course of the program.

Quantitative Imaging Network for the Measurement of Therapy Response

The Quantitative Imaging Network (QIN) has grown to 16 research teams, each dedicated to the mission of improving the role of quantitative imaging for clinical decision making in oncology through the development and validation of data acquisition, analysis methods, and tools to tailor treatment to individual patients and to predict or monitor response to drug or radiation therapy. The multidisciplinary teams include oncologists, radiologists, imaging specialists, medical



NETWORK OF QIN SITES

Brigham & Women's Hospital, Columbia, H. Lee Moffitt Cancer Center, Johns Hopkins, Massachusetts General Hospital, Mayo Clinic, Memorial Sloan Kettering, Mt. Sinai, Oregon Health Sciences, U of Washington, UCSF, Stanford, U of Michigan, U of Iowa, U of Pittsburgh, Vanderbilt

physicists, computer informatics scientists, and others. An Executive Committee consisting of the principal investigators from each of the teams oversees the network and fosters interactions with clinical groups such as ECOG-ACRIN and the other clinical cooperative groups, the cancer centers, and global health initiatives. The QIN is regarded as an important technical resource to these groups.

The teams in QIN are studying cancers such as non-small-cell lung cancer, cancers of the central nervous system, breast cancer, and hepatic cell carcinoma (liver), to name only a few. Using single- and multisite clinical trials (phase 1 through phase 3), these teams are applying a variety of imaging modalities to make quantitative measurements of tumor response to therapies such as drug or radiation treatments. The network is developing algorithms that could eventually become clinical tools to help oncologists make decisions about cancer treatment pathways for individual patients. At present, data are being collected and curated on TCIA. In addition, a number of demonstration projects are under way across the network to evaluate data analysis methods across a number of different imaging platforms and commercial vendors.

In the coming years, the QIN plans to extend its networking to international teams. Groups in the United Kingdom, Canada, and India are looking to the QIN as a standard for efficient network operation and to join the network through submission of applications to NCI. In addition, the QIN will be expanding its membership through the acceptance of associate members. The network will consider research institutes with interests in quantitative imaging, industries (software firms, device manufacturers, and pharmaceutical companies), and other stakeholders in the quantitative imaging research process.

IMAGING INFORMATICS ARCHIVES AND INITIATIVES

The Cancer Imaging Archive

Much cancer imaging research requires access to large, standardized, purpose-built imaging collections. In 2010, CIP leveraged its long-term investment in the development of imaging curation and archiving technology to initiate a funded service that would fill the unmet needs of cross-

disciplinary image researchers for network access to clinical images. In response to an announced Request for Proposals, the **Electronic Radiology Laboratory** at Washington University in St. Louis was selected to host the archive service. To date, TCIA has more than 1,800 registered users and holds over 18 million images in 31 focused collections with extensive metadata and documentation. The archive sets the stage for real-time, multi-institutional image accessibility that could support protocol stratification strategies for a variety of adaptive trials and enable cross-disciplinary research on response measurement fundamentals and analysis reproducibility studies.

Submission and De-identification. Since TCIA would contain a large repository of open-access clinical imaging data, it was necessary to ensure the use of robust methodologies and tools that protect Private Health Information and preserve the scientific utility of the data. Thus, complementary to the archive was further refinement and testing of advanced, standards-based tools to enable de-identification of medical image data for public consumption. In collaboration with the Radiological Society of North America, a Clinical Trial Processor tool has been modified to operationalize current de-identification guidelines from Digital Imaging and Communications in Medicine. The methodology and its multilayered curation were published in the *Journal of Digital Imaging*. The significance of that advance was acknowledged by an editorial, and the methodology has proven its value by being incorporated in numerous institutional laboratories. CIP provides full research-focused de-identification services and makes its tools and knowledge base available to the community.

Full Support for Image Submission and Curation. TCIA has developed extensive procedures and is staffed with curation experts who review and mount the submitted images.

Easy Access to Purpose-Built Image Collections. TCIA maintains full documentation and meta-data for each of its collections, as well as a help desk and dedicated support staff.

Imaging-Genomics Research Support. A major goal of the TCIA service is to support collecting and making available clinical images of patients matched with the tissue specimens being analyzed by TCGA so that researchers could explore the connectivity of cancer image phenotypes with emerging publically accessible omic data. Data hosted in TCIA has



allowed researchers across the world to publish **new scientific findings**. Of particular note, four fully volunteer research teams focusing on tumor-specific, TCGA-related phenotype-to-genotype science explorations have been coordinated by the CIP Informatics team. These voluntary, non-funded teams teleconference weekly to share ideas. Five TCGA-matched imaging collections have been generated from data submitted by multiple institutions and have been made available to these teams, and many additional tissue types are currently in the accrual process. In less than 2 years, the group investigating glioma tissue types has generated four peer-reviewed publications and more than 25 conference abstracts.

Quantitative Imaging Network Support. TCIA facilitates data sharing among CIP's growing **Quantitative Imaging Network**. Fifteen grantees are actively hosting data on TCIA. In several cases, this data sharing is supporting cross-institutional algorithm validation bilaterally or as part of pilot challenges.

National Lung Screening Trial Data Portal. An additional use of the archive has been its availability to absorb and join the images of the two arms of the NLST trial images from both ACRIN and the Lung Screening Study group. The full image set from NLST is hosted under restricted access at TCIA along with a specially developed query tool that supports filtering on associated clinical data parameters. Infrastructure to support associated digital histopathology is being developed.

Community Awareness Building. Taking advantage of the image sharing that TCIA encouraged, CIP proceeded to address the goal of building community awareness and use of that resource. CIP led a joint workshop with the American College of Radiology in Reston, Virginia, in October 2011. The workshop, which was attended by more than 30 leading image researchers and publication editors, was intended to raise awareness in that community of the availability of tumor tissue omic and clinical data in the TCGA Data Portal and the case-matched clinical images residing in TCIA. Official publications resulting from that workshop have encouraged phenotype-to-genotype cross-disciplinary research and have led to considerable attention. CIP hosted meetings in 2011 and 2012 especially focused on imaging and genomics research during the annual meetings of the Radiological Society of North America to stimulate interest and cross-fertilization of ideas. In the 2012 meeting, more than 60 researchers heard 10 presentations of ground-breaking research efforts.

Future Informatics Initiatives

CIP continues to accumulate and host curated image collections in support of case-matched TCGA tissue data, as well as ongoing clinical trials and active QIN research activities. An important focus of ongoing and future informatics activities is to collect, curate, and characterize image data for cases populating TCGA datasets. So far, considerable progress has been made with at least five tissue types: glioblastoma, breast, renal, low-grade gliomas, and lung.

SELECTED PUBLICATIONS

CIP STAFF PUBLICATIONS

CIP staff made 52 oral and poster presentations at scientific conferences in 2011 and 2012.

NCI Image-Guided Drug Delivery Summit,

Tandon P, Farahani K. *Cancer Research*, 2011;71(2):314–317.

<http://www.ncbi.nlm.nih.gov/pubmed/21224356>

- This publication is a brief report of the Image-Guided Drug Delivery Summit, held in conjunction with the American Association for Cancer Research in 2010 to discuss the recent advances, barriers, opportunities, and regulatory issues related to the field of image-guided drug delivery.

Prospective comparison of combined 18F-FDG and 18F-NaF vs. 18F-FDG PET/CT imaging for detection of malignancy, Lin FI, Rao JE, Mittra ES, Nallapareddy K, Chengapa A, Dick DW, Gambhir SS, Jagaru A. *European Journal of Nuclear Medicine and Molecular Imaging*, 2012;39(2):262–270.

<http://www.ncbi.nlm.nih.gov/pubmed/22065013>

- This paper reports the results of a clinical trial in collaboration with investigators at Stanford University investigating the combined use of [18F]fluorodeoxyglucose ([18F]FDG) and [18F]sodium fluoride ([18F]NaF) in positron emission tomography (PET) imaging.

Treatment planning and volumetric response assessment for yttrium-90 radioembolization: semiautomated determination of liver volume and volume of tumor necrosis in patients with hepatic malignancy, Monsky WL, Garza AS, Kim I, Loh S, Lin TC, Li CS, Fisher J, Sandhu P, Sidhar V, Chaudhari AJ, Lin F, Deutsch LS, Badawi RD. *Cardiovascular Interventional Radiology*, 2011;34(2):306–318.

<http://www.ncbi.nlm.nih.gov/pubmed/20683722>

- This paper reports on the results of a study comparing the use of a new semiautomated algorithm for CT volumetric determination versus standard Response Evaluation Criteria in Solid Tumors (RECIST) measurements.

Repeatability of 18F-FDG uptake measurements in tumors: a metaanalysis, de Langen AJ, Vincent A, Velasquez LM, van Tinteren H, Boellaard R, Shankar LK, Boers M,

Smit EF, Stroobants S, Weber WA, Hoekstra OS. *Journal of Nuclear Medicine*, 2012;53(5):701–708.

<http://www.ncbi.nlm.nih.gov/pubmed/22496583>

- In this metaanalysis, the authors evaluated the repeatability of standardized uptake value (SUV) mean and maximum measurements, which is necessary in order to use semiquantitative measurements of FDG uptake in tumors.

The clinical evaluation of novel imaging methods for cancer management, Shankar LK. *Nature Reviews: Clinical Oncology*, 2012;9(12):738–744.

<http://www.ncbi.nlm.nih.gov/pubmed/23149888>

- This invited article outlines the activities undertaken by NCI to enhance the clinical evaluation of novel imaging agents and methods to improve cancer care.

Considerations in the development of circulating tumor cell technology for clinical use, Parkinson DR, Dracopoli N, Petty BG, Compton C, Cristofanilli M, Deisseroth A, Hayes DF, Kapke G, Kumar P, Lee JSh, Liu MC, McCormack R, Mikulski S, Nagahara L, Pantel K, Pearson-White S, Punnoose EA, Roadcap LT, Schade AE, Scher HI, Sigman CC, Kelloff GJ. *Journal of Translational Medicine*, 2012;10:138.

<http://www.ncbi.nlm.nih.gov/pubmed/22747748>

- This article summarizes current thinking on the value and promise of evolving circulating tumor cell technologies for the diagnosis, prognosis, and response to therapy of cancer patients, as well as accelerating oncologic drug development.

Cancer biomarkers: selecting the right drug for the right patient, Kelloff GJ, Sigman CC. *Nature Reviews: Drug Discovery*, 2012;11(3):201–214.

<http://www.ncbi.nlm.nih.gov/pubmed/22322254>

- This article highlights biomarkers that are expressed as a consequence of cancer development and progression, focusing on biomarkers that are most relevant for identifying patients who are likely to respond to a given therapy, as well as those that are most effective for measuring patient response to therapy.

A collaborative enterprise for multi-stakeholder participation in the advancement of quantitative imaging, Buckler AJ, Bresolin L, Dunnick NR, Sullivan DC. *Radiology*, 2011;258(3):906–914.

<http://www.ncbi.nlm.nih.gov/pubmed/21339352>



- The authors formed the Quantitative Imaging Biomarker Alliance, a collaborative program that draws from the successful precedent set by the Integrating the Healthcare Enterprise effort but is adapted to the needs of imaging science.

AACR-FDA-NCI Cancer Biomarkers Collaborative consensus report: advancing the use of biomarkers in cancer drug development, Khleif SN, Doroshow JH, Hait WN; AACR-FDA-NCI Cancer Biomarkers Collaborative. *Clinical Cancer Research*, 2010 1;16(13):3299–3318.

<http://www.ncbi.nlm.nih.gov/pubmed/20501613>

- In 2007, the AACR-FDA-NCI Cancer Biomarkers Collaborative stepped into the national effort to bring together disparate stakeholders to clearly delineate barriers to the use of biomarkers, to develop recommendations for integrating biomarkers into the cancer drug development enterprise, and to set in motion the necessary action plans and collaborations to see the promise of biomarkers come to fruition, efficiently delivering quality cancer care to patients.

THE CANCER IMAGING ARCHIVE

Lung Image Database Consortium (LDRI)–Image Database Resource Initiative (IDRI) Collection

The Lung Image Database Consortium (LIDC)–Image Database Resource Initiative (IDRI) image collection consists of diagnostic and lung cancer screening thoracic CT scans with marked-up annotated lesions. It is a web-accessible international resource for development, training, and evaluation of computer-assisted diagnostic methods for lung cancer detection and diagnosis.

The Lung Image Database Consortium (LIDC) and Image Database Resource Initiative (IDRI): a completed reference database of lung nodules on CT scans, Armato SG III, McLennan G, Bidaut L, McNitt-Gray ME, Meyer CR, Reeves AP, Zhao B, Aberle DR, Henschke CI, Hoffman EA, Kazerooni EA, MacMahon H, Van Beek EJ, Yankelevitz D, Biancardi AM, Bland PH, Brown MS, Engelmann RM, Laderach GE, Max D, Pais RC, Qing DP, Roberts RY, Smith AR, Starkey A, Batrah P, Caligiuri P, Farooqi A, Gladish GW, Jude CM, Munden RF, Petkovska I, Quint LE, Schwartz LH, Sundaram B, Dodd LE, Fenimore C, Gur D, Petrick N, Freymann J, Kirby J, Hughes B, Castele AV, Gupta S, Sallamm M, Heath

MD, Kuhn MH, Dharaiya E, Burns R, Fryd DS, Salganicoff M, Anand V, Shreter U, Vastagh S, Croft BY. *Medical Physics*, 2011;38(2): 915–931.

<http://www.ncbi.nlm.nih.gov/pubmed/21452728>

- Seven academic centers and eight medical imaging companies collaborated to provide the LIDC-IDRI database, a well-characterized repository of computed tomography (CT) scans. This article describes this public-private partnership, which demonstrates the success of a consortium founded on a consensus-based process.

The Cancer Genome Atlas–Glioblastoma Multiforme Collection

A novel volume-age-KPS (VAK) glioblastoma classification identifies a prognostic cognate microRNA-gene signature, Zinn PO, Sathyan P, Mahajan B, Bruyere J, Hegi M, Majumder S, Colen RR. *PLoS One*, 2012;7(8):e41522.

<http://www.ncbi.nlm.nih.gov/pubmed/22870228>

- Although several studies have established prognostic and predictive models for GBM based on age and Karnofsky Performance Status (KPS), very few have evaluated the prognostic and predictive significance of preoperative MRI. The authors present for the first time a biologically relevant and clinically applicable classification for GBM based on tumor volume, patient age, and KPS that can be determined easily and noninvasively upon patient admission.

Radiogenomic mapping of edema/cellular invasion MRI-phenotypes in glioblastoma multiforme, Zinn PO, Mahajan B, Sathyan P, Singh SK, Majumder S, Jolesz FA, Colen RR. *PLoS One*, 2011;6(10):e25451.

<http://www.ncbi.nlm.nih.gov/pubmed/21998659>

- The authors present the first comprehensive radiogenomic analysis using quantitative MRI volumetrics and large-scale gene- and microRNA expression profiling in GBM and propose a novel diagnostic method to screen for molecular cancer subtypes and genomic correlates of cellular invasion.

NETWORK FOR TRANSLATIONAL RESEARCH

Photoacoustic tomography: in vivo imaging from organelles to organs, Wang LV, Hu S. *Science*, 2012;335(6075):1458–1462.

<http://www.ncbi.nlm.nih.gov/pubmed/22442475>

- Photoacoustic tomography (PAT) can create multiscale, multicontrast images of living biological structures ranging from organelles to organs. The authors review the state of the art of PAT for both biological and clinical studies and discuss future prospects for this emerging technology.

In vivo imaging of ligand receptor binding with Gaussia luciferase complementation, Luker KE, Mihalko LA, Schmidt BT, Lewin SA, Ray P, Shcherbo D, Chudakov DM, Luker GD. *Nature Medicine*, 2011;18(1):172–177.

<http://www.ncbi.nlm.nih.gov/pubmed/22138753>

- The authors used Gaussia luciferase protein fragment complementation to quantify the binding of chemokine (C-X-C motif) ligand 12 (CXCL12) to chemokine (C-X-C motif) receptor 4 (CXCR4) and CXCR7 and used this imaging technique to quantify drug-mediated inhibition of CXCL12-CXCR4 binding in living mice. This imaging technology is expected to advance research in areas such as ligand-receptor interactions and the development of new therapeutic agents in cell-based assays and small animals.

Anchoring molecular chromophores to colloidal gold nanocrystals: surface-enhanced Raman evidence for strong electronic coupling and irreversible structural locking, Qian X, Emory SR, Nie S. *Journal of the American Chemical Society*, 2012;134(4):2000–2003.

<http://www.ncbi.nlm.nih.gov/pubmed/22257217>

- The authors report systematic surface-enhanced Raman studies of two organic chromophores, malachite green and its isothiocyanate derivative, that have very different functional groups for surface binding but nearly identical spectroscopic properties. The results indicate that isothiocyanate is an unusual anchoring group that enables strong electronic coupling between gold and the adsorbed dye, leading to more efficient chemical enhancement and higher overall enhancement factors.

Quantification of nanoscale density fluctuations by electron microscopy: probing cellular alterations in early carcinogenesis, Pradhan P, Damania D, Joshi HM, Turzhitsky V, Subramanian H, Roy HK, Taflove A, Dravid VP, Backman V. *Physical Biology*, 2011;8(2):026012.

<http://www.ncbi.nlm.nih.gov/pubmed/21441647>

- Studying the properties of nanoscale disorder, the authors found an increase in the disorder of human colonic epithelial cells in subjects harboring early stages of colon neoplasia. Their results suggest that increased nanoscale disorder correlates with the degree of tumorigenicity.

Seeing it through: translational validation of new medical imaging modalities, Aldrich MB, Marshall MV, Sevick-Muraca EM, Lanza G, Kotyk J, Culver J, Wang LV, Uddin J, Crews BC, Marnett LJ, Liao JC, Contag C, Crawford JM, Wang K, Reisdorph B, Appelman H, Turgeon DK, Meyer C, Wang T. *Biomedical Optics Express*, 2012;3(4):764–776.

<http://www.ncbi.nlm.nih.gov/pubmed/22574264>

- This paper describes the nature and goals of the Network for Translational Research for Optical Imaging.

Advancing the translation of optical imaging agents for clinical medical imaging, Sevick-Muraca EM, Akers W, Joshi B, Luker G, Contag C, Wang T, Azhdarinia A. *Biomedical Optics Express*, 2012;4(1):160–170.

<http://www.ncbi.nlm.nih.gov/pubmed/23304655>

- These authors propose a navigational approach (as opposed to a fixed “roadmap”) for translation of optical imaging agents and describe the pathways by which optical imaging agents are synthesized, qualified, and validated for preclinical testing and ultimately translated for “first-in-humans” studies using investigational optical imaging devices.

QUANTITATIVE IMAGING NETWORK

Comparison of proton magnetic resonance spectroscopy with fluorine-18 2-fluoro-deoxyglucose positron emission tomography for assessment of brain tumor progression, Imani F, Boada FE, Lieberman FS, Davis DK, Deeb EL, Mountz JM. *Journal of Neuroimaging*, 2012;22(2):184–190.

<http://www.ncbi.nlm.nih.gov/pubmed/21155917>

- The authors investigated the accuracy of high-field magnetic resonance spectroscopy and [18F]FDG PET for diagnosis of glioma progression after tumor resection,



stereotactic radiation, and chemotherapy, finding that magnetic resonance spectroscopy enhances detection of glioma progression.

Stability of 3'-Deoxy-3'-[18F]fluorothymidine standardized uptake values in head and neck cancer over time, 2Boles Ponto LL, Menda Y, Dornfeld K, Tewson TJ, Watkins GL, Sunderland J, Graham MM, Buatti J. *Cancer Biotherapy & Radiopharmaceuticals*, 2010;25(3):361–363.
<http://www.ncbi.nlm.nih.gov/pubmed/20578842>

- This study evaluated the consistency of 3'-deoxy-3'-[18F] fluorothymidine standardized uptake values (SUVs) over time during imaging of head and neck cancer. Correlations between the change in SUV with therapy were 0.90 for mean SUV and 0.89 for maximum SUV ($P < 0,0001$).

Investigation of the pharmacokinetics of 3'-deoxy-3'-[18F] fluorothymidine uptake in the bone marrow before and early after initiation of chemoradiation therapy in head and neck cancer, Menda Y, Ponto LL, Dornfeld KJ, Tewson TJ, Watkins GL, Gupta AK, Anderson C, McGuire S, Schultz MK, Sunderland JJ, Graham MM, Buatti JM. *Nuclear Medicine and Biology*, 2010;37(4):433–438.
<http://www.ncbi.nlm.nih.gov/pubmed/20447554>

- The kinetics of the uptake of 3'-deoxy-3'-[(18)F]fluorothymidine (FLT) in bone marrow before and early after initiation of chemoradiation therapy was investigated in patients with head and neck cancer. The results show a marked decrease in FLT uptake in irradiated bone marrow after 10 Gy of radiation therapy due to a significant decrease in the net phosphorylation rate of FLT.

Image-based biomarkers in clinical practice, Bayouth JE, Casavant TL, Graham MM, Sonka M, Muruganandham M, Buatti JM. *Seminars in Radiation Oncology*, 2011;21(2):157–166.
<http://www.ncbi.nlm.nih.gov/pubmed/21356483>

- Cancer treatment planning and assessment of treatment response based on magnetic resonance and PET are essential components of clinical practice and offer the potential of quantitative analysis. This article discusses a multimodal approach to selecting the best combination of imaging methods for clinical trials.

Characterization and identification of spatial artifacts during 4D-CT imaging, Han D, Bayouth J, Bhatia S, Sonka M, Wu X. *Medical Physics*, 2011;38(4):2074–2087.
<http://www.ncbi.nlm.nih.gov/pubmed/21626940>

- The authors characterize the artifacts occurring in helical four-dimensional CT imaging and propose a method that can automatically identify these artifacts.

Current and future trends in magnetic resonance imaging assessments of the response of breast tumors to neoadjuvant chemotherapy, Arlinghaus LR, Li X, Levy M, Smith D, Welch EB, Gore JC, Yankeelov TE. *Journal of Oncology*, 2010;2010.
<http://www.ncbi.nlm.nih.gov/pubmed/20953332>

- This paper highlights how dynamic contrast-enhanced MRI may be able to offer earlier and more precise information about the response to treatment for breast cancer in the neoadjuvant setting than is available through the use of Response Evaluation Criteria in Solid Tumors (RESIST).

Motion correction in diffusion-weighted MRI of the breast at 3T, Arlinghaus LA, Welch EB, Chakravarthy AB, Xu L, Farley JS, Abramson VG, Grau AM, Kelley MC, Mayer IA, Means-Powell JA, Meszoely IM, Gore JC, Yankeelov TE. *Journal of Magnetic Resonance Imaging*, 2011;33(5):1063–1070.
<http://www.ncbi.nlm.nih.gov/pubmed/21509862>

- This work provides a quantitative assessment of motion and distortion correction of diffusion-weighted images of the breast and presents results of registration on the mean apparent diffusion coefficient (ADC). Although reduced variance did not significantly change tumor region measures of ADC, it may have a significant impact on voxel-based analyses.

On the relationship between the apparent diffusion coefficient and extravascular extracellular volume fraction in human breast cancer, Arlinghaus LR, Li X, Rahman AR, Welch EB, Xu L, Gore JC, Yankeelov TE. *Magnetic Resonance Imaging*, 2011;29(5):630–638.
<http://www.ncbi.nlm.nih.gov/pubmed/21531106>

- Magnetic resonance imaging methods can measure apparent diffusion coefficient (ADC), which by conventional reasoning should be proportional to the extravascular extracellular volume fraction $[v(e)]$. The authors found no

statistically significant correlation between ADC and $v(e)$ for 1.5T and 3.0T images on either a voxel-by-voxel or region-of-interest basis.

Radiomics: the process and the challenges, Kumar V, Gu Y, Basu S, Berglund A, Eschrich SA, Schabath MB, Forster K, Aerts HJ, Dekker A, Fenstermacher D, Goldgof DB, Hall LO, Lambin P, Balagurunathan Y, Gatenby RA, Gillies RJ. *Magnetic Resonance Imaging*, 2012;30(9):1234–1248. <http://www.ncbi.nlm.nih.gov/pubmed/22898692>

- Radiomics is defined as the extraction and analysis of large amounts of quantitative imaging features from medical images obtained through CT, PET, or MRI. This article discusses the challenges accompanying this new field of study and proposed approaches to address them.

Phase II trial of induction gemcitabine and carboplatin followed by conformal thoracic radiation to 74 Gy with weekly paclitaxel and carboplatin in unresectable stage III non-small cell lung cancer, Bepler G, Dilling TJ, Wagner H, Hazelton T, Williams C, Chen DT, Greenberg H, Walsh F, Simon G, Tanvetyanon T, Chiappori A, Haura E, Stevens C. *Journal of Thoracic Oncology*, 2011;6(3):553–558. <http://www.ncbi.nlm.nih.gov/pubmed/21289520>

- Improving outcomes in non-small-cell lung cancer will require reducing both local and distal recurrence of disease. The authors conducted molecular studies on serially collected tumor specimens, finding that a regimen of gemcitabine–carboplatin with concurrent paclitaxel–carboplatin and 74-Gy radiation is safe and tolerable and has promising efficacy.

GRANTEE PUBLICATIONS

Tumor-specific imaging through progression elevated gene-3 promoter-driven gene expression, Bhang HE, Gabrielson KL, Latta J, Fisher PB, Pomper MG. *Nature Medicine*, 2011;17(1):123–129. <http://www.ncbi.nlm.nih.gov/pubmed/21151140>

- This paper reports that pairing an imaging reporter gene with a complementary imaging agent can be used to measure gene expression or protein interaction or to track gene-tagged cells in vivo. Progression elevated gene-3 (PEG-3) promoter-driven gene expression is used for facilitating cancer imaging and therapy.

A novel (19)F agent for detection and quantification of human dendritic cells using magnetic resonance imaging, Bonetto F, Srinivas M, Heerschap A, Mailliard R, Ahrens ET, Figdor CG, de Vries IJ. *International Journal of Cancer*, 2011;129(2):365–373.

<http://www.ncbi.nlm.nih.gov/pubmed/20839261>

- This paper reports a novel intracellular 19F labeling for tracking cell therapeutics in vivo by 19F MRI.

Hyperpolarized 13C MR spectroscopic imaging can be used to monitor Everolimus treatment in vivo in an orthotopic rodent model of glioblastoma, Chaumeil MM, Ozawa T, Park I, Scott K, James CD, Nelson SJ, Ronen SM. *Neuroimage*, 2012;59(1):193–201.

<http://www.ncbi.nlm.nih.gov/pubmed/21807103>

- This report presents an example of using hyperpolarized 13C magnetic resonance spectroscopic imaging to monitor the early metabolic response of orthotopic GBM tumors to Everolimus treatment.

MRI-based non-rigid motion correction in simultaneous PET/MRI, Chun SY, Reese TG, Ouyang J, Guerin B, Catana C, Zhu X, Alpert NM, El Fakhri G. *Journal of Nuclear Medicine*, 2012;53(8):1284–1291.

<http://www.ncbi.nlm.nih.gov/pubmed/22743250>

- This paper presents a novel approach for respiratory motion correction using simultaneous PET-MRI. Tagged MRI motion correction in simultaneous PET-MRI significantly improves lesion detection compared with respiratory gating and results in no motion correction while reducing radiation dose.

Imaging CXCR4 expression in human cancer xenografts: evaluation of monocyclam 64Cu-AMD3465, De Silva RA, Peyre K, Pullambhatla M, Fox JJ, Pomper MG, Nimmagadda S. *Journal of Nuclear Medicine*, 2011;52(6):986–993.

<http://www.ncbi.nlm.nih.gov/pubmed/21622896>

- The authors studied a novel PET agent for detecting chemokine receptor 4 (CXCR4)–dependent lesions in metastatic cancer. Their results showed that the agent is capable of detecting lesions in a CXCR4-dependent fashion with high target selectivity and may offer a scaffold for the synthesis of clinically translatable agents.



Choline metabolism in malignant transformation, Glunde K, Bhujwala ZM, Ronen SM. *Nature Review Cancer*, 2011;11(12):835–848.

<http://www.ncbi.nlm.nih.gov/pubmed/22089420>

- This paper summarizes the assessment of abnormal choline metabolism in oncogenesis and tumor progression by noninvasive magnetic resonance spectroscopy.

¹³C-Pyruvate imaging reveals alterations in glycolysis that precede c-Myc–induced tumor formation and regression,

Hu S, Balakrishnan A, Bok RA, Anderton B, Larson PE, Nelson SJ, Kurhanewicz J, Vigneron DB, Goga A. *Cell Metabolism*, 2011;14(1):131–142.

<http://www.ncbi.nlm.nih.gov/pubmed/21723511>

- This study applies hyperpolarized [¹³C]pyruvate magnetic resonance spectroscopic imaging to visualize glycolysis in de novo tumor formation and regression in a switchable model of Myc-driven liver cancer.

Discrimination of benign and malignant breast lesions by using shutter-speed dynamic contrast-enhanced MR imaging,

Huang W, Tudorica LA, Li X, Thakur SB, Chen Y, Morris EA, Tagge IJ, Korenblit ME, Rooney WD, Koutcher JA, Springer CS Jr. *Radiology*, 2011;261(2):394–403.

<http://www.ncbi.nlm.nih.gov/pubmed/21828189>

- The authors evaluated the accuracy of the shutter-speed approach compared with the standard approach of dynamic contrast-enhanced MRI pharmacokinetic analysis in the diagnosis of breast cancer. They found that the shutter-speed approach had significantly higher diagnostic specificity than the standard approach.

Locally advanced breast cancer: MR imaging for prediction of response to neoadjuvant chemotherapy—results from ACRIN 6657/I-SPY TRIAL,

Hylton NM, Blume JD, Bernreuter WK, Pisano ED, Rosen MA, Morris EA, Weatherall PT, Lehman CD, Newstead GM, Polin S, Marques HS, Esserman LJ, Schnall MD; ACRIN 6657 Trial Team and I-SPY 1 TRIAL Investigators. *Radiology*, 2012;263(3):663–672.

<http://www.ncbi.nlm.nih.gov/pubmed/22623692>

- This study compares MRI findings and clinical assessment for prediction of pathologic response to neoadjuvant chemotherapy in patients with stage II or III breast cancer.

Hyperpolarized ¹³C dehydroascorbate as an endogenous redox sensor for in vivo metabolic imaging,

Keshari KR, Kurhanewicz J, Bok R, Larson PE, Vigneron DB, Wilson DM. *Proceedings of the National Academy of Sciences of the United States of America*, 2011;108(46):18606–18611.

<http://www.ncbi.nlm.nih.gov/pubmed/22042839>

- This study reports hyperpolarized 1-[¹³C]dehydroascorbate as a new redox sensor to assess the vulnerability of normal and abnormal tissues to reactive oxygen species by magnetic resonance spectroscopy.

Analysis of cancer metabolism by imaging hyperpolarized nuclei: prospects for translation to clinical research,

Kurhanewicz J, Vigneron DB, Brindle K, Chekmenev EY, Comment A, Cunningham CH, Deberardinis RJ, Green GG, Leach MO, Rajan SS, Rizi RR, Ross BD, Warren WS, Malloy CR. *Neoplasia*, 2011;13(2):81–97.

<http://www.ncbi.nlm.nih.gov/pubmed/21403835>

- This paper is the first consensus document in the field of hyperpolarized magnetic resonance spectroscopic imaging that focuses on the challenges in rapid translation of this technology to assess cancer biology in clinical settings.

Single reporter for targeted multimodal in vivo imaging,

Niers JM, Chen JW, Lewandrowski G, Kerami M, Garanger E, Wojtkiewicz G, Waterman P, Keliher E, Weissleder R, Tannous BA. *Journal of the American Chemical Society*, 2012;134(11):5149–5156.

<http://www.ncbi.nlm.nih.gov/pubmed/22397453>

- This paper describes a multifaceted, highly specific reporter for multimodal in vivo imaging and its application for the detection of brain tumors.

Prostate cancer: feasibility and preliminary experience of a diffusional kurtosis model for detection and assessment of aggressiveness of peripheral zone cancer,

Rosenkrantz AB, Sigmund EE, Johnson G, Babb JS, Mussi TC, Melamed J, Taneja SS, Lee VS, Jensen JH. *Radiology*, 2012;264(1):126–135.

<http://www.ncbi.nlm.nih.gov/pubmed/22550312>

- This study assesses the feasibility of diffusional kurtosis imaging in distinguishing benign from malignant regions and low- from high-grade malignant regions within the peripheral zone of the prostate. Preliminary findings suggest that, compared with standard diffusion-weighted

imaging, diffusional kurtosis imaging has increased value in the assessment of prostate cancer.

Brain MR imaging at ultra-low radiofrequency power,

Sarkar SN, Alsop DC, Madhuranthakam AJ, Busse RF, Robson PM, Rofsky NM, Hackney DB. *Radiology*, 2011;259(2):550–557.

<http://www.ncbi.nlm.nih.gov/pubmed/21357520>

- This report presents a novel approach to decrease the absorbed radiofrequency power by two orders of magnitude at 1.5 T for MRI with image quality preserved within clinically acceptable imaging times.

Protein typing of circulating microvesicles allows real-time monitoring of glioblastoma therapy,

Shao H, Chung J, Balaj L, Charest A, Bigner DD, Carter BS, Hochberg FH, Breakefield XO, Weissleder R, Lee H. *Nature Medicine*, 2012;18(12):1835–1840.

<http://www.ncbi.nlm.nih.gov/pubmed/23142818>

- The authors report on a highly sensitive technique for profiling circulating microvesicles directly from blood samples of patients with GBM. This platform could provide both an early indicator of drug efficacy and a potential molecular stratifier for human clinical trials.

Impact of time-of-flight PET on whole-body oncologic studies: a human observer lesion detection and localization study,

Surti S, Scheuermann J, El Fakhri G, Daube-Witherspoon ME, Lim R, Abi-Hatem N, Moussallem E, Benard F, Mankoff D, Karp JS. *Journal of Nuclear Medicine*, 2011;52(5):712–719.

<http://www.ncbi.nlm.nih.gov/pubmed/21498523>

- The authors evaluated the benefit of fully three-dimensional, time-of-flight PET in clinical whole-body oncology, using human observers to localize and detect lesions in realistic patient anatomic backgrounds.

Self-assembling nanocomplexes by combining ferumoxytol, heparin and protamine for cell tracking by magnetic resonance imaging,

Thu MS, Bryant LH, Coppola T, Jordan EK, Budde MD, Lewis BK, Chaudhry A, Ren J, Varma NR, Arbab AS, Frank JA. *Nature Medicine*, 2012;18(3):463–467.

<http://www.ncbi.nlm.nih.gov/pubmed/22366951>

- This study reports a new magnetic cell-labeling approach to form self-assembling nanocomplexes that can effectively label cells for in vivo MRI.

Prostate cancer: prediction of biochemical failure after external-beam radiation therapy—Kattan nomogram and endorectal MR imaging estimation of tumor volume,

Westphalen AC, Koff WJ, Coakley FV, Muglia VF, Neuhaus JM, Marcus RT, Kurhanewicz J, Smith-Bindman R. *Radiology*, 2011;261(2):477–486.

<http://www.ncbi.nlm.nih.gov/pubmed/21873255>

- The authors sought to determine whether MRI and magnetic resonance spectroscopic imaging findings could improve predictions made with the Kattan nomogram for radiation therapy. They found that MRI data improved the prediction of biochemical failure with the Kattan nomogram after external-beam radiation therapy for prostate cancer.

Translation of near-infrared fluorescence imaging technologies: emerging clinical applications,

Sevick-Muraca, EM. *Annual Review of Medicine*, 2012;63:217–231.

<http://www.ncbi.nlm.nih.gov/pubmed/22034868>

- This review described emerging near-infrared fluorescence imaging technology in the context of nuclear imaging technologies that remain the “gold standard” of molecular imaging.

Combined in vivo molecular and anatomic imaging for detection of ovarian carcinoma-associated protease activity and integrin expression in mice,

Hensley HH, Roder NA, O’Brien SW, Bickel LE, Xiao F, Litwin S, Connolly DC. *Neoplasia*, 2012;14(6):451–462.

<http://www.ncbi.nlm.nih.gov/pubmed/22787427>

- This study demonstrates the feasibility and sensitivity of fluorescence molecular tomography for the detection and quantification of tumor-associated biologic targets in mouse ovarian tumors.



CANCER IMAGING
PROGRAM **CIP**

2012 PROGRAM ACCOMPLISHMENTS

CANCER THERAPY EVALUATION PROGRAM





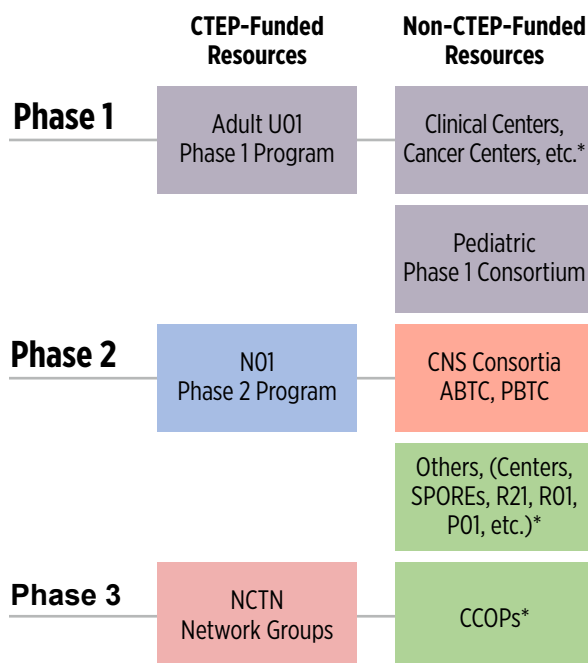
OVERVIEW

The Cancer Therapy Evaluation Program (CTEP) coordinates the clinical treatment development program of the Division of Cancer Treatment and Diagnosis (DCTD). 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 utilized to move the therapy from first-in-human safety trials through definitive, randomized, controlled trials that meet U.S. Food and Drug Administration (FDA) requirements for approval.

CTEP staff directs the monitoring of more than 800 cancer treatment clinical trials that are conducted throughout the nation. These trials are funded by more than 40 cooperative agreements and contracts, and involve about 25,000 patients annually. This level of activity makes CTEP the largest publicly funded clinical trials organization in the world. The program is responsible for many of the major studies that have altered cancer treatment over the last three decades. The trials are conducted by clinical trials networks of U.S. and international members, within which are contained both considerable scientific expertise and accrual capability. The trial networks, supported in whole or in part by CTEP, are aligned as shown in the accompanying diagram.

CTEP staff members comprise physicians, scientists, nurses, pharmacists, and other specialists. Transitioning from phase 0 to phase 3 studies requires a full complement of clinical trials services that reside in CTEP's seven branches:

1. The **Investigational Drug Branch** is responsible for clinical trials of new chemotherapeutic and biological antitumor investigational agents that aim to evaluate their pharmacokinetic, pharmacodynamic, and antitumor efficacy.
2. The **Clinical Investigations Branch** develops and implements disease-oriented treatment strategies across the spectrum of human malignancies through strategy and consensus meetings and treatment program development. Whereas the **Investigational Drug Branch** is drug focused (i.e., developing new agents in early phase trials), the **Clinical Investigations Branch** is disease focused (i.e., integrating investigational agents with already existing standard treatments in phase 2 and especially phase 3 trials). Both branches intersect in the phase 2 interface and work collaboratively to bring these agents to patients as fast as possible.



*Non-CTEP-funded resources. ABTC = Adult Brain Tumor Consortium; CCOPs= Community Clinical Oncology Programs; CNS = central nervous system; NCTN = National Clinical Trials Network; PBTC = Pediatric Brain Tumor Consortium; SPOREs = Specialized Programs of Research Excellence.

3. The **Clinical Grants and Contracts Branch** manages two investigator-initiated grant programs—Clinical Oncology and Surgical Oncology—that encompass the development of clinical agents at the molecular, cellular, and whole-body levels as well as the development of treatment regimens and methodologies.
4. The **Regulatory Affairs Branch** ensures that CTEP meets its regulatory responsibilities as the sponsor of Investigational New Drug applications (INDs) and that the program fosters partnerships with industry by implementing collaborative agreements.
5. The **Pharmaceutical Management Branch** authorizes and distributes CTEP-sponsored new agents to registered physicians and oversees annual investigator registration.
6. The **Clinical Trials Monitoring Branch** manages quality assurance and quality control of clinical therapeutic trials sponsored by DCTD and of prevention trials sponsored by the Division of Cancer Prevention.

7. The **Clinical Trials Operations and Informatics Branch** manages the Protocol and Information Office and is responsible for the CTEP Enterprise System (the relational database that allows all CTEP branches to conduct their operations) and development of all new software and hardware needs.

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. CTEP holds more than 100 INDs 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 the diagram) adds significantly to the industry drug development plan, which is focused primarily on FDA registration. 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, a particular niche filled by CTEP in recent years involves early combination trials with experimental agents from two or more companies. CTEP has been able to forge multicompany partnerships through the creation of a novel intellectual property (IP) agreement that enables collaborators to share IP when they co-develop drug combinations. More than 49 novel combinations of targeted investigational agents have entered into clinical trials sponsored by CTEP in recent years.

When promising signals of biologic activity are seen in phase 2 trials performed by CTEP's early-trials networks, the Cooperative/Network Group Program (i.e., the National Clinical Trials Network [NCTN]) is prepared to move these ideas into controlled, randomized, phase 3 trials. Some recent examples include:

- **Phase 3 Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma:** This phase 3 study was recently approved to evaluate a new molecularly targeted therapy for a specific subset of patients with a rare disease

in a potentially curative clinical setting. This trial follows a 2009 scientific advance that demonstrated a survival advantage for patients who have advanced gastric and gastroesophageal junction adenocarcinoma that overexpresses HER2 and who received trastuzumab in combination with chemotherapy. This trial will screen 500 to 700 patients to identify the estimated 25–32% of patients with tumors that overexpress HER2 in order to evaluate the benefit of adding trastuzumab to trimodality adjuvant therapy in esophageal adenocarcinoma. This trial was activated in January 2011, and as of January 2013, 218 patients had been screened. Of those screened, 35% were identified with HER2-positive tumors, and 72% of those with HER2-positive tumors were randomized.

- **Chimeric 14.18 Monoclonal Antibody:** CTEP sponsored a study of chimeric 14.18 monoclonal antibody in neuroblastoma as a complement to the Children's Oncology Group (COG) phase 3 study to allow for FDA approval of this novel treatment regimen.
- **RxPONDER: A Clinical Treatment Trial for Positive-Node, Endocrine-Responsive Breast Cancer:** This intergroup trial, led by SWOG (formerly the Southwest Oncology Group), is a randomized clinical trial of standard adjuvant endocrine therapy with or without chemotherapy in patients with one to three positive lymph nodes and hormone receptor-positive, HER2-negative breast cancer with a recurrence score of 25 or lower. This phase 3 study is designed to determine the utility of the Oncotype Dx test, a 21-gene assay that provides an individual, quantitative assessment of the likelihood of disease recurrence, to determine the value of chemotherapy in women with hormone receptor-positive breast cancer and one to three positive lymph nodes. The trial will randomize approximately 4,000 patients and complete accrual in 2017.

CTEP's trial systems have undergone rigorous evaluation by National Cancer Institute (NCI) scientific advisory boards, Congress, and the public. This is understandable and appropriate, as clinical trials represent for the public its most tangible contact with the promise offered by cancer research. Consecutive reviews of CTEP and NCI clinical trials in general have called for greater efficiency in developing trials and enrolling patients, enhanced use of technology to improve methodology and reduce costs, and more transparent and prioritized review systems to ensure that the most important trials are performed. The NCI has responded to these challenges with sweeping changes in how it conducts trials and reviews science. The most important changes include:



- **Disease-Specific Steering Committees:** Committees focused on specific diseases refine, evaluate, and prioritize new agents and trial concepts. The committees include leadership from all of NCI's major clinical trial mechanisms (Cooperative Groups and Network Groups, Specialized Programs of Research Excellence [SPORs], early clinical trial networks) as well as community physicians, patient advocates, ad hoc experts, and NCI staff. Disease-specific steering committees conduct Clinical Trials Planning Meetings to evaluate ideas with the relevant investigator community and provide evaluations that form the basis for prioritizing the most important trial questions for each cancer type. Each committee member has one vote (NCI staff represent less than 25% of the committee).
- **Central Institutional Review Board:** Numerous surveys of investigators have indicated that institutional review boards pose a significant barrier to the speedy development of clinical trials and enrolling patients in trials. NCI responded by creating the first government-sponsored central institutional review board (CIRB) in 1999. The CIRB has expanded to review all phase 3 adult Cooperative Group trials (more than 200 trials) and all trials performed by COG (an NCTN group). In 2012, the CIRB received accreditation by the Association for the Accreditation of Human Research Protection Programs. Three hundred institutional review boards, representing more than 700 sites nationwide, have joined the CIRB, which plans to expand its scope to include multicenter phase 1 and 2 clinical trials. NCI trials that are reviewed by the CIRB no longer have to go through duplicative review by hundreds of NCTN sites. This single review can reduce workloads at sites and reduce costs, which in turn can encourage sites to participate in more trials. Additionally, the reduction of the CIRB review time to 4 weeks also helps to speed the process of protocol implementation.
- **Cancer Trials Support Unit (CTSU):** The CTSU supports the newly configured Cooperative Group program, renamed the NCI National Clinical Trials Network (NCTN). The CTSU offers a contract mechanism through which all NCTN trials are made available for patient enrollment via a single online menu. This approach allows investigators in any group to enter patients on relevant trials, regardless of whether they belong to the group leading the trial. The CTSU has matured and is now a one-stop shop for online regulatory filing, patient registration, and data management. With the transformation of the Cooperative Group program into the NCTN program, the CTSU will serve as the common centralized enrollment system for all trials supported by the program.
- **CTEP Enterprise and Clinical Trials Systems:** CTEP has embraced standards and consistency in the design, monitoring, and reporting of clinical trials. Among the many IT products whose use CTEP currently requires in the trials it sponsors, those most frequently accessed are:
 - Common Case Report Forms and Common Data Elements
 - Adverse Event Expedited Reporting System
 - Common Data Update System
 - Clinical Data Management System (MediData Rave)
- **Operational Efficiency:** On the basis of recommendations from an NCI advisory board, CTEP and its investigator community have agreed to collaborate on new timelines to promote rapid implementation of protocols. Phase 1 and 2 studies are now targeted to move from LOI (or concept stage) to protocol activation within 7 months, and phase 3 studies will target a 10-month timeline. Achievement of these goals will represent a 75% improvement over past timelines. This improvement will be achieved by employing new personnel to assist clinical trialists, leveraging technology to track timelines and monitor performance, and providing incentives to investigators by rewarding compliance. In addition, absolute deadlines have been introduced for all trials that will result in disapproval of a trial should it fail to meet the deadline.
- **Informatics Technology Innovation:** In 2012, CTEP's Regulatory Affairs Branch and Clinical Trials Operations and Informatics Branch received an award from the **Four Bridges Forum (4BF)** in the Collaboration category for innovative uses of public key infrastructure (PKI) and PKI bridges. 4BF is a coalition of national agencies and organizations made up of federal agencies, the pharmaceutical and health care industries, aerospace and defense contractors, and colleges and universities that came together to create a secure cyber-infrastructure in which to share sensitive and confidential information. The award was presented to CTEP for its pioneering use of PKI-based interoperable digital identities allowing government and industry cancer researchers to accelerate the startup phase of clinical trials by securely accessing, reviewing, signing, and exchanging cloud-based documents. In addition to speeding the process, the use of digital identities dramatically reduced costs.

JEFFREY S. ABRAMS

ASSOCIATE DIRECTOR



Jeffrey S. Abrams, MD, has led CTEP as Associate Director since June 2007. Dr. Abrams has been a member of CTEP since 1993, when he joined as a clinical research scientist to oversee the breast cancer treatment trials portfolio and participate in clinical trials at the National Institutes of Health (NIH) Clinical Center. In 2004, Dr. Abrams was appointed Chief of the Clinical Investigations Branch and was responsible for the direction of the NCI Clinical Trials Cooperative Group program. As Associate Director, Dr. Abrams supervises a staff that collectively oversees, reviews, and coordinates more than 150 active phase 3 trials and more than 700 early-phase trials in all varieties of cancer and all modalities of treatment. He pioneered the Cancer Trials Support Unit, which has established a national network of physicians to participate in NCI-sponsored phase 3 treatment trials, and has overseen the implementation of NCI's Central Institutional Review Board.

Dr. Abrams, whose NCI achievements have been recognized by numerous NIH Director and Merit Awards, is the author of more than 80 publications in the field of breast cancer and clinical trials and numerous book chapters.

PROGRAM ACCOMPLISHMENTS

INVESTIGATIONAL DRUG BRANCH

The **Investigational Drug Branch (IDB)** oversees the portfolios of approximately 100 IND agents, nearly all of which are being developed under agreements with biotechnology and pharmaceutical companies. IDB staff members evaluate agents for potential clinical development by NCI, initiate drug development plans, review study proposals, and oversee the conduct and analyze the data of trials under CTEP INDs. IDB carries out mostly phase 1 and 2 studies, focusing entirely on acquiring and developing novel agents. Staff members meet regularly with pharmaceutical companies, serve on multiple NCI drug development committees, and interact with academic, industry, and FDA investigators. A major focus of CTEP drug development is exploration of investigational drug combinations based upon strong rationale and preclinical data. CTEP is well positioned to be a leader in testing novel combinations because of its large IND portfolio and long tradition as a safe harbor for IP.

NCI Investigational Drug Steering Committee

The **NCI Investigational Drug Steering Committee (IDSC)** was established in November 2005 on the recommendation of the Clinical Trials Working Group, which reviewed the national clinical research enterprise. The IDSC is composed of a steering committee and nine task forces. Members of the IDSC include the principal investigators of NCI's early drug development grants and contracts, representatives from the Cooperative Groups, a patient advocate, biostatisticians, and NCI staff.

IDSC goals are to:

- Provide external strategic input into the prioritization of phase 1 and 2 trials for new agents
- Increase transparency of the prioritization process
- Optimize clinical trial designs to improve effectiveness of early-phase therapeutics



Date	Agent	Class
October 2009	ARQ197	cMet inhibitor
	AT13387	Hsp90 inhibitor
September 2010	MLN-8237	Aurora kinase A inhibitor
July 2010	AMG386	Angiopoietin 1/2 inhibitor
January 2011	MK-1775	Wee1 inhibitor
	MK-8776	Chk1 inhibitor
June 2011	Ipilimumab	Anti-CTLA4 antibody
October 2011	L32711	SMAC mimetic
	Ibrutinib	BTK inhibitor
	Cabozantinib	cMet inhibitor



CTEP DRUG DEVELOPMENT PLANS REVIEWED BY THE IDSC

The phase 1 Clinical Trials Program uses the U01 grant mechanism to achieve its goals. In this program, there are 14 Cooperative Agreements with 17 NCI-designated Cancer Centers distributed across the United States and Canada. The phase 2 N01 Clinical Trials Program comprises seven contracts and includes 29 NCI-designated Cancer Centers distributed across the United States and Canada. These contracts underwent re-competition in 2010.

Accomplishments

Solicitations for Trials. Fifteen solicitations for trials were issued in 2011–2012, and four more are currently planned for 2013 (see table). Additional agents are being reviewed by the NCI Experimental Therapeutics (NEXT) program.

Letters of Intent. During 2011–2012, 15 new-agent solicitations were issued, and 60 of 295 (20%) solicited LOIs were approved. Of 255 unsolicited LOIs, 70 (27%) were approved.

Phase 1 U01 Program. Since the early 1970s, CTEP has managed the Early-Phase Experimental Therapeutics Program with Phase 1 Emphasis, now known as the Phase 1 U01 program. This is an early therapeutics development program that has contributed to the clinical development of many anticancer agents. Through this program, hundreds of agents, both conventional and immunologic, have been made available for collaborative development. CTEP currently holds approximately 125 INDs for investigational agents. Effective development of these agents requires a systematic

development plan for phase 1 trials and pilot trials, followed by phase 2 trials that, it is hoped, will conclude in definitive phase 3 trials.

From 2008 to 2012, investigators submitted 285 LOIs. A total of 15 mass solicitations were issued during this period, resulting in 48 of 173 (28%) LOI submissions approved for protocol development. In addition, 46 of 88 (52%) unsolicited LOIs were approved. During this same period, 100 studies were administratively completed; of these, 68 were phase 1 trials. During this same period, 79 trials were completed (21 were administratively completed). Of the 118 trials closed to accrual or accrual and treatment, 69 were phase 1 studies. Other studies completed or closed during this period were pilot studies, phase 1/2 investigations, or early phase 2 studies that fit within the scope of the work performed using U01 grant funding. Currently there are 105 active trials of 38 investigational agents and 85 combinations with an NCI investigational agent. The CTEP phase 1 trials account for more than 50% of phase 1 trials (excluding pediatric, Center for Cancer Research studies, and others) performed under NCI sponsorship, and all CTEP-sponsored first-in-human studies were conducted in the Phase 1 U01 program.

The agent classes studied under the Phase 1 U01 program 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 cancer stem cell inhibitors, tyrosine kinase inhibitors, epidermal growth factor receptor inhibitors, angiogenesis inhibitors, mTOR inhibi-

Year	Agent	Mechanism of Action
2011	AFP-464	DNA cross-linking agent
	AMG 386	Antiangiogenic targeting the Ang-Tie2 pathway
	MLN8237 (alisertib)	Aurora kinase A inhibitor
	TRC 105	Chimeric antiangiogenic mAb that binds CD105
	ARQ 197 (tivantinib)	c-MET inhibitor
	Ipilimumab (MDX-010)	anti-CTLA-4 mAb
	2012	PCI-32765
Cabozantinib (XL184)		Inhibitor of multiple RTKs, including c-Met and VEGFR2
GSK2118436 (dabrafenib)		BRAF inhibitor (including V600X mutant BRAF)
MK-1775		Wee1 kinase inhibitor
MK-8776 (formerly SCH9000076)		CHK-1 inhibitor
GSK1120212 (trametinib)		MEK-1 inhibitor
AZD1480		JAK2 inhibitor
MLN0128 (formerly INK128)		TORC1/TORC2 inhibitor
Planned for 2013	AMG103 (formerly MT103) (blinatumomab)	Bispecific anti-CD3/anti-CD-19 mAb
	AT13387	Hsp90 inhibitor
	BMS-936558	Anti-PD-1 mAb
	MK-3475	Anti-PD-1 mAb
	TL32711 (BIRINAPANT)	SMAC mimetic
	POMALIDOMIDE	Immunomodulatory drug

mAb = monoclonal antibody; RTK = receptor tyrosine kinase; VEGFR = vascular endothelial growth factor receptor.

tors, cell cycle inhibitors, histone deacetylase inhibitors, proteasome inhibitors, heat shock protein inhibitors, poly(ADP ribose) polymerase (PARP) inhibitors, novel cytotoxics, and angiopoietin 1 and 2 inhibitors. Types of agents under evaluation include small molecules, antibodies, antibody–drug conjugates, vaccines, and an oncolytic virus.

The Phase 1 U01 program has been characterized by special populations (organ dysfunction), novel study designs (accelerated titration, isotonic design, continual reassessment method, and other various randomized designs), and unique translational (pharmacodynamic, pharmacokinetic, BRCA-mutation) efforts. Ongoing program efforts will focus on transforming current approaches to include molecular

characterization of all patients as appropriate, increasing consortium collaboration through the establishment of a Phase 1 network, and taking a team-based scientific approach to the development of experimental therapeutics projects.

Phase 2 N01 Program. The Early Therapeutics Development with Phase 2 Emphasis, now the Phase 2 N01 Program, has created a flexible platform so that early clinical trials consortia are prepared to rapidly evaluate the biologic effects of NCI-sponsored anticancer agents on their molecular targets and to determine clinically relevant correlates. The current program includes seven contracts with consortia that comprise 29 NCI Cancer Centers distributed across the United States and Canada.



THE PHASE 2 N01 NETWORK

Member Institutions and Consortia:

- MD Anderson California Consortium**
UC Davis, City of Hope, USC, U of Pittsburgh
- University of Chicago**
U of C network, U of Michigan, U of Maryland, College of Wisconsin
- NY Phase 2 Consortium**
Montefiore, Weill Cornell, Mt. Sinai, Columbia, North Shore, U Conn, Sydney
- Mayo Phase 2 Consortium**
U of Wisconsin, Johns Hopkins, Wayne State, Washington U, UCSF, CTRG Pacific Rim), Mayo Arizona and Jacksonville, U of Colorado, U of Iowa
- Memorial Sloan-Kettering**
- Princess Margaret Phase 2 Consortium**
Hamilton, Kingston, London, Edmonton, McGill, Halifax, Sunnybrook, Vancouver, Roswell Park, Fox Chase
- Ohio State University**
- Southeast Phase 2 Consortium**
Moffitt, UNC, Vanderbilt, Emory, Virginia Commonwealth, Medical University of South Carolina

The network currently has about 800 patients enrolled in approximately 90 clinical trials. Approximately 50 investigational combination trials have been initiated under the program, including 10 involving more than one unapproved agent [“novel/novel”]. Examples include:

- **Protocol 8867:** Randomized Phase II Trial of MAP Kinase Inhibition with AZD6244 Hydrogen Sulfate in Combination with MK-2206 in Patients with BRAF V600E Mutant Advanced Melanoma Who Have Previously Failed Prior Therapy with a Selective BRAF Inhibitor (Principal Investigator: Jeff Sosman, MD, Southeast Phase II Consortium). This trial targets an ever-increasing and important population in metastatic melanoma. Melanoma

patients whose tumors express a BRAF V600 mutation are very sensitive to treatment with BRAF inhibitors such as RG7204 and GSK436. In most patients, however, the disease becomes refractory to this treatment within a year and begins to progress. The trial is aimed at this population of patients. It examines the use of a MEK inhibitor alone (AZD6244) or in combination with an AKT inhibitor, MK-2206, and includes a number of correlative studies.

- **Protocol 8233:** A Phase 2 Trial of Temozolomide and Bevacizumab in Patients with Endometrial, Ovarian, Hepatocellular Carcinoma, Carcinoid, and Islet Cell Cancer (Principal Investigator: Charles Erlichman, MD,

Mayo Clinic). Based on single-agent data in patients and preclinical data for the combination, approximately 250 patients have been enrolled in five separate tumor cohorts. All seven N01 contractors are participating. This trial rapidly enrolled via the CTSU, which managed registration and data, and electronic remote data capture and blood and tumor specimen collection for future analysis has been completed for all patients. Although four of the five tumors that were studied failed to demonstrate adequate activity to justify further evaluation, 13 of 25 (52%) patients with islet cell tumors exhibited partial responses that were confirmed by an independent review. This response rate is far greater than has been seen with either agent alone, and the agent combination will be studied further in this disease.

These trials are for multiple cancer indications, including rare diseases not likely to be evaluated in company-sponsored trials, such as hepatobiliary cancer and adenoid cystic carcinoma. Promising response rates and/or survival outcomes have opened new areas for further exploration, including AZD6244 (MEK) in uveal melanoma, bevacizumab in hepatocellular carcinoma, and sorafenib for imatinib- and sunitinib-resistant gastrointestinal stromal tumor. Correlative studies have shed light on molecular characteristics of tumors. For example, in a study of imatinib for patients with stage III/IV melanoma with c-kit mutations, three of nine patients harboring a somatic alteration of exon 11 of the c-kit gene had major responses to imatinib.

Accelerating Clinical Trials of Novel Oncologic Pathways (ACTNOW). Supported by funding from the American Recovery and Reinvestment Act, the Accelerating Clinical Trials of Novel Oncologic Pathways (ACTNOW) program is designed to further NCI's goal of developing personalized cancer medicine. The goal of ACTNOW is to accelerate the initiation and completion of 37 early-phase clinical trials of new treatment regimens. The program has dedicated \$31 million for phase 1 and 2 trials and \$5 million for support contracts, including those to assist investigators with data monitoring and statistical analysis. Support for the clinical trials included hiring of staff, acquisition of technologies for diagnostic scans, specimen sample collection, assay development, and the reimbursement of research costs associated with data management at the participating sites. Examples of ACTNOW trials include studies of the Hedgehog inhibitor GDC-0449 in adults and children with medulloblastoma and of the PARP inhibitor ABT-888 in patients with BRCA 1/2-mutated breast and ovarian cancer.

CTEP-Sponsored Phase 2 Trials Leading to Pivotal Trials.

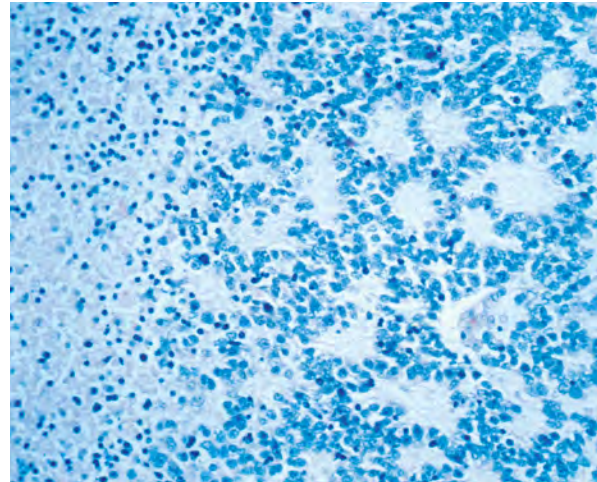
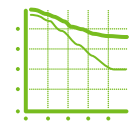
A number of phase 2 studies sponsored by CTEP have led to pivotal clinical trials. Examples include the following:

- The 40% overall response rate in cutaneous T-cell lymphoma seen in the NCI Clinical Center's multicenter, phase 2 trial of single-agent romidepsin led to a company-sponsored, pivotal, single-arm, phase 2 international trial of romidepsin in cutaneous T-cell lymphoma that confirmed the NCI trial results. The FDA approved romidepsin for cutaneous T-cell lymphoma in November 2009.
- Patients treated with bortezomib for mantle cell lymphoma in a CTEP-sponsored early clinical trial exhibited a high response rate, leading to a company-sponsored pivotal trial that resulted in approval of the agent for this indication in December 2006.
- A CTEP-sponsored study of chimeric 14.18 monoclonal antibody for neuroblastoma was carried out as a complement to a COG phase 3 study, which led to FDA approval of this novel regimen.

IDB Staff Fostering Career Development of Junior Clinical Investigators. The Career Development LOI (CrDL) program is intended to increase the LOI success rate and facilitate the career development of junior investigators. The CrDL process is designed to promote junior faculty by providing a competitive advantage for LOIs submitted by junior investigators. The program provides mentoring in the LOI development and review process, including expert commentary on clinical trial proposals. Of the 323 CrDLs submitted since the program's inception in November 2007, 96 (30%) have been approved. These results indicate that junior investigators have achieved parity with their senior counterparts. CrDLs have come in from all funding mechanisms, reflecting broad acceptance of the CrDL process.

Ten to twenty fellows and junior faculty from institutions around the country rotate at CTEP each year, during which they participate in:

- CTEP review of LOIs and protocols
- Scientific presentations by biotechnology and pharmaceutical companies seeking CTEP collaboration
- Initiation of projects that interrogate the large CTEP Theradex Phase 1 database containing data from thousands of patients enrolled in CTEP clinical trials



Future Initiatives

A number of intra- and interdivisional collaborations are under way or in the planning stages:

- Increased integration of imaging and correlative sciences into CTEP clinical trials:
 - With the DCTD Cancer Imaging Program, incorporation of molecular imaging in CTEP trials of IND agents carried out in the Phase 2 N01 Program
 - With the DCTD Molecular Characterization Laboratory, DNA sequencing of patient tumors to identify actionable genetic abnormalities
- Phase 1/2 trials of irradiation combined with targeted agents with the DCTD Radiation Research Program
- Evaluation of drug–drug interactions and pharmacology, using human hepatic microsomes with the University of Pittsburgh, the AIDS Malignancy Consortium, and the CTEP Organ Dysfunction Working Group

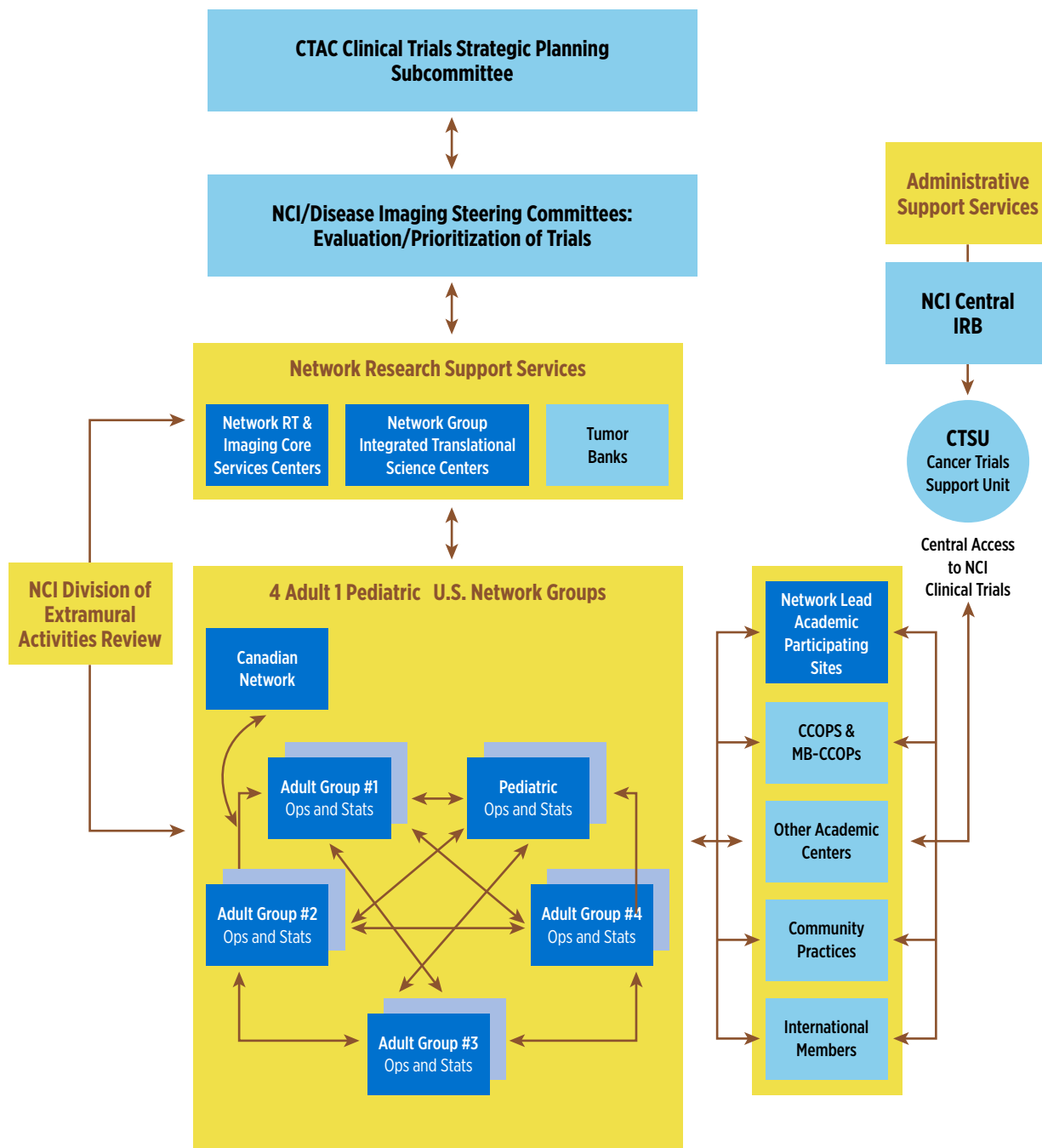
CLINICAL INVESTIGATIONS BRANCH

The **Clinical Investigations Branch (CIB)** is responsible for the scientific coordination and oversight of definitive, practice-changing clinical trials of innovative oncology treatments. These mostly phase 2 and 3 studies include investigations of single-agent, multiple-agent, or combined modality interventions and targeted therapies for adult, adolescent, and pediatric populations, conducted nationally by the extramural scientific community:

- NCI National Clinical Trials Network Program
- Pediatric and Adult Brain Tumor clinical trials consortia
- Pediatric Phase 1 Consortium, New Approaches to Neuroblastoma Consortium, Pediatric Preclinical Testing Program, and the Childhood Cancer Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Initiative

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

- Cancer Trials Support Unit, which provides centralized patient enrollment 24 hours a day, 7 days a week (24/7) as well as administrative and regulatory support for the conduct of clinical trials
- NCI CIRBs for adult and pediatric Cooperative/Network Group (NCTN) trials
- Coordination with other NCI programs regarding the collection, banking, and use of clinical biospecimens in conjunction with validated data from multi-institutional clinical trials
- Collaborations with international clinical trial organizations on treatment trials



NCI NATIONAL CLINICAL TRIALS NETWORK

Organizational structure of the new National Clinical Trials Network program. Dark blue boxes identify the six key components (each under a separate Funding Opportunity Announcement) of the NCTN. CTAC = Clinical Trials and Translational Research Advisory Committee; MB-CCOP = Minority-Based CCOP; RT = radiation therapy.



CRIZOTINIB IS HIGHLY ACTIVE FOR A CHILDHOOD LYMPHOMA

In 2012, COG researchers presented results from a phase 1 clinical trial that administered the anaplastic lymphoma kinase (ALK) and MET inhibitor crizotinib to children with recurrent cancers. Remarkably, seven of the eight children with anaplastic large-cell lymphoma showed complete responses to crizotinib. Almost all cases of anaplastic large-cell lymphoma in children have a chromosomal alteration resulting in activation of ALK, providing an explanation for the high level of anticancer activity for crizotinib against this disease.

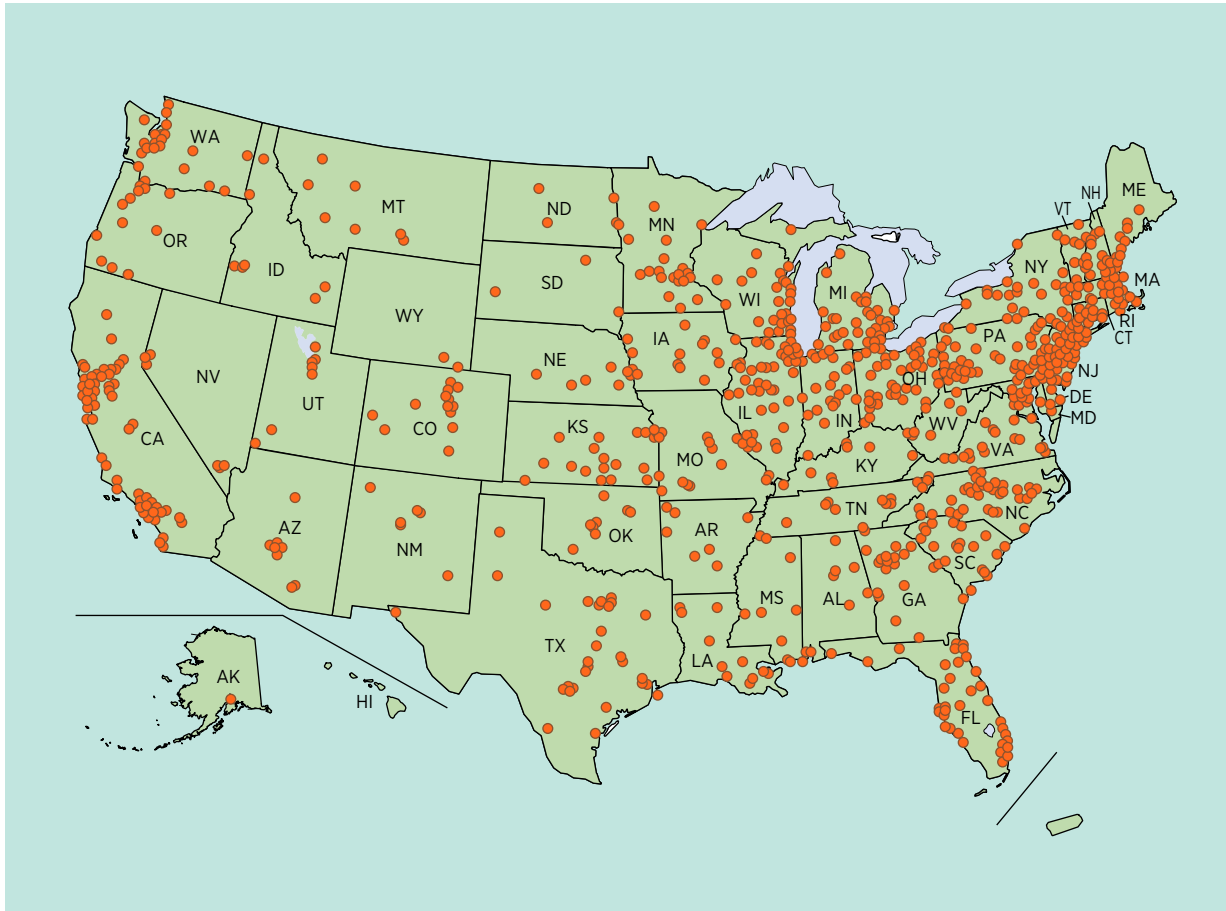
Crizotinib was also highly active in patients with inflammatory myofibroblastic tumors, a rare childhood cancer that also has chromosomal alterations leading to ALK activation. Anticancer activity was also observed for some children with neuroblastoma with ALK point mutations.

COG researchers are now developing a clinical trial in which crizotinib will be given in combination with standard chemotherapy to children with newly diagnosed anaplastic large-cell lymphoma, with the hope of curing 90% of children with this lymphoma.



Clinical Trials Program

For more than 50 years, the NCI Clinical Trials Cooperative Group Program has been distinct among randomized, large-scale, NIH-supported clinical trials programs because it provides a standing infrastructure for clinical trials that is continuously available to test new therapeutic interventions. Currently participating in this program are a total of 2,097 sites, including NCI Comprehensive Cancer Centers, other academic and community institutions, 50 Community Clinical Oncology Programs (CCOPs), and 13 minority-based CCOPs, as well as more than 18,000 registered investigators from the extramural scientific community. In 2012, in response to recommendations from the Institute of Medicine and other stakeholders across the oncology community, CTEP instituted a comprehensive plan to transform this program into the new NCTN. An integral component of this plan is to consolidate the multiple separate organizations that were funded under the previous program to conduct cancer treatment and primary advanced imaging trials into a new, consolidated, and integrated network. The new NCTN will promote collaboration and allow institutional members of any network group to enroll patients on all phase 3 and selected large phase 2 trials conducted by the network, irrespective of the specific network group leading the trial. Six Funding Opportunity Announcements were released in 2012 to establish the new NCTN, whose anticipated start date is March 2014.



DISTRIBUTION OF U.S. INSTITUTIONS PARTICIPATING IN THE CURRENT COOPERATIVE GROUP/NCTN PROGRAM

Phase	2007 Studies/Patients	2008 Studies/Patients	2009 Studies/Patients	2010 Studies/Patients	2011 Studies/Patients	2012 Studies/Patients
Phase 1	33 / 341	30 / 276	36 / 488	34 / 602	38 / 544	37 / 737
Phase 2	211 / 3,947	179 / 3,298	164 / 2,933	152 / 3,548	152 / 4,546	141 / 3,819
Phase 3	117 / 19,843	117 / 21,807	128 / 25,370	125 / 18,890	124 / 14,516	113 / 16,485
Other (pilot)	20 / 488	19 / 301	18 / 430	13 / 406	10 / 168	6 / 88
Total	381 / 24,619	345 / 25,682	346 / 29,221	324 / 23,446	324 / 19,774	297 / 21,129

ACCRUAL AND TRIAL NUMBERS FOR OPEN COOPERATIVE GROUP/NCTN TREATMENT AND PRIMARY ADVANCED IMAGING CLINICAL TRIALS, FISCAL YEARS 2007-2012



Approximately 340 group treatment and primary advanced imaging trials are open to accrual in any given year. An additional 90 trials are closed to accrual but still have patients on active study therapy each year. These numbers represent an average over the last 6 years.

A new process for evaluating prospective large-scale trials has been put into place to promote utilization of the broadest expertise for selecting these trials and to ensure an open, transparent process. Disease-Specific Steering Committees were established in 2006. Each committee includes expertise from across the oncology community in the particular disease or organ system, including representatives from the Cooperative/Network Groups (NCTN), Cancer Centers, SPOREs, community oncologists, basic and translational scientists, biostatisticians, patient advocates, and NCI oncologists. The committees break out into task forces to serve as think tanks for new ideas and develop Clinical Trial Planning Meetings as appropriate to engage the community in seeking the most important questions to pose in new trials. As of May 2012, the committees had reviewed more than 130 phase 2 and 3 trials.

CTSU and Flex Programs. The CTSU was established in 2002 to increase physician and patient access to NCI-sponsored clinical trials, reduce the regulatory burden on investigators participating in clinical trials, and streamline and standardize trial data collection and reporting. Since its inception, CTSU has:

- Increased phase 3 trial cross-group accrual from 20% to 40%, resulting in wider access of trials to the extramural community and enrollment of more than 8,000 patients in collaborative trials annually
- Diminished the regulatory and administrative burden for trial enrollment, handling more than 10,000 IRB approvals (initial, continuing, and amendments) each month
- Provided standardized data management services for multiple phase 3 clinical trials
- In 2009, initiated the Oncology Patient Enrollment Network (OPEN), a Web-based registration system for patient enrollments into group trials that is integrated with CTSU regulatory/roster data and with each group's registration/randomization systems, providing the ability to enroll patients on a 24/7 basis via one centralized system

A pilot program, the CTSU-Flex program, was instituted in 2007 to extend the infrastructure support of the CTSU to other NCI-supported clinical trial networks, including Cancer Center Phase 2 Consortia trials supported by the IDB, cancer control and symptom management trials sponsored by the NCI Division of Cancer Prevention, and trials initiated by SPORE investigators. Since its inception, the CTSU-Flex program has supported approximately 40 clinical trials and contributed more than 3,100 enrollments to trials led by Cooperative Groups, cancer centers (including the NIH Clinical Center and non-Group CCOP Research bases) and various consortia and networks.

Novel Cooperative Group Phase 3 Clinical Trials and International Collaborations. Following are examples of major phase 3 trials incorporating novel treatment strategies and molecularly targeted therapies. These trials are also examples of studies that would not have been conducted by industry alone, and several require international collaboration:

- **Study Evaluating Clinical Benefit of Extended Surgical Removal of Pelvic Lymph Nodes in Bladder Cancer:** Radical cystectomy attempts to cure patients with muscle-invasive bladder cancer. In single-institution experience, extended removal of pelvic lymph nodes is associated with longer survival and reduced risk of local recurrence. This S1011 clinical trial, led by the Southwest Oncology Group, randomizes patients to either standard or extended lymph node dissection at the time of radical cystectomy for muscle-invasive bladder cancer. This technically and logistically demanding study will enroll 630 patients in an attempt to provide the definitive answer to the question of whether clinical benefit can be derived from extended pelvic lymphadenectomy in patients with bladder cancer. Although such surgical studies are known to be difficult to conduct, S1011 has been accruing well and is likely to be completed in the planned timeframe of 4 years. In addition, tumor tissue will be banked for correlative studies of molecular biology of muscle-invasive and metastatic bladder cancer.
- **Phase 3 Randomized Study to Evaluate the Best Transplant Strategy Followed by Lenalidomide Maintenance Therapy in Multiple Myeloma:** This intergroup trial is being led by the Blood and Marrow Clinical Trials Network, cosponsored by NCI and the National Heart, Lung, and Blood Institute. The study was activated in June 2010 and, as of October 2012, had enrolled 487 of the planned 750 patients. The importance of the study derives from findings in several randomized phase 3 trials that lenalidomide maintenance therapy after transplant improved progression-free survival in patients with multiple myeloma. One of the trials showed a survival advantage. Tandem transplant and transplant followed by consolidation chemotherapy improved outcomes compared with single transplant. However, it is not known whether the improved outcomes associated with the additional transplant and consolidation chemotherapy persist when lenalidomide maintenance is provided after transplant. This study seeks to answer this question. Because lenalidomide is very active, ongoing maintenance therapy with the well-tolerated agent may improve outcomes for patients in all three arms of the study. Another possibility is that it will equalize the outcomes such that the single transplant, which entails less toxicity and expense, will be as effective as the more expensive and toxic strategies.
- **Using a Molecular Marker to Predict Survival Benefit of Chemotherapy in Anaplastic Gliomas—CODEL (N0577) and RTOG 9402:** Led by the North Central Cancer Treatment Group, CODEL began as a phase 3 international study of radiotherapy alone versus radiotherapy plus temozolomide in patients with 1p/19q co-deleted anaplastic glioma. When the study began, in 2009, the benefit of chemotherapy in these patients had not been established. RTOG 9402, begun in 1994, was a CTEP-funded, phase 3 intergroup trial evaluating the benefit of adding procarbazine–lomustine–vincristine (PCV) chemotherapy to surgical resection and radiation in patients with anaplastic gliomas. Although the significance of 1p/19q co-deletion in gliomas was not known in 1994, the tumor tissue was banked for possible future studies. In an analysis of mature survival data in 2011–2012, by which time the 1p/19q co-deletion status of the majority of the tumors had become available, RTOG 9402 established that 1p/19q co-deletion in anaplastic gliomas predicted a doubling of overall survival from the addition of chemotherapy to standard treatment. With these results in hand, CODEL is being revised to add a PCV chemotherapy regimen.
- **Phase 3 Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma:** This phase 3 study was recently approved to evaluate a new molecularly targeted therapy for a specific subset of patients with a rare disease in a potentially curative clinical setting. The trial follows a 2009 scientific advance that demonstrated a survival advantage for patients who have advanced gastric and gastroesophageal junction adenocarcinoma that overexpresses HER2 and who received trastuzumab in combination with chemotherapy. This trial will screen 500–700 patients to identify the estimated 25–32% who have disease that overexpresses HER2 in order to evaluate the benefit of adding trastuzumab to trimodality adjuvant therapy in esophageal adenocarcinoma. This trial was activated in January 2011, and as of January 2013, 218 patients had been screened; approximately 35% had been identified with HER2-positive tumors, and 72% of those with HER2-positive tumors had been randomized.



Accomplishments

Each year, extramural investigators of CTEP-supported clinical trial programs present primary trial results and other outcomes from research associated with their clinical trials in 300–400 publications and abstracts. Group trials have also led to FDA approval of multiple new agents for several indications, resulting in widespread access of these agents to patients in the United States.

In December 2012, the Association for the Accreditation of Human Research Protection Programs awarded full accreditation to the NCI CIRB, the first NIH entity to receive this recognition. The association awards accreditation to organizations demonstrating the highest ethical standards in clinical research. The accreditation was the culmination of a year-long process that involved the completion, submission, and review of a complex application and a 2-day site visit involving dozens of interviews. Achieving this accreditation establishes that the NCI CIRB has robust review processes in place to ensure the safety and protection of people who participate in NCI-funded clinical studies.

In conjunction with accreditation, the NCI CIRB changed its review model to an independent review model to enable participating research sites to rely solely on the CIRB to meet all institutional review board regulatory requirements. A pilot of the independent model was performed during 2012 in 22 sites that conduct clinical research. Results from an independent survey of the pilot showed that participants enthusiastically supported the independent model: 78% were “very satisfied” or “extremely satisfied” with the independent

model, and 84% would recommend the independent model to colleagues. This model further reduces the administrative burden necessary to open multi-institutional, NCI-funded clinical trials and assists the restructuring of the NCI National Clinical Trials Network, which aims to reduce the length of time it takes to complete cancer clinical trials and bring new cancer treatments to patients. Key strengths of the newly accredited NCI CIRB include recognition of the high quality of review, reduced workload at the local level, faster times to the start of accrual for trials, and the ability to offer more clinical trials.

Current and Future Initiatives

CTEP Initiatives to Expand Access to Cancer Clinical Trials to HIV-Infected Persons. Cancer has emerged as the leading cause of death in HIV-infected persons in the United States and other countries where effective combination antiretroviral therapy is widely available. Most cancer clinical trials, however, have traditionally excluded persons with HIV infection because, prior to the availability of this therapy, HIV-associated morbidity and mortality made these patients vulnerable to excess risk. Three new CTEP initiatives, funded by the NCI Office of the Director, will provide the evidence required to address barriers that prevent wide inclusion of HIV-infected persons in cancer clinical trials:

1. HIV-infected patients are being included as separate cohorts in selected randomized phase 3 and large phase 2 oncology treatment trials to provide preliminary information on feasibility and safety. In addition, most new studies approved by CTEP currently do not exclude

HIV-infected patients who have never experienced HIV-related complications, including advanced immune suppression. Increasingly, the community of NCI-supported investigators appreciate the value of including these patients unless specific reasons are identified that would create excess risk for their participation.

2. Two transplant trials are being conducted through the National Heart, Lung, and Blood Institute and the NCI co-sponsored Blood and Marrow Transplant Clinical Trials Network in collaboration with the NCI AIDS Malignancy Consortium to assess the safety and feasibility of autologous or allogeneic stem cell transplantation in HIV-infected persons with hematologic cancers. These trials will seek to identify human leukocyte antigen-matched donors who are homozygous for the CCR5 Δ 32 mutation, which renders individuals not infectable by the most common HIV strains. Recipients may be removed from combination antiretroviral therapy and assessed by using ultrasensitive single-copy HIV mRNA assays to investigate the possibility that HIV eradication can be achieved in this manner. The autograft study is approaching the accrual ceiling, and the allogeneic study is just starting to accrue patients.
3. Several studies are being funded to define agent doses that can be safely used in various antiretroviral combinations. As these interactions are defined and found to be safe, NCI-sponsored trials that currently exclude patients with HIV infection because of concerns regarding pharmacokinetic interactions will be amended to include these patients, thus expanding their access to a large number of trials. The first of these studies has been completed; it has defined the dose of sunitinib according to the type of combination antiretroviral therapy patients are taking. Three additional studies have been developed and will be accruing patients in the coming year.
4. A large study of HIV seroprevalence in cancer patients is being developed to assess the burden of HIV infection in newly diagnosed cancer patients across the United States. SWOG is conducting this study in its major academic and community centers (including CCOP) in order to capture potential variations in geography and practice settings. This study has the potential to inform policy regarding routine HIV testing in cancer patients and to better describe whether cancer patients with HIV infection already know their HIV status.

Implementation of a Common Group-Wide Clinical Data Management System.

A common clinical data management system, Medidata Rave, has been successfully implemented across the Cooperative/Network Group (NCTN) program. Several other NCI multicenter organizations (Adult Brain Tumor Consortium, Pediatric Brain Tumor Consortium, COG Phase 1) were also included in this initiative. An Institute of Medicine report (Institute of Medicine of the National Academies Report. A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program. Committee on Cancer Clinical Trials and the NCI Cooperative Group Program Board on Health Care. Nass SJ, Moses HL, and Mendelsohn J, Editors. National Academies Press, Washington, DC; April 2010). has projected that implementation of a common clinical data management system will increase consistency across trials and conserve resources. Some projected benefits include:

- Promotion of efficient, accurate, and timely data entry
- Scalability for use in other study types (e.g., prevention, cancer control)
- Minimization of training and other administrative costs
- Reduction of data management burden and costs for multicenter coordinating centers and participating investigators and sites

CTEP's clinical data management system is a common system for remote capture of data for all networks. It features electronic protocol authoring that allows rapid development of protocol documents and electronic case report forms for rapid and standardized collection of clinical data. The deployment of a common clinical data management system supports and facilitates the transition of the current Cooperative Groups to the new NCI NCTN program.

Integration of NCI Applications with the Common Clinical Data Management System.

Further integration of the clinical data management system with other NCI systems will result in significant efficiency gains for CTEP-supported clinical trial networks. Integration of the system with the NCI safety reporting system (the CTEP Adverse Event Expedited Reporting System) and other routine data reporting tools (the Common Data Update System and the Clinical Trials Reporting Program) will eliminate duplicative effort, inconsistencies, and reconciliation activities. Finally, the NCI



is moving toward integrating selected information from the clinical data management system with the Cooperative/Network Group (NCTN) Biorepository databases, thus providing a link between clinical and genetic/translational research.

Development of a New NCI Informed Consent Document Template. Tension exists between the requirement to provide adequate information about a cancer clinical trial in an informed consent document and the need to keep the document concise to maximize readability and comprehension. All too often, the informed consent document has been viewed by sponsors as a legal tool to limit investigator and site liability rather than, as originally proposed in the [Belmont Report](#), part of a process to ensure that the key ethical principles for human experimentation—autonomy, beneficence, and justice—are respected. (Sharp 2004). There is concern that the balance has tipped in favor of comprehensiveness instead of comprehension.

In 1997, the NCI developed and promulgated an informed consent boilerplate document, known as the NCI Informed Consent Template, for use by its Clinical Trials Cooperative Group Program and others. Although the informed consent template has certainly made NCI-sponsored trial consent forms more harmonious, the length of the consent forms has grown over the ensuing years to the point where there is now concern that readability and comprehension have been compromised. To address this problem, an NCI Planning Committee took on the challenge of revising the NCI Consent Form Template to result in more concise consent forms that still accurately capture the required explanations and elements of informed consent. Five working groups comprising internal and external stakeholders from across the scientific, academic, regulatory, and advocacy communities, including representation of clinical trialists and individuals with expertise in institutional review boards, were tasked with revising the template to result in shorter consent forms. The resulting NCI Consent Form Template serves authors of consent forms by supplying draft text and section length limits to discourage consent forms from again becoming increasingly long and complex.

Accrual Assessment and Interventions. NCI analyzed phase 3 trials activated between 2000 and 2007 and found that 41 of 191 trials had an inadequate accrual rate. Using this information, a pilot project began in 2012 to work collaboratively with the Cooperative Groups on the early identification of trials with potential challenges to accrual feasibility in order

to develop focused interventions to address them. When scientific steering committees raise issues regarding accrual feasibility during the concept evaluation of a trial, CIB therapeutic disease leaders hold conference calls with the principal investigators, Lead Cooperative Group, CTEP staff, and members of NCI's Office of Communication and Education to consider how to facilitate adequate accrual rates.

NCI's Office of Communication and Education has worked with colleagues in CTEP and Cooperative Groups to create Office of Management and Budget–approved online survey templates to gather broad input on approved concepts and trials that are under way. These templates will be used to better understand accrual challenges due to difficult randomization, trial complexities, level of potential clinical impact and interest, and other issues. Extramural investigators and their research teams provide anonymous feedback, which is used to refine accrual interventions. In addition, CTSU data collected through the Regulatory Support Service on approvals of protocol-specific requirements are analyzed to assess difficulties with site activation processes, and adjustments are made when possible.

Thus far, interventions to facilitate accrual have included educational and promotional efforts, including the use of social media, to increase awareness and understanding of the importance of clinical trials. In addition, groups have amended trials to adjust patient eligibility requirements, streamline the steps needed for trial activation, and reduce complexities. Trial accrual is being monitored quarterly to evaluate progress and assess the need for further support. CTEP Early Stopping Guidelines for Slow Accruing Trials are used to determine whether further survey or accrual interventions are needed to avoid closure due to inadequate accrual. These efforts are also responsive to recommendations made by NCI's Clinical Trials Working Group and the IOM Report "[A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program](#)."

Pediatric Translational and Clinical Research Programs. CTEP staff members also support a comprehensive research program for children with cancer that ranges from the discovery of new therapeutic targets, to the 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 pharmaceutical companies lack the market incentives to justify the systematic study

Year	Drug	Sponsoring Organization	Cancer Site
2004	Letrozole	National Cancer Institute of Canada, Intergroup	Breast
	Oxaliplatin	North Central Cancer Treatment Group, Intergroup	Colon
	Taxotere	Southwest Oncology Group	Breast
	Nelarabine	Children's Oncology Group	Leukemia
2006	Bevacizumab	Eastern Cooperative Oncology Group, Intergroup	Colon, lung
	Trastuzumab	National Surgical Adjuvant Breast and Bowel Project, North Central Cancer Treatment Group, Intergroup	Breast
2008	Bevacizumab	Eastern Cooperative Oncology Group, Intergroup	Breast
	Imatinib mesylate	American College of Surgeons Oncology Group	Gastrointestinal stromal tumor
2009	Bevacizumab	Cancer and Leukemia Group B, Intergroup	Renal Cell
BLA Currently in Preparation	Anti-GD2 ch14.18 monoclonal antibody	Children's Oncology Group	Neuroblastoma

SELECTED NCI-SUPPORTED COOPERATIVE GROUP TRIALS SUPPORTING FDA-APPROVED INDICATIONS

BLA = Biologics License Application (FDA).

of novel treatments in the pediatric oncology setting. CTEP sponsors pediatric clinical trials, primarily through COG, its phase 1 consortium, the New Approaches to Neuroblastoma Therapy Consortium, and the Pediatric Brain Tumor Consortium.

• Children's Oncology Group

COG develops and coordinates cancer clinical trials at more than 200 member institutions, including the cancer centers of all major universities and teaching hospitals throughout the United States and Canada, as well as sites in Europe and Australia. COG clinical trials are the primary source of data used to define the standard of care for childhood cancers. Examples of recent advances identified in COG phase 3 clinical trials include:

- Addition of imatinib to standard chemotherapy improves outcomes for children with Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL).
- Compressing the interval between treatment courses improves outcomes for children with Ewing sarcoma.
- Dexamethasone during induction improves outcome for children under age 10 with high-risk ALL, and high-dose methotrexate improves outcome when used as a component of postremission therapy for children with high-risk ALL.

• COG Phase 1/Pilot Consortium

The COG Phase 1/Pilot Consortium efficiently and expeditiously develops and implements pediatric phase 1 and pilot studies, thus facilitating the integration of advances in cancer biology and therapy into the treatment of childhood cancer. The consortium includes approximately 20 institutions competitively selected from among COG member institutions. Recent examples of important phase 1 studies include:

- The anaplastic lymphoma kinase (ALK) inhibitor PF-2341066, with a specific focus on patients with ALK-mutant neuroblastoma and ALK-positive anaplastic large cell lymphoma
- The anti-insulin-like growth factor-1R monoclonal antibody IMC-A12, studied both as a single agent and in combination with the mTOR inhibitor temsirolimus
- The JAK2 inhibitor ruxolitinib (INCB18424), which is of particular interest for patients with ALL and JAK2 translocations

• Pediatric Brain Tumor Consortium

The primary objective of the Pediatric Brain Tumor Consortium is to rapidly conduct phase 1 and 2 clinical evaluations of new therapeutic drugs, intrathecal agents, delivery technologies, biological therapies, and radiation



treatment strategies for children with brain tumors. A focus of the consortium is conducting the initial studies in children of targeted agents that directly address recurring genomic lesions in pediatric brain tumors, as illustrated by the following clinical trials:

- The initial pediatric phase 2 study of the hedgehog pathway inhibitor GDC-0449, which is highly relevant to medulloblastoma cases with sonic hedgehog pathway activation
- A phase 1 trial of the MEK inhibitor AZD6244 for children with recurrent or progressive pilocytic astrocytoma; BRAF activation through its fusion to a nearby gene is observed in most cases of pilocytic astrocytoma
- **Childhood Cancer TARGET**
The childhood cancer TARGET initiative, a collaborative effort with the NCI Office of Cancer Genomics and COG, systematically applies genomic characterization methods to identify genes that are recurrently altered in specific childhood cancers, under the hypothesis that these altered genes provide therapeutically relevant insights into the pathways on which cancers depend for growth and survival. The TARGET initiative first studied ALL and neuroblastoma. Important discoveries through the ALL TARGET initiative include identifying the poor outcome associated with IKZF1 (Ikaros) alterations, identifying activating JAK family mutations in high-risk B precursor ALL, and identifying novel gene fusions involving the CRLF2 gene in a subset of patients with high-risk B-precursor ALL. The TARGET initiative has expanded

to include a total of five different childhood cancers: ALL, acute myeloid leukemia (AML), neuroblastoma, high-risk Wilms tumor, and osteosarcoma.

- **The Pediatric Preclinical Testing Program**
The Pediatric Preclinical Testing Program systematically tests novel anticancer agents against pediatric preclinical models to develop datasets to assist clinical researchers in selecting the agents and combination therapies that are most likely to be effective for childhood solid tumors and leukemias. Since 2005, more than 30 agents or combinations of agents have been tested against the program's molecularly characterized panel of childhood cancers. The results have identified agents with high-level preclinical activity that warrant clinical prioritization, including:
 - The HDM2 inhibitor RG-7112
 - The antimitotic agent eribulin
 - The MEK inhibitor AZD6244 for children with recurrent pilocytic astrocytoma

CLINICAL GRANTS AND CONTRACTS BRANCH

The **Clinical Grants and Contracts Branch (CGCB)** manages grant programs in clinical and surgical oncology. The branch supports investigator-initiated therapeutic research projects by coordinating multiple activities that include:

- Annual review of grant progress, financial accounting, and approval and oversight of amended aims and plans for recompetition

- Identification of potential areas of scientific investigation that overlap among investigators to promote collaborations and support for grantee projects by facilitating the procurement of agents, resources, or trial support from other CTEP and NCI branches
- Promotion of broad national programs of clinical consortia, including the Chronic Lymphocytic Leukemia Research Consortium, the Blood and Marrow Transplant Clinical Trials Network, the Adult Brain Consortium, and the Cancer Immunotherapy Trials Network
- Advice to extramural investigators on funding opportunities and mechanisms and the grant application process

Mechanism	Number
P01	31
R01	119
R00	2
R13	8
R21	18
R37	2
U01 CGCB	2
U24 CGCB	2
TOTAL	253

FY 2012 CGCB PORTFOLIO*

*Exclusive of cooperative agreements (U10, U01, U24s) assigned to CIB and IDB.

Team science is the hallmark of the research carried out in the CGCB portfolio, which usually requires collaboration among different investigators in different disciplines. As it moves from the R series grant mechanism to program project grants (P01s) and U01 cooperative agreements, team science becomes more complex and requires more coordination on the part of CGCB staff.

Accomplishments

Major accomplishments of the team science projects supported under investigator-initiated R01, R21, and R37 grants include the following:

- A microfluidic device was developed to isolate highly purified circulating tumor cells from the blood of patients. This led to confirmation of the expected epidermal growth

factor receptor-activating mutation T790M in circulating tumor cells in 92% of blood samples from patients with advanced non-small-cell lung cancer who were resistant to gefitinib in a multicenter clinical trial.

- An approach was developed to test the adoptive transfer of genetically engineered T cells expressing a chimeric antigen receptor to target the CD19 molecule found on the malignant B lymphoblast from patients with chronic lymphocytic leukemia (CLL). The approach was found to successfully treat these patients, in whom sustained complete remissions were achieved.
- Several advantages are offered by the use of umbilical cord blood as a source of stem cells for stem cell transplant in the treatment of hematologic malignancies. The use of cord blood, however, has been limited due to the low cell doses obtained from a single cord, which limits engraftment. Recent studies tested whether co-culture of umbilical cord with mesenchymal stromal cells ex vivo would expand the stem cells. These tests led to a 30-fold expansion of stem cells. Patients undergoing transplant with 1 unit each of expanded and unmanipulated cords had a significant increase in the median time to neutrophil and platelet engraftment compared with patients transplanted with two unmanipulated cords. These results provide impetus to the use of cord blood as a donor source for patients who lack a suitable human leukocyte antigen-matched donor.
- Investigators recently examined the hypothesis that interaction of AML cells with the bone marrow stromal micro-environment limits the efficacy of chemotherapy, resulting in disease relapse. Their results showed that a small-molecule antagonist of binding of the chemokine CXCR4 expressed on AML blasts to its ligand, CXCL12 (plexifor), resulted in a twofold mobilization of AML blasts into the circulation. This novel mode of chemosensitization resulted in increased rates of remission in a phase 1/2 study of patients with relapsed or refractory AML.
- In preclinical studies testing the use of combination epigenetic therapies, it was found that a novel histone deacetylase inhibitor upregulates the microRNA miR-29b, leading to increased sensitivity to the hypomethylating agent decitabine. This finding provides an important new treatment approach to treating diseases, such as AML, which have had limited clinical response to these epigenetic therapies.



The P01 grants in particular serve as an important bridge between the preclinical and the clinical sciences. Through the P01 mechanism, many basic scientific advances are discovered, refined, and then developed into testable clinical hypotheses. The U01 cooperative agreements continue the progress made under P01 grants through multicenter phase 2 and 3 clinical trials. Finally, the U24 cooperative agreements, a resource-related mechanism, provide important infrastructure for investigator-initiated research activities.

Major NCI-Supported Multisite Initiatives

Chronic Lymphocytic Leukemia Research Consortium.

The Chronic Lymphocytic Leukemia Research Consortium is a premier example of translational science activity. Research findings from this P01 unveiled the potential role of oncogenes and microRNAs in the pathogenesis of CLL and the skewed expression of ultraconserved noncoding RNAs in human CLL relative to normal lymphocytes. MicroRNA34a, which is induced by activation of TP53, is involved in post-transcriptional silencing of the gene encoding the zeta-associated protein of 70 kilodaltons (ZAP-70). A mouse model of CLL developed under this P01 has permitted the evaluation of the capacity of lenalidomide to reverse the defective immunologic synapse observed in patients with CLL. During the conduct of this clinical study, laboratory work on patient samples revealed the role of an oncofetal protein, ROR1, and its defined ligand, Wnt5f, in the pathogenesis of CLL. Of particular interest, AD-ISF35 gene therapy induces anti-ROR1 autoantibodies in patients. Several promising drugs, including flavopiridol, 9-(2-phosphonylmethoxyethyl)guanine, GS-9219, beta-phenylethyl isothiocyanate, and XIAP antagonists, are also in development in this highly interactive P01.

Myeloproliferative Disease Research Consortium. The Myeloproliferative Disease Research Consortium is an international consortium of medical centers established in 2005 under the P01 mechanism. It consists of five core centers conducting six projects, and 22 ancillary sites. All are served by three shared resource cores. Its function is to conduct basic research in Philadelphia-negative myeloproliferative diseases—in particular, polycythemia vera and primary myelofibrosis—and to design and perform new clinical trials in these diseases. Six protocols have been activated in the consortium, and three are in various stages of accrual. A recently published study from the consortium showed that the spleens of myelofibrosis patients contain malignant

stem cells, indicating that myelofibrosis is characterized by hematopoiesis not only in the marrow but also in extramedullary sites.

Phase 3 Melanoma Trials (P01). The principal investigator at the John Wayne Cancer Institute has been awarded two P01 grants supporting international, multisite, randomized, phase 3 trials in melanoma. Three trials from these grants are currently funded by NIH Comparative Effectiveness Research funds from the American Recovery and Reinvestment Act. The results of these trials are likely to have an important impact on the treatment of cutaneous melanoma:

1. Multicenter Selective Lymphadenectomy Trial (MSLT)-I examines the accuracy and clinical efficacy of sentinel-node biopsy as a staging alternative to complete lymphadenectomy in patients with clinical stage I melanoma.
2. MSLT-II asks the provocative clinical question of whether melanoma patients with a positive sentinel-node biopsy need additional immediate complete lymphadenectomy.
3. A Phase 3 Randomized Trial of Surgical Resection With or Without BCG versus Best Medical Therapy as Initial Treatment in Stage IV Melanoma seeks to determine whether surgery as a first treatment for Stage IV melanoma will lengthen the survival time and the time to disease recurrence or progression compared with nonsurgical therapy.

Brain Tumor Consortium. The Adult Brain Tumor Consortium, supported under the U01 mechanism, is a multi-institutional consortium that has initiated more than 50 clinical trials in the last 5 years. More than 2,000 patients have been studied with more than 18 new chemotherapy agents and strategies. This work has resulted in more than 80 publications and has initiated several original approaches:

- In the field of neuro-oncology, giving experimental drugs preoperatively to assess tumor pharmacokinetic and pharmacodynamic endpoints
- Conducting gene transfer using adenoviral p53 in a novel design of biopsy, gene transfer, rapid resection of gene transfer, and further assessment of gene transfer
- Systematically describing the interaction of anticonvulsant enzyme-inducing agents with numerous chemotherapy agents

Cancer Childhood Survivor Study. The U24 Childhood Cancer Survivor Study is composed of two retrospectively ascertained cohorts of pediatric cancer survivors. The first cohort comprises approximately 20,000 survivors of pediatric cancers diagnosed between 1970 and 1986 at 27 contributing clinical centers and approximately 4,000 of their siblings. The second group is an equally large cohort of survivors diagnosed between 1987 and 1999. Major accomplishments of the study are:

- Assembling a cohort of pediatric cancer survivors of this scale—the largest in the world
- Initiating, between 1998 and 2008, a total of 134 distinct studies; of studies for which analysis is complete, 64 have so far resulted in at least one peer-reviewed publication

Major Co-Funded Networks

Pharmacogenomics Research Network (U01). The Pharmacogenomics Research Network, supported by the U01 mechanism, has been funded since 2000 under a trans-NIH initiative led by the National Institute of General Medical Sciences. The goal of the network is to fund the highest-quality pharmacogenomics research for understanding the genomic basis of variable drug responses, both therapeutic and adverse, with the potential for significance and/or impact leading to eventual translation into clinical application. The network has deposited data and information for sharing into the Pharmacogenomics Knowledge Base. CGCB has co-funded three Pharmacogenomics Research Network sites. Their major accomplishments include:

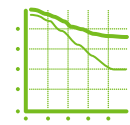
- Providing FDA with information on the association of UGT1A1 polymorphisms with toxicity and the pharmacokinetics of irinotecan for a label change
- Reporting a preliminary clinical observation on a significant effect of polymorphisms in ABC and SLC transporter genes on the pharmacokinetics and pharmacodynamics of irinotecan
- First demonstration of the relationship between tamoxifen metabolism and its clinical effects that led the NCI to adopt endoxifen as a drug for intramural development and clinical use
- Reporting a significant association between potent wild-type CYP2D6 (inherited gene) activity and low HOXB13/IL17BR (tumor genes) expression ratio with increased

disease-free survival and overall survival in patients with tamoxifen-treated, estrogen receptor-positive breast cancer

Blood and Marrow Transplant Clinical Trials Network (U10).

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) was created through the U01 mechanism to address important issues in hematopoietic stem cell transplantation and to evaluate promising therapies for the treatment of both hematopoietic malignancies and nonmalignant disease. This network, renewed in 2011, has been a particularly effective and flexible structure composed of 20 core clinical centers and a data coordinating center and with the ability to add affiliate clinical centers as needed to help with accrual. The network is supported by a partnership between NCI and the National Heart, Lung, and Blood Institute, which serves as the lead institute. The network collaborates with other consortia, such as NCI Clinical Trials Cooperative Groups, to perform multisite clinical trials.

- The BMT CTN performs multicenter phase 2 and 3 clinical trials. Since its inception in 2003, the network has opened 27 clinical trials, of which 11 are active and 16 are closed to accrual and are either in follow-up or data analysis or have published studies. Several new protocols are also in development. More than 4,000 patients have been accrued to BMT CTN trials since 2003.
- In 2011, the BMT CTN completed analysis of a landmark study comparing two sources of stem cells, bone marrow and granulocyte colony-stimulating factor-mobilized peripheral blood stem cells, for allogeneic transplants from unrelated donors for treatment of hematologic malignancies. This is an important comparison given the widespread use of peripheral blood stem cells over bone marrow as a donor source. The widely publicized results showed that survival of patients did not differ when comparing the two sources. There was, however, a statistically significant difference in the incidence of chronic graft-versus-host disease, but not acute graft-versus-host disease or relapse. These findings indicate that peripheral blood stem cells may be preferred for patients at risk for graft failure (due to high stem cell counts in peripheral blood stem cells), but that marrow should be preferred for others due to risk of chronic graft-versus-host disease.
- In a second completed study, tandem autologous transplantation was compared with autologous transplantation followed by matched sibling allogeneic transplantation with a nonmyeloablative conditioning regimen in patients



with multiple myeloma. Autologous transplantation is widely accepted as a standard of care for these patients, but disease progression remains an issue. Allogeneic transplantation offers a potential graft-versus-myeloma effect but is often associated with treatment-related mortality. This study addressed whether allogeneic transplantation offers additional benefit compared with tandem autologous transplantation. The results showed that progression-free and overall survival did not differ between the two treatment arms, indicating that further enhancement of the graft-versus-myeloma effect and/or reduction of treatment-related mortality are needed to improve the allogeneic approach to transplant in this disease.

- An example of the benefits of collaboration with other consortia, the BMT CTN has helped the Cooperative Groups finish four trials that were lagging in accrual before the network joined and recently joined a fourth trial. For example, a trial to test the benefit of maintenance lenalidomide postinduction therapy and transplant in multiple myeloma (CALGB 100104) was in danger of closing due to lack of accrual prior to the participation of the BMT CTN. The trial closed early, in late 2011, after reaching a positive outcome on the treatment arm, when it was determined that this therapy extends the time to disease progression by 19 months overall, a benefit that could be reached far faster with the boost to accrual provided by BMT CTN participation in this trial. Similarly, the Cooperative Groups have joined the majority of BMT CTN-led studies for treatment of hematopoietic malignancies.

New Initiative: The Cancer Immunotherapy Network.

Immunotherapeutic approaches to treat cancers have demonstrated limited success despite considerable progress in understanding the biology of antitumor immune responses. A number of key immune modulators have shown a great deal of promise in preclinical studies, but these immune-modifying agents have yet to find a way to the clinic. To address this deficiency, a Request for Applications (RFA) was developed to fund a new Cancer Immunotherapy Trials Network. The RFA funds a single consortium of leading investigators in immunotherapy to jointly develop and conduct phase 1 and early phase 2 multi-institutional clinical trials that could not be conducted efficiently by a single institution. Operationalized in 2011, the network specifically consists of a Central Operations and Statistical Center, which serves as the organizational center through which protocols are developed; 26 member institutions across the country to implement the trials; and laboratory core sites for testing samples from trials for immune-monitoring correlates. A number of working committees have been established to develop concepts to test agents, such as for the cytokines interleukin (IL)-15 and IL-7, the agonistic antibody anti-CD40, and an inhibitor of the immunosuppressive enzyme indolamine 2,3-dioxygenase. All of these agents are deemed to be of particularly high priority for translation. The teams will use agents that have only recently become available for clinical testing. Concepts from these teams are in various stages of protocol development and approval; the first patients are expected to accrue on the first two protocols early in 2013.

REGULATORY AFFAIRS BRANCH

Background

The Regulatory Affairs Branch (RAB) develops partnerships with industry and academics that allow for co-development of novel therapeutics and ensures that CTEP meets all its regulatory responsibilities with the FDA regarding INDs.

Accomplishments

RAB has developed standard non-negotiable agreement clauses that include multiparty data-sharing language, which is critical to CTEP's success in conducting combination studies of agents proprietary to different companies. As part of CTEP's initiative to decrease the interval between Senior Advisory Committee approval and execution of the CRADA for the development of an agent, CTEP has created a CTEP-specific model CRADA that eliminates or minimizes the need for negotiation of much of the agreement. The absolute deadline of 6 months from approval to execution has been met 100% of the time.

In April 2011, a revision to the IP option was finalized and posted on the CTEP website. The new IP option categorizes inventions as either agent related (Section A) or biomarker or assay related (Section B) and provides different options to collaborators depending on the invention category. This new IP option addresses the use of human specimens and clinical data, important areas that were not previously addressed.

The establishment of an Alternate Technology Development Coordinator for CTEP within DCTD has markedly enhanced the ability to execute agreements for CTEP. Following are the numbers of agreements executed for 2011–2012:

- New CRADAs: 16
- CRADA Amendments: 13
- Clinical Trials Agreement Amendments: 8
- New Material Transfer Agreements: 162
- New Confidential Disclosure Agreements: 26
- New IDSC Confidential Disclosure Agreements: 10

EXAMPLES OF TARGETED AND/OR NOVEL AGENTS UNDER CTEP IND

EGFR/HER pathway:	Anti-angiogenesis:
Erlotinib (OSI Pharm)	Sunitinib (Pfizer)
Gefitinib (AstraZeneca)	Bevacizumab (Genentech)
Cetuximab (ImClone)	Aflibercept (Aventis)
Trastuzumab (Genentech)	Sorafenib (Bayer)
Lapatinib (GSK)	Cediranib (AstraZeneca)
IGF-1R : Cixutumumab (ImClone)	Cilengitide (EMD)
Linsitinib (Astellas)	BCL-2 family:
MEK: Selumetinib (AstraZeneca)	Gossypol (Ascenta)
Tivantinib (Daiichi Sankyo Pharma)	Navitoclax (Abbott)
mTOR: Temsirolimus (Pfizer)	HDAC inhibitors:
AKT: MK2206 (Merck)	Vorinostat (Merck)
Signal transduction/ cell cycle:	Belinostat (TopoTarget)
Flavopiridol (Sanofi)	Romidepsin (Celgene)
Dinaclitib (Merck)	Protease/chaperone:
Stem cell-targeted agents:	Bortezomib (Millennium)
Vismodegib (Genentech)	PU-H71 (DCTD)
Other:	Immune modulators:
Dasatinib (BMS)	Ipilimumab (Medarex)
Tipifarnib (J&J)	1-Methyltryptophan (New Link Genetics)
Imatinib (Novartis)	PARP inhibitors:
IPdR (DCTD)	Veliparib (Abbott)
Z-Endoxifen (DCTD)	Aurora kinase A inhibitor:
	Alisertib (Millenium)

EGFR = epidermal growth factor receptor; HDAC = histone deacetylase; IGF-1R = insulin-like growth factor 1 receptor.



IND Title	Agent Name(s)	Target/MOA	Drug Company
MK-2206 + AZD 6244 Combination IND	MK-2206	AKT Inhibitor	Merck
	AZD6244 hydrogen sulfate	MAP kinase Inhibitor	AstraZeneca
PU-H71	PU-H71	Hsp90 inhibitor	Samus Therapeutics
iABT-888 + SCH727965 Combination IND	ABT-888 (Veliparib)	PARP inhibitor	Abbott
	SCH 727965 (dinaciclib)	CDK inhibitor	Merck
OSI-906	OSI-906	IGF-1R inhibitor	OSI/Astellas
ARQ 197	MLN 8237	cMet inhibitor	ArQule
MLN8237	ARQ 197 (tivantinib)	Aurora kinase inhibitor	Millennium
Bevacizumab— head & neck cancers	Bevacizumab (rhuMAb VEGF)	Anti-VEGF antibody	Genentech
Bevacizumab— gastrointestinal cancers	Bevacizumab (rhuMAb VEGF)	Anti-VEGF antibody	Genentech
Bevacizumab—rare cancers	Bevacizumab (rhuMAb VEGF)	Anti-VEGF antibody	Genentech
Bevacizumab— breast cancers	Bevacizumab (rhuMAb VEGF)	Anti-VEGF antibody	Genentech
Bevacizumab— gynecologic cancers	Bevacizumab (rhuMAb VEGF)	Anti-VEGF antibody	Genentech
Bevacizumab— genitourinary cancers	Bevacizumab (rhuMAb VEGF)	Anti-VEGF antibody	Genentech
Trastuzumab—breast cancer	Herceptin (trastuzumab)	Anti-HER2 antibody	Genentech
AMG 386	AMG 386	Ang 1/2-neutralizing peptibody	Amgen
Bortezomib and sorafenib for hematologic malignancies	Nexavar (sorafenib)	Serine/threonine and receptor tyrosine kinase inhibitor	Millennium
		Reverse inhibitor of 26S proteasome	
AZD2171 and sunitinib malate—sarcoma	SU011248 L-malate; Sutent (sunitinib malate) AZD2171; Recentin (cediranib)	Receptor tyrosine kinase inhibitor	Pfizer
		VEGFR-1, -2, and -3 inhibitor	AstraZeneca
TRC 105	TRC 105	Anti-CD105 antibody	Tracon
TL32711	TL32711 (birinapant)	Smac mimetic	TetraLogic
SCH 727965 + MK-2206	SCH 727965 (dinaciclib)	CDK inhibitor	Merck
	MK-2206	AKT inhibitor	Merck
Cabozantinib (XL184)	XL184 (cabozantinib s-malate)	c-MET and VEGFR2 inhibitor	Exelixis
Recombinant human interleukin-15	Recombinant human IL-15	Immune stimulator	N/A

INDS FILED IN 2011 AND 2012

BTK = Bruton tyrosine kinase; CDK = cyclin-dependent kinase;
MAP = mitogen-activated protein; MOA = mechanism of action;
VEGFR = vascular endothelial growth factor receptor.

IND Title	Agent Name(s)	Target/MOA	Drug Company
MK-1775	MK-1775	Wee1 inhibitor	Merck
MLN8237—Specific indication not specified: several tumor types	MLN 8237	Aurora kinase inhibitor	Millennium
MK-1775	MK-1775	Wee1 inhibitor	Merck
Biomarker-directed therapies	MK-1775	Wee1 inhibitor	Merck
	ABT-888 (Veliparib)	PARP inhibitor	Abbott
	GSK1120212B (trametinib)	MEK inhibitor	GSK
MK-8776	MK-8776 (SCH 900776))	Chk1 inhibitor	Merck
Brentuximab Vedotin (SGN-35)	SGN-35 (brentuximab vedotin)	Anti-CD30 antibody–drug conjugate	Seattle Genetics
ARQ 197 (tivantinib)—solid tumors	ARQ 197 (tivantinib)	cMet inhibitor	ArQule
Ibrutinib (PCI-32765)	PCI-32765 (ibrutinib)	BTK inhibitor	Pharmacyclics

INDS FILED IN 2011 AND 2012 (CONT.)

BTK = Bruton tyrosine kinase; CDK = cyclin-dependent kinase; MAP = mitogen-activated protein; MOA = mechanism of action; VEGFR = vascular endothelial growth factor receptor.

The average time from Senior Advisory Committee approval to CRADA execution was 160 days, compared with an average of 495 days for the 10 CRADAs executed through the Technology Transfer Center from 2008 to 2011.

Examples of novel combination studies that are moving forward due to CTEP-sponsored CRADAs using IP agreement terms include:

- A pilot study to determine the pharmacodynamic effects of combining an AKT inhibitor (MK-2206) with an MEK inhibitor (AZD6244) in colorectal cancer, based on synergistic effects seen in a mouse model of colorectal cancer
- Combination of a PARP inhibitor (ABT-888) with a CDK inhibitor (SCH727965), based on preclinical studies suggesting that CDK inhibitors may disrupt BRCA1 and sensitize cells to PARP-1 inhibition
- Combination of an AKT inhibitor (MK-2206) with a CDK inhibitor (SCH727965) in pancreatic cancer, based on preclinical studies demonstrating a synergistic effect of this combination in pancreatic cancer

RAB actively manages a portfolio of approximately 100 INDs, representing a wide variety of agents. From 2011 through 2012, RAB was responsible for:

- Submitting 3,939 IND amendments to the CTEP DCTD portfolio
- Managing responses to 66 FDA “Request for Information” letters
- Filing 365 IND Safety Reports
- Coordinating four Pre-IND/End-of-Phase 2 FDA meetings for potential licensing studies

To facilitate interactions among the FDA, NCI, and industry, RAB coordinates an FDA–NCI monthly meeting with the FDA Oncology Director and staff. This standing meeting is used to discuss issues of common interest related to oncology drugs and their approval and has the ultimate goal of streamlining drug development.



RAB has expanded its interactions with the FDA to include the Office of In Vitro Diagnostics Evaluation and Safety in the Center for Devices and Radiological Health. RAB is CTEP's liaison with this office with respect to queries about regulatory support for an investigational treatment-determining assay used in a CTEP-supported trial. In certain instances, RAB handles these queries via the center's Pre-Submission consultative pathway. A monthly meeting with colleagues in the Center for Devices and Radiological Health, coordinated by DCTD's Cancer Diagnosis Program, is also used to discuss issues of common interest, including an assay's impact on patient safety and its potential impact on drug development and approval.

PHARMACEUTICAL MANAGEMENT BRANCH

Background

The **Pharmaceutical Management Branch (PMB)** provides pharmaceutical services for clinical trials sponsored by CTEP. Because CTEP manages clinical trials of more than 100 investigational agents, research pharmacists in PMB must be focused on the latest advances in oncology practice and provide guidance for the thousands of sites around the world performing research with these novel agents. In brief, this branch provides a unique national and international resource for experimental oncology products and supports CTEP's clinical research effort by providing the extramural community with specific pharmaceutical services, regulatory oversight, and administrative support.

Accomplishments

Active Investigator and Associate Registration. More than 21,000 investigators are registered with PMB to receive shipments of investigational anticancer agents. Of these investigators, more than 18,000 (88%) are domestic and more than 2,500 (12%) are international researchers. More than 14,500 individuals with associate or paraprofessional degrees (Clinical Research Associates, Registered Pharmacists, Registered Nurses, etc.) are registered.

In 2012, PMB processed more than 30,000 requests for clinical agents in support of CTEP-sponsored trials:

- Foreign clinical agent requests: 1,300 (15 countries)
- "Blinded-order" clinical agent requests: 11,000 (for 30 blinded protocols accruing patients)
- Standard-order Clinical Shipment Requests: 19,000
- Shipment accuracy rate: 99.991% (<1 error in 10,000 shipments)

Specialized Resources Available to Support Randomized, Placebo-Controlled Studies. The development, implementation, support, and monitoring of blinded trials require the development of specialized computer programming for each trial to ensure that the correct medication or placebo reaches the appropriate patient in a timely manner. A total of 30 blinded trials are either active or closed to accrual, and 13 more are in development.

Treatment Referral Center. The Treatment Referral Center (TRC) provides information to community oncologists about therapeutic options for cancer patients, emphasizing referrals to Cooperative Group studies or Cancer Centers. In the event that an ongoing study cannot be found, the TRC facilitates access through other, nontraditional mechanisms (i.e., TRC protocols and Special Exceptions). These mechanisms are intended to provide investigational agents with established toxicity profiles and potential efficacy in the target disease to patients who may not fit the strict eligibility criteria for an investigational protocol. Special Exceptions are patient-specific protocols similar to FDA single-patient INDs. In 2012, the TRC established a release program for chimeric 14.18 monoclonal antibody to be used in pediatric neuroblastoma patients. This program has provided access to the agent for more than 20 neuroblastoma patients who were not eligible for ongoing investigational protocols.

Investigator Community Service and Support Projects. PMB provides a number of support services to the research community. The PMB website provides investigators and the associated community with valuable and time-saving online tools to meet regulatory requirements. The website receives about 11,000 hits per month. The *Inside PMB* newsletter is an innovative and creative publication that has been distributed quarterly since 2003 to investigators and associates. The newsletter is distributed electronically, and all editions are posted on the website for reference. PMB also has an after-hours e-mail address where investigators and support staff can send questions 24 hours a day, 7 days a week, 365 days per year. The address is particularly helpful for sites outside the continental United States and international sites. The routine response time is one business day, and there are more than 6,000 inquiries per year. PMB also distributes Investigator Brochures containing confidential and important information required by investigators to develop and conduct clinical trials. PMB has implemented a responsive and cost-effective method of distributing the brochures to investigators by e-mail. For institutions that cannot receive the documents electronically, PMB provides a CD by mail; 86% are sent via e-mail and 14% via CD. Nearly 9,000 Investigator Brochures are distributed annually. More than 7,500 requests are made annually to the Identity and Access Management/ Investigator Registration/Enterprise Core Module Help Desk Teams to address account management and investigator registration issues. Finally, in 2012, PMB implemented the use of an online clinical agent request process. The Online Agent Order Processing application provides capabilities for

online ordering of agents, reviewing order status, shipment tracking information, and assistance with selecting data elements of requests for clinical agents to facilitate and expedite the ordering process. Nearly all orders are now processed electronically.

CLINICAL TRIALS MONITORING BRANCH

Background

The **Clinical Trials Monitoring Branch (CTMB)** supports the phase 1, phase 2, and Cooperative Group Programs by providing a quality assurance system for CTEP-sponsored trials. This system ensures that data are reliable and compliant with protocols and that they meet regulatory and Good Clinical Practice requirements.

Accomplishments

The Quality Assurance Program includes:

- Establishing standards for evaluating the conduct of research and the reporting of audit findings
- Ensuring the protection of research patients
- Monitoring the conduct of clinical trials by conducting onsite audits to ensure data quality, compliance with the protocol, and adherence to regulatory requirements, NCI policies, and Good Clinical Practice requirements
- Continuing education of investigators and research institutional sites through onsite audits to share information on data quality, data management, and other aspects of quality assurance

Scope of Program. The Quality Assurance Program includes institutions conducting phase 1 and phase 2 trials (including N01 sites), Cooperative Groups, CCOPs, 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.

New Initiatives and Recent Accomplishments

- In April 2012, CTEP's clinical data management system, Medidata Rave, was launched for early-phase clinical trials. Medidata Rave has replaced a variety of electronic and paper-based data capture systems that were used



Organization/Type Study	Audits	Protocols	Patient Cases
Phase 1/2 studies	121	442	1,030
Cooperative Groups	1,720	10,956	11,185
Cancer Centers and single institutions	35	120	708

AUDIT STATISTICS, JANUARY 2011 TO DECEMBER 2012

by the groups for many years and establishes a common clinical data management system (CDMS) across the Cooperative Groups, NCI-funded networks, and the Early Therapeutics Program. In an effort to make the transition from paper-based reports, and coinciding with the deployment of Medidata Rave, IDB and CTMB staff have been collaborating closely with Theradex (an NCI contractor) to develop and deploy a Web-based reporting system that will provide IDB staff with 24/7 access to clinical data. The system will include modules for patient demographics, protocol compliance, and reporting of adverse events, as well as an end-of-study module. Together representatives from IDB and CTMB staff have also been actively engaged in the development of electronic case report forms for the collection of genomic and pharmacodynamic data.

- In October 2012, CTMB issued revisions to the [Guidelines for Auditing of Clinical Trials for Cooperative Groups, CCOP Research Bases, and the Cancer Trials Support Unit \(CTSU\)](#).
- CTMB has been exploring the utilization of an informatics infrastructure to perform robust remote data monitoring to identify trends in data elements that are suggestive of data irregularities. To this end, the program is exploring the feasibility of utilizing the informatics infrastructure to support remote data auditing of source documents contained in electronic medical records, thereby reducing costs associated with logistical issues such as travel and site preparation.

CLINICAL TRIALS OPERATIONS AND INFORMATICS BRANCH

The [Clinical Trials Operations and Informatics Branch \(CTOIB\)](#) supports the development and management of CTEP-sponsored clinical trials through the use of information technology tools and systems and the business activities of the Protocol Information Office. CTOIB oversees these two functional areas, which serve as the backbone for the CTEP trial review and management process.

Protocol and Information Office

Item	2011	2012
Unsolicited LOIs	141	138
Mass-solicited LOIs	106	168
Concepts	41	78
New protocols	214	197
Protocol revisions	322	306
Protocol amendments	1,997	1,328

ITEMS PROCESSED BY THE PROTOCOL AND INFORMATION OFFICE, 2011-2012

Since 2010, the Protocol and Information Office has been working on improvements to the protocol review and development process as part of the Operational Efficiency Working Group initiative. Improvements include utilization of an electronic distribution process that eliminates the use of paper-generated protocol packets, use of Microsoft SharePoint to create electronic repositories and workflows to streamline the review and comment process, and use of Microsoft Word Track Changes to assist sites with the addition of administrative comments following CTEP reviews.

CTEP Enterprise System

The CTEP Enterprise System (ESYS) is the central information technology system used to manage the development and conduct of CTEP-sponsored clinical trials. The CTEP ESYS also supports trials sponsored by the Division of Cancer Prevention's CCOP and DCTD's Cancer Imaging Program. The CTEP ESYS comprises 25 applications that are both

internal and external facing. As part of its involvement in the development of NCI-centralized protocol databases (i.e., the Clinical Trials Registration Program), CTOIB has been in the process of modernizing the CTEP ESYS to facilitate the complete integration of all required NCI internal databases. CTOIB integration activities include:

- Clinical Trials Reporting Program
- Electronic case report forms related to use of common data elements in the Clinical Data Update System
- Electronic protocol authoring, review, and commenting tools
- Rave integration specific to adverse event reporting via the Cancer Adverse Event Reporting System (caAERS)
- LaserFiche integration with CTEP ESYS in support of moving to the Shady Grove campus

The CTEP ESYS has been utilized since 1997 and allows CTEP to report data on adverse events, accrual, demographics, and response to interested parties to reliably assess the performance of clinical trials.

The CTEP ESYS contains data on:

- 10,873 LOIs
- 1,034,171 patient records
- 1,256 concepts
- 163,070 expedited adverse event reports
- 22,483 protocols
- 1,227,355 expedited and routine adverse event reports

The CTEP ESYS contains three critical components used for submitting information to CTEP:

1. **Adverse event reporting system**—Used by members of the external community to inform IND sponsors and the FDA of serious adverse events occurring during trials. Current CTOIB activities related to adverse event reporting include customizing CaAERS for use by sites reporting on CTEP-sponsored studies. This includes integrating Rave with caAERS to allow Rave users to submit reports of serious adverse events while using Rave, as well as updating tools used by CTEP to review and assess submitted adverse event reports.

2. **Clinical Data Update System**—Used by the external community to submit patient accrual information, demographic makeup of accrued patients, response data, and routine adverse events to CTEP to facilitate stronger oversight of trial conduct. Current CTOIB activities related to the Clinical Data Update System is the assessment of approved common data elements that are stored within the the Cancer Data Standards Repository and will be utilized by electronic case report forms and what CDUS elements need to be updated to match this activity.
3. **Identity and Access Management**—Used by members of the external community and CTEP to securely manage access to applications. Identity and Access Management allows for single-source sign-on to all CTEP-managed applications and reduces the need for multiple usernames and passwords. The CTEP ESYS also stores all of the data related to the Common Toxicity Criteria for Adverse Events, which allows for usage of current terminology when submitting adverse-event data. CTOIB is currently working with NCI's Center for Biomedical Informatics and Information Technology to extend the usage of Identity Access Management to include the NIH Lightweight Directory Access Protocol to provide all CTEP ESYS users with true single-sign-on capability.

Two new applications have been developed since 2010—the Integrated Platform for Agents and Diseases (IPAD) and the Online Agent Ordering and Processing (OAOP) application. IPAD serves as a search engine for anyone seeking information contained within the CTEP ESYS, which allows for customized queries that can be saved and exported as needed along with access to protocol-related documents linked within the CTEP ESYS. OAOP replaces a manual process, whereby clinical trial sites order agent(s) from PMB, with an electronic process that has vastly reduced the error rate.

Operational Efficiency Working Group Involvement

To support recommendations from the Operational Efficiency Working Group to improve timelines for protocol development, CTOIB is opening its services to use by extramural investigators. The timeline reports website will provide a centralized protocol tracking service so that all investigators will have 24/7 online access to information about the status of their protocols in the development and approval process. This will help CTEP and its investigators to reduce protocol development timelines by more than 75%.



Protocol Tracker

Document Tracker

Track LOIs/Concepts/Protocols Sequential View Gantt View

Document Number: LOI XXXXXX
Status: [Consensus Review sent to PI](#)
Status Date: 02/21/2011
Principal Investigator: John Smith
Lead Organization: Group ABC
Associated INDs: 1111, 2222
Associated Agents: AAA1, BBB2

Document Milestones	Milestone Date	LOI/Concept/Protocol
Stage 1a: Initial LOI Consensus Evaluations		
LOI received	04/01/2010	LOI
IDB reviewed	04/7/2010	LOI
PRC reviewed	04/8/2010	LOI
Consensus Review completed	04/15/2010	LOI
Consensus Review sent to PI	04/15/2010	LOI

Tracking results provided by Document Tracker 04/22/2010 4:36 P.M. ET

NOTICE: This is for tracking the Protocol Development Timelines.

CTOIB'S PROTOCOL TRACKER

FUTURE DIRECTIONS

CTEP will focus on four key areas over the next 5 years:

1. Expand efforts in targeted therapeutics in early-phase trials.
2. Assist in the development of the NCTN/Cooperative Groups into a highly integrated system capable of performing cutting-edge, definitive trials with molecularly targeted agents.
3. Improve development and accrual timelines for phase 1–3 trials.
4. Increase contributions to the mentoring of the next generation of clinical investigators.

Expand targeted therapeutics in early-phase trials:

To remain at the forefront of cancer treatment, CTEP must increasingly focus its efforts and resources on clinical trials

that have the greatest likelihood of disrupting the most important mechanisms of cancer cell growth, differentiation, and metastasis. Translating scientific discoveries into clinically effective and safe interventions will require CTEP to:

- Continue to serve as the key clinical facilitator for the newly created NExT program, designed to reinvigorate the ability of academic investigators to bring novel agents into the clinic.
- Improve and expand relationships with pharmaceutical and biotechnology companies to leverage their investments in drug discovery as agents increasingly target smaller, molecularly defined populations.
- Develop the Early Trials–Clinical Trials Network into an effective mechanism in which all patients entering trials have their tumors profiled for specific molecular targets.
- Design trials enriched with biomarkers, using improved technology, especially in solid tumors, to enable pre- and post-therapy assessments of tissue, blood, and functional imaging.

- Integrate and align drug development efforts with other major NCI biomarker and pathway discovery programs, such as the Clinical Assay Development Program, Patient Characterization Centers, and the Center for Cancer Genomics.

Develop the NCTN/Cooperative Groups into an effective mechanism for cutting-edge, definitive trials that precisely characterize patient populations:

- Assist with funding from the Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP) for these trials.
- Aid in the development of the new Translational Centers in the NCTN.
- Collaborate with the NCTN and industry in trial designs and public-private partnership agreements.

Improve timelines for developing and accruing to large phase 2 and 3 trials:

- Monitor and track target timelines for every CTEP-sponsored protocol.
- Develop metrics that allow realistic expectations of the workload (number of trials) that can be supported with the resources provided to investigators by CTEP.
- Coordinate with patient advocates, community physicians, and other allies to educate cancer patients about clinical trials and the benefits of participation.
- Leverage technology to promote consistent standards, templates, tools, and reports so that clinical trial methods become more uniform throughout the NCI system.

Expand CTEP contributions to mentoring the next generation of clinical investigators:

- Expand the CTEP fellowship program, whereby U.S. oncology fellows spend 1–3 months at CTEP participating in protocol review.
- Increase attendance from U.S. fellows at CTEP's Early Drug Development Meetings.
- Continue the CrDL program for new fellows.
- Continue annual meetings of the American Society of Clinical Oncology with young investigators hosted by CTEP.

SELECTED PUBLICATIONS

INVESTIGATIONAL DRUG BRANCH

Pediatric phase I trial and pharmacokinetic study of dasatinib: a report from the Children's Oncology Group Phase I Consortium, Aplenc R, Blaney SM, Strauss LC, Balis FM, Shusterman S, Ingle AM, Agrawal S, Sun J, Wright JJ, Adamson PC. *Journal of Clinical Oncology*, 2011;29(7):839–844. <http://www.ncbi.nlm.nih.gov/pubmed/21263099>

- In a phase 1 study of dasatinib in pediatric patients with refractory solid tumors or imatinib-refractory, Philadelphia chromosome-positive leukemia, drug disposition and tolerability of dasatinib were similar to those observed in adult patients. There were three complete cytogenetic responses, three partial cytogenetic responses, and two partial/minimal cytogenetic responses observed in evaluable patients with CML.

Early tumor progression associated with enhanced EGFR signaling with bortezomib, cetuximab, and radiotherapy for head and neck cancer, Argiris A, Duffy AG, Kummar S, Simone NL, Arai Y, Kim SW, Rudy SF, Kannabiran VR, Yang X, Jang M, Chen Z, Suksta N, Cooley-Zgela T, Ramanand SG, Ahsan A, Nyati MK, Wright JJ, Van Waes C. *Clinical Cancer Research*, 2011;17(17):5755–5764. <http://www.ncbi.nlm.nih.gov/pubmed/21750205>

- Combining bortezomib with cetuximab and radiation therapy showed unexpected early progression of squamous cell carcinoma of the head and neck (SCCHN), evidence for stabilization of epidermal growth factor receptor (EGFR), increased prosurvival signaling, and SCCHN-related cytokine expression, warranting avoidance of this combination.

A phase II study of sunitinib in patients with recurrent epithelial ovarian and primary peritoneal carcinoma: an NCIC Clinical Trials Group Study, Biagi JJ, Oza AM, Chalchal HI, Grimshaw R, Ellard SL, Lee U, Hirte H, Sederias J, Ivy SP, Eisenhauer EA. *Annals of Oncology*, 2011;22(2):335–340. <http://www.ncbi.nlm.nih.gov/pubmed/20705911>

- The authors conducted a two-stage phase 2 study to evaluate the objective response rate of oral sunitinib in recurrent epithelial ovarian cancer. Single-agent sunitinib had modest activity in recurrent platinum-sensitive ovarian cancer, but only at the 50-mg intermittent dose



schedule, suggesting that dose and schedule may be vital considerations in further evaluation of sunitinib in this cancer setting.

A multiinstitutional phase 2 trial of pazopanib monotherapy in advanced anaplastic thyroid cancer, Bible KC, Suman VJ, Menefee ME, Smallridge RC, Molina JR, Maples WJ, Karlin NJ, Traynor AM, Kumar P, Goh BC, Lim WT, Bossou AR, Isham CR, Webster KP, Kukla AK, Bieber C, Burton JK, Harris P, Erlichman C, Mayo Phase 2 Consortium; Mayo Clinic Endocrine Malignancies Disease-Oriented Group. *Journal of Clinical Endocrinology and Metabolism*, 2012;97(9):3179–3184.

<http://www.ncbi.nlm.nih.gov/pubmed/22774206>

- Prompted by the impressive activity of pazopanib in progressive metastatic differentiated thyroid cancer, the authors investigated this kinase inhibitor in anaplastic thyroid cancer (ATC). Despite preclinical *in vivo* activity in ATC, pazopanib had minimal single-agent clinical activity in advanced ATC.

Phase 2 study of dasatinib in the treatment of head and neck squamous cell carcinoma, Brooks HD, Glisson BS, Bekele BN, Johnson FM, Ginsberg LE, El-Naggar A, Culotta KS, Takebe N, Wright J, Tran HT, Papadimitrakopoulou VA. *Cancer*, 2011;117(10):2112–2119.

<http://www.ncbi.nlm.nih.gov/pubmed/21523723>

- In light of the scarce treatment options for advanced SCCHN, this phase 2 study was conducted to evaluate the safety, tolerability, pharmacokinetics, and efficacy of dasatinib in this setting. Single-agent dasatinib failed to demonstrate significant activity in patients with advanced SCCHN, despite c-Src inhibition.

Sunitinib in relapsed or refractory diffuse large B-cell lymphoma: a clinical and pharmacodynamic phase II multicenter study of the NCIC Clinical Trials Group, Buckstein R, Kuruvilla J, Chua N, Lee C, Macdonald DA, Al-Tourah AJ, Foo AH, Walsh W, Ivy SP, Crump M, Eisenhauer EA. *Leukemia & Lymphoma*, 2011;52(5):833–841.

<http://www.ncbi.nlm.nih.gov/pubmed/21463120>

- This phase 2 trial evaluated sunitinib, a multitargeted vascular endothelial growth factor receptor (VEGFR) kinase inhibitor. Despite some activity in solid tumors, sunitinib showed no evidence of response in relapsed or refractory diffuse large B-cell lymphoma and had greater-than-expected hematologic toxicity.

KIT as a therapeutic target in metastatic melanoma,

Carvajal RD, Antonescu CR, Wolchok JD, Chapman PB, Roman RA, Teitcher J, Panageas KS, Busam KJ, Chmielowski B, Lutzky J, Pavlick AC, Fusco A, Cane L, Takebe N, Vemula S, Bouvier N, Bastian BC, Schwartz GK. *Journal of the American Medical Association*, 2011;305(22):2327–2334.

<http://www.ncbi.nlm.nih.gov/pubmed/21642685>

- The authors used imatinib mesylate to explore the effects of KIT inhibition in advanced melanoma harboring activating mutations and amplification of this type III transmembrane receptor tyrosine kinase. A subset of patients had a significant clinical response to imatinib, although the authors observe that this response may be limited to tumors harboring KIT alterations of proven functional relevance.

Phase I study of the combination of sorafenib and temsirolimus in patients with metastatic melanoma, Davies MA, Fox PS, Papadopoulos NE, Bedikian AY, Hwu WJ, Lazar AJ, Prieto VG, Culotta KS, Madden TL, Xu Q, Huang S, Deng W, Ng CS, Gupta S, Liu W, Dancey JE, Wright JJ, Bassett RL, Hwu P, Kim KB. *Clinical Cancer Research* 2012;18(4):1120–1128.

<http://www.ncbi.nlm.nih.gov/pubmed/22223528>

- This phase 1 clinical trial was conducted to determine the safety, efficacy, and molecular effects of sorafenib with temsirolimus in patients with advanced melanoma. Tumor biopsies were analyzed for activating mutations in BRAF and NRAS and for expression of P-extracellular signal-regulated kinase (P-ERK) and P-S6 proteins. The combination therapy resulted in significant toxicity at higher dose levels, failed to achieve any clinical responses in a genetically unselected patient population, and did not inhibit P-ERK.

Phase II study of aflibercept in recurrent malignant glioma: a North American Brain Tumor Consortium study, de Groot JE, Lamborn KR, Chang SM, Gilbert MR, Cloughesy TE, Aldape K, Yao J, Jackson EF, Lieberman F, Robins HI, Mehta MP, Lassman AB, Deangelis LM, Yung WK, Chen A, Prados MD, Wen PY. *Journal of Clinical Oncology*, 2011;29(19):2689–2695.

<http://www.ncbi.nlm.nih.gov/pubmed/21606416>

- This single-arm, phase 2 study evaluated the efficacy of aflibercept (VEGF Trap), a recombinantly produced fusion protein that scavenges both VEGF and placental growth factor in patients with recurrent malignant glioma.

Aflibercept monotherapy had moderate toxicity and minimal evidence of single-agent activity in unselected patients with recurrent malignant glioma.

Emerging therapeutics for advanced thyroid malignancies: rationale and targeted approaches, Harris PJ, Bible KC. *Expert Opinion on Investigational Drugs*, 2011;20(10):13571375.

<http://www.ncbi.nlm.nih.gov/pubmed/21910667>

- In this review, the authors discuss the characteristics of the three major histological subtypes of thyroid cancer—differentiated, medullary, and anaplastic—and review data from studies of new and investigational agents with demonstrated efficacy or therapeutic promise in these cancers.

Phase I trial of bortezomib (PS-341; NSC 681239) and alvocidib (flavopiridol; NSC 649890) in patients with recurrent or refractory B-cell neoplasms, Holkova B, Perkins EB, Ramakrishnan V, Tombes MB, Shrader E, Talreja N, Wellons MD, Hogan KT, Roodman GD, Coppola D, Kang L, Dawson J, Stuart RK, Peer C, Figg WD Sr, Kolla S, Doyle A, Wright J, Sullivan DM, Roberts JD, Grant S. *Clinical Cancer Research*, 2011;17(10):3388–3397.

<http://www.ncbi.nlm.nih.gov/pubmed/21447728>

- This phase 1 study evaluated the combination of bortezomib and alvocidib in patients with B-cell malignancies (multiple myeloma, indolent lymphoma, and mantle cell lymphoma). Two complete responses (12%) and five partial responses (31%) were observed at the maximum tolerated dose (MTD) (overall response rate = 44%). The combination therapy appeared to be active in patients with relapsed and/or refractory multiple myeloma or non-Hodgkin's lymphoma.

Evaluation of KRAS mutations, angiogenic biomarkers, and DCE-MRI in patients with advanced non-small-cell lung cancer receiving sorafenib, Kelly RJ, Rajan A, Force J, Lopez-Chavez A, Keen C, Cao L, Yu Y, Choyke P, Turkbey B, Raffeld M, Xi L, Steinberg SM, Wright JJ, Kummer S, Gutierrez M, Giaccone G. *Clinical Cancer Research*, 2011;17(5):1190–1199.

<http://www.ncbi.nlm.nih.gov/pubmed/21224376>

- The goal of this phase 2 trial was to determine whether sorafenib is active in non-small-cell lung cancer and to determine the impact of K-Ras mutation status. Neither

K-Ras nor EGFR mutational status were correlated with response, progression-free survival, or overall survival.

An international, multicenter phase II trial of bortezomib in patients with hepatocellular carcinoma, Kim GP, Mahoney MR, Szydlo D, Mok TS, Marshke R, Holen K, Picus J, Boyer M, Pitot HC, Rubin J, Philip PA, Nowak A, Wright JJ, Erlichman C. *Investigational New Drugs*, 2012;30(1):387–394.<http://www.ncbi.nlm.nih.gov/pubmed/20839030>

- This international, multicenter trial evaluated bortezomib as monotherapy in patients with unresectable hepatocellular carcinoma. Despite the lack of significant activity, this report serves as a baseline clinical experience for the development of future dual biologic approaches including bortezomib.

Phase I study of PARP inhibitor ABT-888 in combination with topotecan in adults with refractory solid tumors and lymphomas, Kummur S, Chen A, Ji J, Zhang Y, Reid JM, Ames M, Jia L, Weil M, Speranza G, Murgu AJ, Kinders R, Wang L, Parchment RE, Carter J, Stotler H, Rubinstein L, Hollingshead M, Melillo G, Pommier Y, Bonner W, Tomaszewski JE, Doroshow JH. *Cancer Research* 2011;71(17):5626–5634.

<http://www.ncbi.nlm.nih.gov/pubmed/21795476>

- This phase 1 trial of ABT-888 (veliparib), a PARP inhibitor, in combination with topotecan, a topoisomerase I–targeted agent, was carried out in patients with refractory solid tumors and lymphomas. The results indicate that PARP inhibition can modulate the capacity to repair topoisomerase I–mediated DNA damage in the clinic.

Dose-escalating and pharmacological study of bortezomib in adult cancer patients with impaired renal function: a National Cancer Institute Organ Dysfunction Working Group Study, Leal TB, Remick SC, Takimoto CH, Ramanaathan RK, Davies A, Egorin MJ, Hamilton A, LoRusso PA, Shibata S, Lenz HJ, Mier J, Sarantopoulos J, Mani S, Wright JJ, Ivy SP, Neuwirth R, von Moltke L, Venkatakrishnan K, Mulkerin D. *Cancer Chemotherapy and Pharmacology*, 2011;68(6):1439–1447.

<http://www.ncbi.nlm.nih.gov/pubmed/21479634>

- This study was carried out to evaluate the safety, tolerability, and maximum tolerated dose (MTD) of bortezomib and to characterize its pharmacokinetic and pharmacodynamic profile in adults with advanced malignancies and



renal dysfunction. The agent was found to be well tolerated in patients with severe renal dysfunction, including dialysis patients, at the full dose established to be effective in the general patient population.

Phase I/II study of sorafenib in combination with temsirolimus for recurrent glioblastoma or gliosarcoma:

North American Brain Tumor Consortium study 05-02,

Lee EQ, Kuhn J, Lamborn KR, Abrey L, DeAngelis LM, Lieberman F, Robins HI, Chang SM, Yung WK, Drappatz J, Mehta MP, Levin VA, Aldape K, Dancey JE, Wright JJ, Prados MD, Cloughesy TF, Gilbert MR, Wen PY. *Neuro-oncology*, 2012;14(12):1511–1518.

<http://www.ncbi.nlm.nih.gov/pubmed/23099651>

- In this phase 1/2 study, combination therapy with sorafenib and temsirolimus had minimal activity and substantial toxicity in patients with glioblastoma multiforme (GBM). At interim analysis, the study was terminated and did not proceed to the second stage, as no patients remained progression free at 6 months. The toxicity of this combination therapy resulted in a maximum tolerated dose of temsirolimus that was only 1/10th of the single-agent dose. Minimal activity in recurrent glioblastoma multiforme was seen at the MTD of the two combined agents.

Phase I/II trial and pharmacokinetic study of cixutumumab in pediatric patients with refractory solid tumors and Ewing sarcoma: a report from the Children's Oncology Group.

Malempati S, Weigel B, Ingle AM, Ahern CH, Carroll JM, Roberts CT, Reid JM, Schmechel S, Voss SD, Cho SY, Chen HX, Krailo MD, Adamson PC, Blaney SM. *Journal of Clinical Oncology*, 2012;30(3):256–262.

<http://www.ncbi.nlm.nih.gov/pubmed/22184397>

- This phase 1/2 study found cixutumumab (IMC-A12) to be well tolerated in children with refractory solid tumors.

A dose escalation and pharmacodynamic study of triapine and radiation in patients with locally advanced pancreas cancer,

Martin LK, Grecula J, Jia G, Wei L, Yang X, Otterson GA, Wu X, Harper E, Kefauver C, Zhou BS, Yen Y, Bloomston M, Knopp M, Ivy SP, Grever M, Bekaii-Saab T. *International Journal of Radiation Oncology, Biology, Physics*, 2012;84(4):e475–481.

<http://www.ncbi.nlm.nih.gov/pubmed/22818416>

- This phase 1 study assessed the safety and tolerability of a novel inhibitor of the M2 subunit of ribonucleotide reduc-

tase and a potent radiosensitizer, in combination with radiation therapy in 12 patients with locally advanced pancreatic cancer. Ninety-two percent of patients (100% at dose level 3) experienced freedom from local tumor progression. In 75% of patients who eventually experienced progression, metastases developed without local progression. Levels of ribonucleotide reductase did not seem to predict outcome. The combination was found to be tolerable, with interesting activity, in this patient population.

Phase I trial of cixutumumab combined with temsirolimus in patients with advanced cancer, Naing A, Kurzrock R, Burger A, Gupta S, Lei X, Busaidy N, Hong D, Chen HX, Doyle LA, Heilbrun LK, Rohren E, Ng C, Chandhasin C, LoRusso P. *Clinical Cancer Research*, 2011;17(18):6052–6060.

<http://www.ncbi.nlm.nih.gov/pubmed/21750201>

- The objectives of this phase I study were to evaluate the tolerability and activity of temsirolimus combined with cixutumumab. The combination was well tolerated, and the authors are currently enrolling expansion cohorts at the MTD for patients with Ewing sarcoma and adrenocortical carcinoma.

Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma, Piekarz RL, Frye R, Prince HM, Kirschbaum MH, Zain J, Allen SL, Jaffe ES, Ling A, Turner M, Peer CJ, Figg WD, Steinberg SM, Smith S, Joske D, Lewis I, Hutchins L, Craig M, Fojo AT, Wright JJ, Bates SE. *Blood*, 2011;117(22):5827–5834.

<http://www.ncbi.nlm.nih.gov/pubmed/21355097>

- This phase 2 study of romidepsin (depsipeptide or FK228), a histone deacetylase inhibitor that is one of a new class of agents active in T-cell lymphoma, was conducted in patients with cutaneous (CTCL) and peripheral (PTCL) T-cell lymphoma. Major and durable responses in CTCL patients supported the approval of romidepsin for this cancer. Romidepsin had single-agent clinical activity associated with durable responses in patients with relapsed PTCL.

Phase I pharmacokinetic and pharmacodynamic study of SJG-136, a novel DNA sequence selective minor groove cross-linking agent, in advanced solid tumors, Puzanov I, Lee W, Chen AP, Calcutt MW, Hachey DL, Vermeulen WL,

Spanswick VJ, Liao CY, Hartley JA, Berlin JD, Rothenberg ML. *Clinical Cancer Research*, 2011;17(11):3794–37802.
<http://www.ncbi.nlm.nih.gov/pubmed/21346148>

- This phase 1 study evaluated SJG-136, a sequence-specific DNA cross-linking agent, in patients with advanced cancer. The MTD was established with no myelosuppressive effects. Coupled with supportive management, SJG-136 is now advancing to a phase 2 trial in ovarian cancer.

Phase II randomized trial of bevacizumab versus bevacizumab and thalidomide for relapsed/refractory multiple myeloma: a California Cancer Consortium trial, Somlo G, Lashkari A, Bellamy W, Zimmerman TM, Tuscano JM, O'Donnell MR, Mohrbacher AF, Forman SJ, Frankel P, Chen HX, Doroshow JH, Gandara DR. *British Journal of Haematology* 2011;154(4):533–535.
<http://www.ncbi.nlm.nih.gov/pubmed/21517811>

- In this phase 2 trial, the efficacy and safety of bevacizumab alone and in combination with thalidomide was evaluated in patients with multiple myeloma. The study was closed early due to poor accrual, which prevented correlation of VEGF or VEGFR1/VEGFR2 expression with response. In this limited sample of 12 evaluable patients, combination therapy yielded results that were similar to those of single-agent thalidomide.

Increased survival of glioblastoma patients who respond to antiangiogenic therapy with elevated blood perfusion, Sorensen AG, Emblem KE, Polaskova P, Jennings D, Kim H, Ancukiewicz M, Wang M, Wen PY, Ivy P, Batchelor TT, Jain RK. *Cancer Research*, 2012;72(2):402–407.
<http://www.ncbi.nlm.nih.gov/pubmed/22127927>

- The authors used MRI to assess tumor blood perfusion in 30 patients with recurrent glioblastoma who were undergoing treatment with cediranib, a pan-VEGF receptor tyrosine kinase inhibitor. Tumor blood perfusion increased durably for more than 1 month in 7 of 30 patients, in whom it was associated with longer survival. The findings offer direct clinical evidence in support of the hypothesis that vascular normalization can increase tumor perfusion and help improve patient survival.

Management of cardiac toxicity in patients receiving vascular endothelial growth factor signaling pathway inhibitors, Steingart RM, Bakris GL, Chen HX, Chen MH, Force T, Ivy SP, Leier CV, Liu G, Lenihan D, Lindenfeld J,

Maitland ML, Remick SC, Tang WH. *American Heart Journal*, 2012;163(2):156–163.
<http://www.ncbi.nlm.nih.gov/pubmed/22305831>

- The NCI Cardiovascular Toxicities Panel reviewed published literature and clinical experience on the use of VEGF signaling pathway inhibitors in the management of cancer patients with cardiovascular disease. This report presents the panel's expert opinion on the current clinical use and future investigation for safer, more expansive use of these drugs.

Targeting cancer stem cells by inhibiting Wnt, Notch, and Hedgehog pathways. Takebe N, Harris PJ, Warren RQ, Ivy SP. *Nature Reviews; Clinical Oncology*, 2011 Feb;8(2):97–106.
<http://www.ncbi.nlm.nih.gov/pubmed/21151206>

- In this review, the authors describe the role played by embryonic signaling pathways in the function of cancer stem cells (CSCs), the development of new anti-CSC therapeutic agents, and the complexity of potential CSC signaling cross-talk.

International models of investigator-initiated trials: implications for Japan, Trimble EL, Ledermann J, Law K, Miyata T, Imamura CK, Nam BH, Kim YH, Bang YJ, Michaels M, Ardron D, Amano S, Ando Y, Tominaga T, Kurokawa K, Takebe N. *Annals of Oncology*, 2012;23(12):3151–3155.
<http://www.ncbi.nlm.nih.gov/pubmed/22843420>

- In May 2010, experts from Japan, the Republic of Korea, the United Kingdom, and the United States met to discuss how policies related to the conduct of clinical trials may be applied to other regions of the world. This paper examines, from the viewpoint of local, national, and international concerns, how best practices in cancer clinical trial programs could be further adopted by the four participating countries.

CLINICAL INVESTIGATIONS BRANCH

Selected Practice-Changing NCI-CTEP-Supported Group Phase 3 Trials

Breast Cancer. CALGB-40101: Six cycles of doxorubicin and cyclophosphamide or paclitaxel are not superior to four cycles as adjuvant chemotherapy for breast cancer in women with zero to three positive axillary nodes: Cancer and Leukemia Group B 40101. Shulman LN, Cirrincione



CT, Berry DA, Becker HP, Perez EA, O'Regan R, Martino S, Atkins JN, Mayer E, Schneider CJ, Kimmick G, Norton L, Muss H, Winer EP, Hudis C. *Journal of Clinical Oncology*, 2012;30(33):4071-4076.

<http://www.ncbi.nlm.nih.gov/pubmed/22826271>

- This study compared four and six cycles of doxorubicin–cyclophosphamide or single-agent paclitaxel in patients with early breast cancer. No differences between the two regimens were found with respect to 4-year relapse-free survival or overall survival rates. Unplanned subset analyses showed no interaction between the number of cycles of therapy and tumor estrogen receptor or HER2 status, suggesting that no subgroup benefited from more prolonged therapy. The study had a 2x2 factorial design and also examined the effects of doxorubicin–cyclophosphamide versus single-agent paclitaxel. Final results of this second research question are still pending.

Breast Cancer. S0226: Combination anastrozole and fulvestrant in metastatic breast cancer, Mehta RS, Barlow WE, Albain KS, Vandenberg TA, Dakhil SR, Tirumali NR, Lew DL, Hayes DF, Gralow JR, Livingston RB, Hortobagyi GN. *New England Journal of Medicine*, 2012;367(5):435–444.

<http://www.ncbi.nlm.nih.gov/pubmed/22853014>

- This study demonstrated a statistically significant improvement in progression-free survival (the primary endpoint) for the combination of anastrozole and fulvestrant compared with either anastrozole alone or sequential anastrozole and fulvestrant for the treatment of hormone receptor–positive metastatic breast cancer. Overall survival was also longer with combination therapy than with standard treatment.

Ewing Sarcoma (Pediatrics). AEWS0031: Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group, Womer RB, West DC, Krailo MD, Dickman PS, Pawel BR, Grier HE, Marcus K, Sailer S, Healey JH, Dormans JP, Weiss AR. *Journal of Clinical Oncology*, 2012;30(33):4148–4154.

<http://www.ncbi.nlm.nih.gov/pubmed/23091096>

- The Children's Oncology Group conducted this randomized phase 3 study in newly diagnosed children, adolescents, and young adults to address the question of whether intensification of therapy by interval compression could improve the prognosis for patients with

localized Ewing sarcoma. The 5-year event-free survival rate was higher in patients who received therapy every 2 weeks (73%) than in those who received it every 3 weeks (65%) ($P = 0.048$). Interval compressed treatment is now considered standard treatment for patients with newly diagnosed, localized Ewing sarcoma.

Leukemia (ALL—Pediatrics). CCG-1961: Effect of alternate-week versus continuous dexamethasone scheduling on the risk of osteonecrosis in paediatric patients with acute lymphoblastic leukaemia: results from the CCG-1961 randomised cohort trial, Mattano LA, Devidas M, Nachman JB, Sather HN, Hunger SP, Steinherz PG, Gaynon PS, Seibel NL. *Lancet Oncology*, 2012;13(9):906–915.

<http://www.ncbi.nlm.nih.gov/pubmed/22901620>

- These investigators show that the dosing schedule of dexamethasone supersedes cumulative exposure as a key factor in the development of treatment-related osteonecrosis. They identify a simple dose modification of dexamethasone administration that can significantly reduce the incidence of osteonecrosis and improve ALL outcome.

Leukemia (ALLPediatrics). Childhood TARGET Project: Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia, Roberts KG, Morin RD, Zhang J, Hirst M, Zhao Y, Su X, Chen SC, Payne-Turner D, Churchman ML, Harvey RC, Chen X, Kasap C, Yan C, Becksfort J, Finney RP, Teachey DT, Maude SL, Tse K, Moore R, Jones S, Mungall K, Birol I, Edmonson MN, Hu Y, Buetow KE, Chen IM, Carroll WL, Wei L, Ma J, Kleppe M, Levine RL, Garcia-Manero G, Larsen E, Shah NP, Devidas M, Reaman G, Smith M, Paugh SW, Evans WE, Grupp SA, Jeha S, Pui CH, Gerhard DS, Downing JR, Willman CL, Loh M, Hunger SP, Marra MA, Mullighan CG. *Cancer Cell*, 2012;22(2):153–166.

<http://www.ncbi.nlm.nih.gov/pubmed/22897847>

- Children's Oncology Group ALL Committee investigators, working in collaboration with the NCI-supported Childhood Cancer TARGET project, identified a subtype of high-risk B-progenitor ALL with a gene expression profile similar to that of BCR-ABL1–positive ALL and with poor outcome, which they dubbed Ph-like ALL. Ph-like ALL cases were found to have rearrangements involving ABL1, JAK2, PDGFRB, CRLF2, and EPOR; activating mutations of IL7R and FLT3; and deletion of SH2B3, which encodes the JAK2-negative regulator LNK. Importantly, several of these alterations induce transformation that is attenuated

with tyrosine kinase inhibitors, suggesting that the treatment outcome of these patients may be improved with targeted therapy.

Acute Promyelocytic Leukemia. *C9710: Arsenic trioxide improves event-free and overall survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710*, Powell BL, Moser B, Stock W, Gallagher RE, Willman CL, Stone RM, Rowe JM, Coutre S, Feusner JH, Gregory J, Couban S, Appelbaum FR, Tallman MS, Larson RA ; Cancer and Leukemia Group B. *Blood*, 2010;116(19):3751–3757.

<http://www.ncbi.nlm.nih.gov/pubmed/20705755>

- This trial demonstrated both an event-free and overall survival advantage when patients are treated with arsenic trioxide as an added part of standard therapy for acute promyelocytic leukemia. Arsenic is added to treatment after the initial standard induction therapy as part of ongoing consolidation and maintenance therapy.

Multiple Myeloma. *CALGB-100104-ECOG-10014-BMT-CTN-0704: Lenalidomide after stem-cell transplantation for multiple myeloma*, McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, Giralt S, Stadtmauer EA, Weisdorf DJ, Vij R, Moreb JS, Callander NS, Van Besien K, Gentile T, Isola L, Maziarz RT, Gabriel DA, Bashey A, Landau H, Martin T, Qazilbash MH, Levitan D, McClune B, Schlossman R, Hars V, Postiglione J, Jiang C, Bennett E, Barry S, Bressler L, Kelly M, Seiler M, Rosenbaum C, Hari P, Pasquini MC, Horowitz MM, Shea TC, Devine SM, Anderson KC, Linker C. *New England Journal of Medicine*, 2012;366(19):1770–1781.

<http://www.ncbi.nlm.nih.gov/pubmed/22571201>

- Results from this trial established the effectiveness of long-term lenalidomide maintenance therapy following autologous transplantation for multiple myeloma in slowing disease progression and prolonging survival.

Glioblastoma Multiforme. *Patterns of care and survival for patients with glioblastoma multiforme diagnosed during 2006*. Yabroff KR, Harlan L, Zeruto C, Abrams J, Mann B. *Neuro-Oncology*, 2012;14(3):351–359.

<http://www.ncbi.nlm.nih.gov/pubmed/22241797>

- This pattern-of-care study was conducted after the publication of a pivotal phase 3 clinical trial showing the survival advantage of concurrent temozolomide

and radiotherapy over radiotherapy alone after surgical resection for GBM. This study documented treatment and outcomes of patients with GBM in the United States, using data from 14 Surveillance, Epidemiology, and End Results (SEER) registries. Reporting on current treatment approaches in one of the largest published cohorts of adult GBM patients, the study demonstrated that a new standard of treatment in the United States for adult patients with newly diagnosed GBM was rapidly diffused in the community setting after the publication of results from a pivotal clinical trial.

Lymphoma. *S0016: Phase III randomized intergroup trial of CHOP plus rituximab compared with CHOP chemotherapy plus (131)iodine-tositumomab for previously untreated follicular non-Hodgkin lymphoma: SWOG S0016*. Press OW, Unger JM, Rimsza LM, Friedberg JW, LeBlanc M, Czuczman MS, Kaminski M, Brazier RM, Spier C, Gopal AK, Maloney DG, Cheson BD, Dakhil SR, Miller TP, Fisher RI. *Journal of Clinical Oncology*, 2013;31(3):314–320. <http://www.ncbi.nlm.nih.gov/pubmed/23233710>

- This study showed no advantage to adding radio-immunotherapy to standard R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride [hydroxydaunomycin], vincristine sulfate [Oncovin], prednisone) in patients with follicular lymphoma. The results demonstrate that the more complicated and expensive therapy is not needed and highlight the need for continuing the search for improved therapeutics in this disease.

Prostate Cancer. *RTOG 94-08: Radiotherapy and short-term androgen deprivation for localized prostate cancer*, Jones CU, Hunt D, McGowan DG, Amin MB, Chetner MP, Bruner DW, Husain SM, Rotman M, Souhmai L, Sandler HM, Shipley WU; Radiation Oncology Group. *New England Journal of Medicine*, 2011;365(2):107–118.

<http://www.ncbi.nlm.nih.gov/pubmed/21751904>

- This randomized phase 3 clinical trial enrolled more than 2,000 men with early-stage prostate cancer and demonstrated that the addition of short-term hormone therapy to radiation therapy increased overall survival. In the intermediate-risk participants, prostate cancer deaths at 10 years were reduced from 10% to 3%, while no reduction in deaths was seen in low-risk patients.



Prostate Cancer: Role of Active Surveillance. National Institutes of Health State-of-the-Science Conference: role of active surveillance in the management of men with localized prostate cancer, Ganz PA, Barry JM, Burke W, Col NF, Corso PS, Dodson E, Hammond ME, Kogan BA, Lynch CF, Newcomer L, Seifter EJ, Tooze JA, Viswanath K, Wessells H. *Annals of Internal Medicine*, 2012;156(8):591–595.

<http://www.ncbi.nlm.nih.gov/pubmed/22351514>

- CTEP's Clinical Investigations Branch planned and led the development of this NIH State of the Science Conference in conjunction with other programs at NCI, the Centers for Disease Control and Prevention, and the NIH Office of Medical Applications of Research. The aim of the conference was to provide health care providers, patients, and the general public with a responsible assessment of currently available data on the use of active surveillance and other observational management strategies for low-grade, localized prostate cancer. The participants concluded that active surveillance has emerged as a viable option that should be

Surgery. ACOSOG-Z0011: Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastases: a randomized clinical trial, Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall LM, Morrow M. *Journal of the American Medical Association*, 2011;305(6):569–575.

<http://www.ncbi.nlm.nih.gov/pubmed/21304082>

- This trial was undertaken to determine the effects of complete axillary lymph node dissection on survival of patients with sentinel lymph node metastasis of breast cancer. The results demonstrated that, among patients with limited sentinel lymph node metastatic breast cancer treated with breast conservation and systemic therapy, the use of sentinel lymph node dissection alone did not result in lower survival rates than those resulting from axillary lymph node dissection.

CLINICAL GRANTS AND CONTRACTS BRANCH

Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia, Porter DL, Levine BL, Kalos M, Bagg A, June CH. *New England Journal of Medicine*, 2011;365(8):725–733.

<http://www.ncbi.nlm.nih.gov/pubmed/21830940>

- The authors designed a lentivirus vector expressing a chimeric antigen receptor with specificity for the B-cell antigen CD19, coupled with CD137 (a costimulatory receptor in T cells [4-1BB]) and CD3-zeta (a signal transduction component of the T-cell antigen receptor) signaling domains. A low dose of autologous chimeric antigen receptor–modified T cells reinfused into a patient with refractory CLL expanded to a level that was more than 1,000 times as high as the initial engraftment level in vivo and resulted in delayed development of the tumor lysis syndrome and complete remission that persisted at 10 months.

Cord-blood engraftment with ex vivo mesenchymal-cell coculture, de Lima F, McNiece I, Robinson SN, Munsell M, Eapen M, Horowitz M, Alousi A, Saliba R, McMannis JD, Kaur I, Kebriai P, Parmer S, Popat U, Hosing C, Champlin R, Bollard C, Moldrem JJ, Jones RB, Nieto Y, Andersson BS, Shah N, Oran B, Cooper L, Worth L, Qazilbash MH, Korbling M, Rondon G, Cirurea S, Bosque D, Maewal I, Simmons PJ, Shpall EJ. *New England Journal of Medicine*, 2012;367(24):2305–2315.

<http://www.ncbi.nlm.nih.gov/pubmed/23234514>

- This study was carried out to determine whether cord blood engraftment would be improved by transplanting cord blood that has been expanded ex vivo with mesenchymal stromal cells. This technique appeared to be safe and effective. Expanded cord blood in combination with unmanipulated cord blood significantly improved engraftment over unmanipulated cord blood only.

A Phase 1/2 study of chemosensitization with the CXCR4 antagonist plerixafor in relapsed or refractory acute myeloid leukemia. Uy GL, Rettig MP, Motabi IH, McFarland K, Trinkhaus KM, Hladnik LM, Kulkarni S, Abboud CM, Cashen AF, Stocker-Goldstein KE, Vij R, Westervelt P, Dpersio JF. *Blood*, 2012;119(17):3917–3924.

<http://www.ncbi.nlm.nih.gov/pubmed/22308295>

- In this phase 1/2 study, the authors hypothesized that inhibition of the CXCR4/CXCL12 axis by plerixafor, a small-molecule inhibitor, would disrupt the interaction of leukemic blasts with the environment and increase the sensitivity of AML blasts to chemotherapy. Correlative studies demonstrated a twofold mobilization in leukemic blasts into the peripheral circulation, with no evidence of symptomatic hyperleukocytosis or delayed count recovery with the addition of plerixafor. The authors concluded

that the addition of plerixafor to cytotoxic chemotherapy is feasible in AML and results in encouraging rates of remission.

Increased anti-leukemia activity of decitabine via AR-42-induced upregulation of miR-29b: a novel epigenetic-targeting approach in acute myeloid leukemia. Mims A, Walker AR, Huang X, Sun J, Wang H, Santhanam R, Dorrance AM, Walker C, Hoellerbauer P, Tarighat SS, Chan KK, Klisovec RB, Perroti D, Caligiuri MA, Byrd JC, Chen CS, James LL, Jacob S, Mrozek K, Bloomfield CD, Blum W, Garzon R, Schwind S, Marcucci G. *Leukemia*, 2012;342:1–8. <http://www.ncbi.nlm.nih.gov/pubmed/23178755>

- The authors hypothesized that priming AML cells with the novel histone deacetylase (HDAC) inhibitor AR-42 would result in increased response to decitabine treatment via upregulation of miR-29b. AR-42 was a potent HDAC inhibitor in AML, increasing miR-29b levels and leading to downregulation of known miR-29b targets. The sequential administration of AR-42 followed by decitabine resulted in a stronger anti-leukemic activity in vitro and in vivo than decitabine followed by AR-42 or either drug alone. These preclinical results with AR-42 priming before decitabine administration represent a promising, novel treatment approach and a paradigm shift with regard to the combination of epigenetic-targeting compounds in AML, where decitabine has been traditionally given before HDAC inhibitors.

Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial, Krishnan A, Pasquini MC, Logan B, Stadtmauer EA, Vesole DH, Alyea E 3rd, Antin J, Comenzo R, Goodman S, Hari P, Laport G, Qzailbash MH, Rowley S, Sahebi F, Somlo G, Volgl DT, Wesidorf D, Ewell M, Wu J, Geller NL, Horowitz MM, Giralt S, Maloney DG; Blood and Marrow Clinical Trials Network (BMT CTN). *Lancet Oncology*, 2011;12(13):1195–1203. <http://www.ncbi.nlm.nih.gov/pubmed/21962393>

- This study assessed the effectiveness of allogeneic hematopoietic stem cell transplantation (HSCT) with non-myeloablative conditioning after autologous HSCT compared with tandem autologous HSCT. Patients with multiple myeloma received either autologous HSCT followed by allogeneic HSCT or tandem autologous HSCT. Non-myeloablative allogeneic HSCT after autologous HSCT was

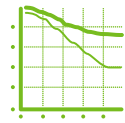
not more effective than tandem autologous HSCT for patients with standard-risk multiple myeloma. Further enhancement of the graft-versus-myeloma effect and reduction in transplant-related mortality are needed to improve the allogeneic HSCT approach.

Peripheral-blood stem cells versus bone marrow from unrelated donors, Anasetti C, Logan BR, Lee SJ, Waller EK, Weisdorf DJ, Wingard JR, Cutler CS, Westervelt P, Woolfrey A, Couban S, Ehniger G, Johnston L, Maziarz RT, Pulsipher MA, Porter DL, Mineishi S, Mc Carty JM, Khan SP, Anderlini P, Bensinger WI, Leitman SF, Rowley SD, Bredneson C, Carter SL, Horowitz MM, Confer DL; Blood and Marrow Clinical Trials Transplant Network. *New England Journal of Medicine*, 2012;367(16):1487–1496. <http://www.ncbi.nlm.nih.gov/pubmed/23075175>

- In this phase 3, multicenter, randomized trial, transplantation of peripheral-blood stem cells was compared with transplantation of bone marrow from unrelated donors to detect differences in 2-year survival probabilities. No significant survival differences were found between patients receiving the two types of transplantation procedures. Peripheral-blood stem cells may reduce the risk of graft failure, whereas bone marrow may reduce the risk of chronic graft-versus-host disease.

Lenalidomide after stem-cell transplantation for multiple myeloma, McCarthy PL, Owzar K, Hoffmeister CC, Hurd DD, Hassoun H, Richardson PG, Giralt S, Stadtmauer EA, Weisdorf DJ, Vij R, Moreb JS, Callander NS, Van Besien K, Gentile T, Isola L, Maziarz RT, Gabriel DA, Bashey A, Landau H, Martin T, Qzailbash MH, Levitan D, McClune B, Schlossman R, Hars V, Postiglione J, Jiang C, Bennet E, Barry S, Bressler L, Kelly M, Seiler M, Rosenbaum C, Parameswaran H, Pasquini MC, Horowitz MM, Shea TC, Devine SM, Anderson K, Linker C. *New England Journal of Medicine*, 2012;366(19):1770–1781. <http://www.ncbi.nlm.nih.gov/pubmed/22571201>

- This study sought to determine whether lenalidomide maintenance therapy would prolong the time to disease progression after autologous hematopoietic stem cell transplantation in patients with multiple myeloma. Lenalidomide maintenance therapy, initiated at day 100 after hematopoietic stem cell transplantation, was associated with more toxicity and second cancers but a significantly longer time to disease progression and significantly improved overall survival among patients with myeloma.



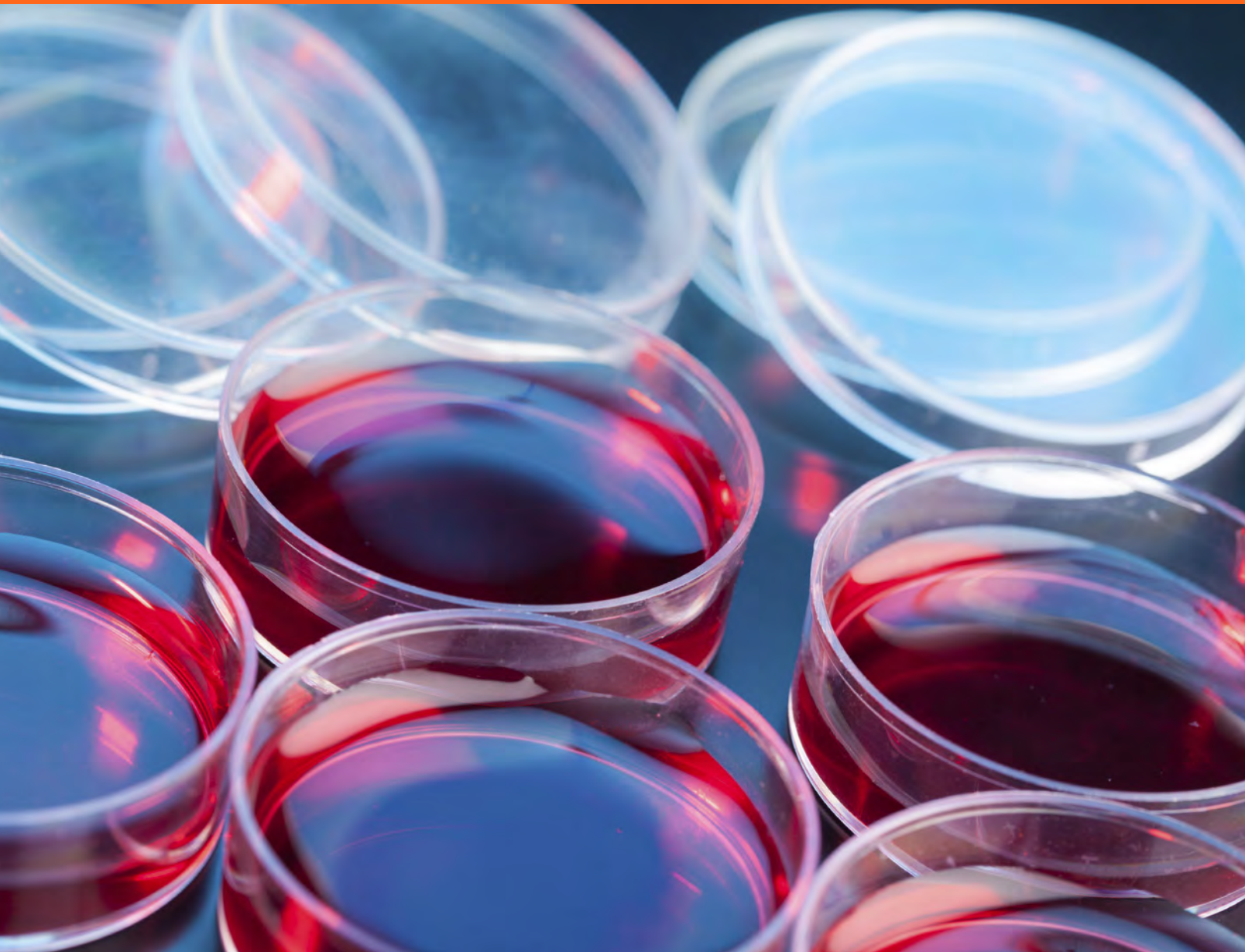
Spleens of myelofibrosis patients contain malignant hematopoietic stem cells, Wang X, Prakash S, Lu M, Tripodi J, Ye F, Najfeld M, Li Y, Schwartz M, Weinberg R, Roda P, Orazi A, Hoffman R. *Journal of Clinical Investigation*, 2012;122(11):3888–3899.

<http://www.ncbi.nlm.nih.gov/pubmed/23023702>

- The data from this study document the existence of myelofibrosis stem cells that reside in the spleens of patients with myelofibrosis and demonstrate that these cells retain a differentiation program that is identical to that of normal hematopoietic stem cells.

2012 PROGRAM ACCOMPLISHMENTS

DEVELOPMENTAL THERAPEUTICS PROGRAM





OVERVIEW

The Developmental Therapeutics Program (DTP) provides services, resources, and leadership to the academic and private-sector research communities worldwide to facilitate the discovery and development of new cancer therapeutic and imaging agents. In addition to these efforts to assist extramural researchers, DTP has historically been directly involved in the discovery or development of more than half of the anticancer therapeutics on the market today. Since 2009, DTP has contributed to the preclinical development of five newly marketed agents approved by the U.S. Food and Drug Administration (FDA).

DTP provides unique services to the cancer research community:

- Materials:
 - Samples of individual compounds for research
 - Large plated sets of compounds for high-throughput screening
 - Biopharmaceuticals, such as monoclonal antibodies and cytokines
 - Tumor cell lines and cell line extracts (DNA, RNA)
 - Laboratory animals
- Datasets and data mining tools:
 - Data from in vitro screening of compounds submitted by investigators

- Web-based databases of historical screening records
- Data mining tools, such as COMPARE, and the molecular targets program
- Grants: 700 active grants managed in 2012

DTP maintains resources for a robust discovery and development infrastructure:

- Natural product collection, extraction, and characterization
- Compound libraries, chemical synthesis, and structure-activity modeling
- Preclinical efficacy testing in vitro and in vivo
- Pharmaceutical optimization, formulation, and manufacturing under current Good Manufacturing Practice (cGMP)
- Pharmacology and toxicology testing under current Good Laboratory Practice
- Preparation and review of technical documents for Investigational New Drug (IND) applications to the FDA
- Academic investigator access to research and development resources through the [National Cancer Institute \(NCI\) Experimental Therapeutics \(NExT\) program](#)

DTP provides leadership to the cancer research community by helping to overcome financial and technical barriers to high-risk projects and addressing unmet medical needs.

Drug (Trade Name)	Year Approved	Indication
Omacetaxine, homoharringtonine (Synribo)	2012	CML with resistance and/or intolerance to >2 TKIs
Eribulin (Halaven)	2010	Second-stage treatment of refractory breast cancer
Sipuleucel-T (Provenge)	2010	Prostate cancer
Pralatrexate (Folotyn)	2009	Peripheral T-cell lymphoma
Romidepsin (Istodax)	2009	Cutaneous T-cell lymphoma

FDA-APPROVED DRUGS DEVELOPED WITH DTP PRECLINICAL INVOLVEMENT, 2009–2012

JERRY M. COLLINS

ASSOCIATE DIRECTOR



Jerry M. Collins, PhD, is an internationally recognized pharmacologist who has been closely associated with NCI's drug development efforts for more than 30 years, first as an NCI intramural investigator and then as the Chief of NCI's Pharmacokinetics Section. From 1988 until 2005, Dr. Collins served as the Director of the FDA Laboratory of Clinical Pharmacology, where he headed the development of new methods to facilitate research on human tissue metabolism to create an *in vitro* model to reduce adverse drug reactions. Dr. Collins was named Associate Director of the Developmental Therapeutics Program in the Division of Cancer Treatment and Diagnosis in September 2005.

Dr. Collins's areas of expertise are clinical pharmacology, the application of pharmacokinetic and pharmacodynamic principles to cancer research, and increasing biomarker efficacy with positron emission tomography (PET). He received his bachelor degree from Drexel University and his master and doctoral degrees from the University of Pennsylvania. He has authored or co-authored 200 papers in the field of clinical pharmacology, primarily emphasizing the applications of pharmacokinetic and pharmacodynamic principles in the field of cancer. His current work also includes extending these principles with PET imaging.

RECENT LEADERSHIP EXAMPLES

DTP provides services, resources, and leadership to the academic and private sector worldwide to facilitate the discovery and development of new cancer therapeutic and imaging agents.

CHIMERIC 14.18 MONOCLONAL ANTIBODY FOR HIGH-RISK NEUROBLASTOMA

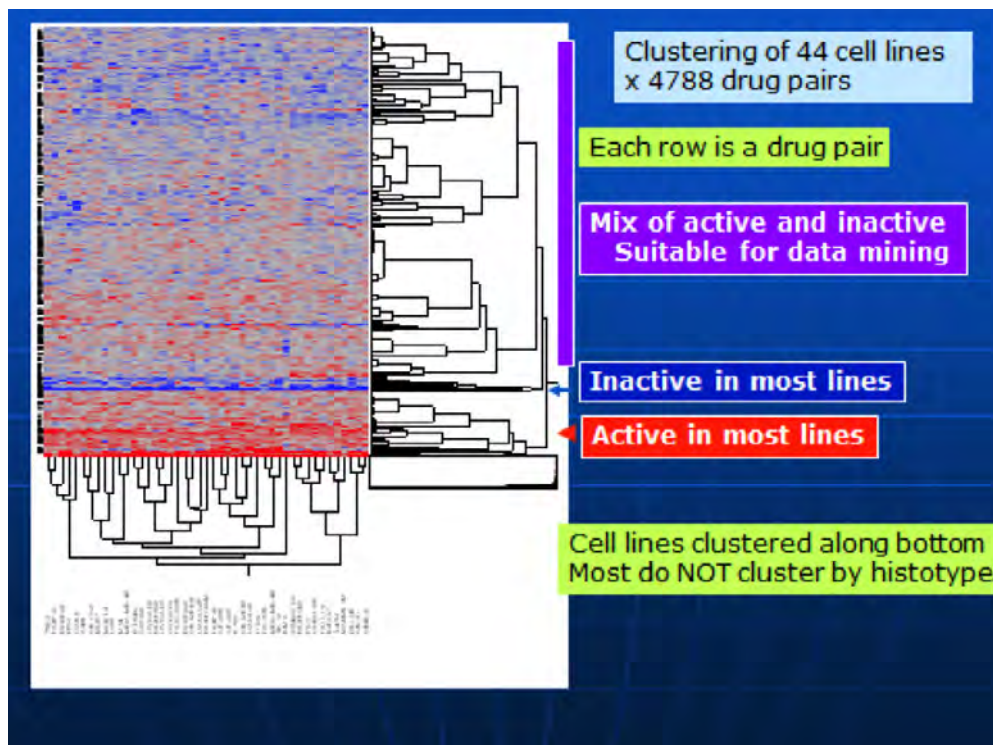
Approximately 500 patients are newly diagnosed with high-risk neuroblastoma each year in the United States. Chimeric (ch)14.18 monoclonal antibody targets a specific glycolipid, disialoganglioside, on the surface of neuroblastoma cells. In 2010, ch14.18 antibody in combination with granulocyte macrophage–colony-stimulating factor (GM-CSF), interleukin 2 (IL-2), and isotretinoin became the new standard treatment for pediatric neuroblastoma. The combination increased overall survival to 66%; this compares with 46% for the previous standard of care. DTP, the sole manufacturer of ch14.18 antibody, will supply all eligible patients in clinical trials until a marketing partner receives FDA approval of the antibody. (For additional details, see “Biological Resources Branch.”)

RE-INVIGORATED NATURAL PRODUCTS INITIATIVE

Pharmaceutical companies have largely abandoned the development of molecules derived from natural products. Approximately 78% of drugs in the cancer treatment arena between January 1981 and June 2006 were derived from natural products either directly or indirectly (e.g., competitively inhibiting a natural product substrate). DTP has the world's largest natural-product repository and is evaluating potential new opportunities related to fungi, the conditions under which they are grown, and the modulation of the products they produce. DTP provided 155,000 natural-product extracts to a NExT project seeking inhibitors of apoptosis. (For additional details, see “Natural Products Branch.”)

ERIBULIN

Eribulin is a total synthetic molecule modeled on the ring structure of the naturally occurring antitubulin compound halichondrin B. The halichondrins potently inhibited the NCI-60 cell line screening panel at low nanomolar levels and had a potentially different binding site to paclitaxel–



CLUSTER ANALYSIS ON THE NCI-60 DATASET LEADS TO IDENTIFICATION OF THE MOST SUITABLE DRUG PAIRS FOR DATA MINING

docetaxel and the vinca alkaloids–colchicines. DTP’s Natural Products Branch was tasked with finding adequate supplies of halichondrin B for development. With approval from the government of New Zealand, DTP collected and purified halichondrin from 1 metric ton of sponge. In 1996, DTP reported that the New Zealand–purified halichondrin B was functional in a late-stage xenograft model.

Positive xenograft data reported by NCI staff attracted the interest of scientists at Eisai Research Institute and Harvard University, who made analogs. DTP conducted a comparative evaluation of analogs from Eisai. A Clinical Cooperative Research and Development Agreement (CRADA) was negotiated between Eisai Research Institute and NCI to develop E7389 (eribulin). DTP conducted IND-directed pre-clinical toxicology, analytical methodology, formulation, and clinical trials through phase 2. Eisai continued with a much larger phase 3 clinical trial on eribulin, which received FDA marketing approval in 2010 for the second-stage treatment of refractory breast cancer.

NCI’s involvement in the development of eribulin was initiated in 1986 and continued through phase 2 clinical trials. Extensive work and investment of NCI, as well as the

interplay of academia, industry, and government, played important roles in bringing this agent to market. The critical point, demonstrated by DTP scientists, that eribulin was more efficacious than pure halichondrin B persuaded Eisai to continue the study and development of this agent.

NCI-60 COMBINATION STUDY

It is now feasible to perform cluster analysis on the NCI-60 data set and identify the most suitable drug pairs for data mining. In 2012, DTP completed the testing of 5,000 different combinations of 100 approved cancer drugs in the NCI-60 cell line panel in the hope of finding new pairings that could ultimately provide patients with more effective and safer treatments. Because these are all approved clinical agents, there is the potential to rapidly advance the promising combinations to clinical testing. A DTP presentation was one of the highlights of the 2012 meeting of the European Organisation for Research and Treatment of Cancer (EORTC)–NCI–American Association for Cancer Research (AACR).

APPROVED CANCER TREATMENT DRUGS DEVELOPED WITH DTP INVOLVEMENT

2012	Omacetaxine (homoharringtonine, NSC 141633)	1978	Cisplatin (cis-platinum) (NSC 119875)
2010	Eribulin (NSC 707389)	1977	Carmustine (BCNU) (NSC 409962)
	Sipuleucel-T (NSC 720270)	1976	1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) (NSC 9037)
2009	Romidepsin (NSC 630176)	1975	Dacarbazine (NSC 45388)
	Pralatrexate (NSC 713204)	1974	Doxorubicin (NSC 123127)
2004	Cetuximab (NSC 632307)		Mitomycin C (NSC 26980)
2003	Bortezomib (NSC 681239)	1973	Bleomycin (NSC 125066)
1998	Denileukin diftitox (NSC 697979)	1970	Floxuridine (FUDR) (NSC 27640)
1996	Polifeprosan 20 with carmustine implant (NSC 714372)		Mithramycin (NSC 24559)
	Topotecan (NSC 609699)		Mitotane (o-p'-DDD) (NSC 38721)
1995	All-trans retinoic acid (NSC 122758)	1969	Cytarabine (ARA-C) (NSC 63878)
1992	2-Chlorodeoxyadenosine (NSC 105014)		Procarbazine (NSC 77213)
	Paclitaxel (NSC 125973)	1967	Hydroxyurea (NSC 32065)
	Teniposide (NSC 122819)	1966	Pipobroman (NSC 25154)
1991	Fludarabine phosphate (NSC 312887)		Thioguanine (NSC 752)
	Pentostatin (NSC 218321)	1964	Melphalan (NSC 8806)
1990	Hexamethylmelamine (NSC 13875)		Actinomycin D (NSC 3053)
	Levamisole (NSC 177023)	1963	Vincristine (NSC 67574)
1989	Carboplatin (NSC 241240)	1962	Fluorouracil (NSC 19893)
1988	Ifosfamide (NSC 109724)	1961	Vinblastine (NSC 49842)
1987	Mitoxantrone (NSC 301739)	1959	Cyclophosphamide (NSC 26271)
1983	Etoposide (NSC 141540)		Thiotepa (NSC 6396)
1982	Streptozotocin (NSC 85998)	1957	Chlorambucil (NSC 3088)
1979	Daunorubicin (NSC 82151)		



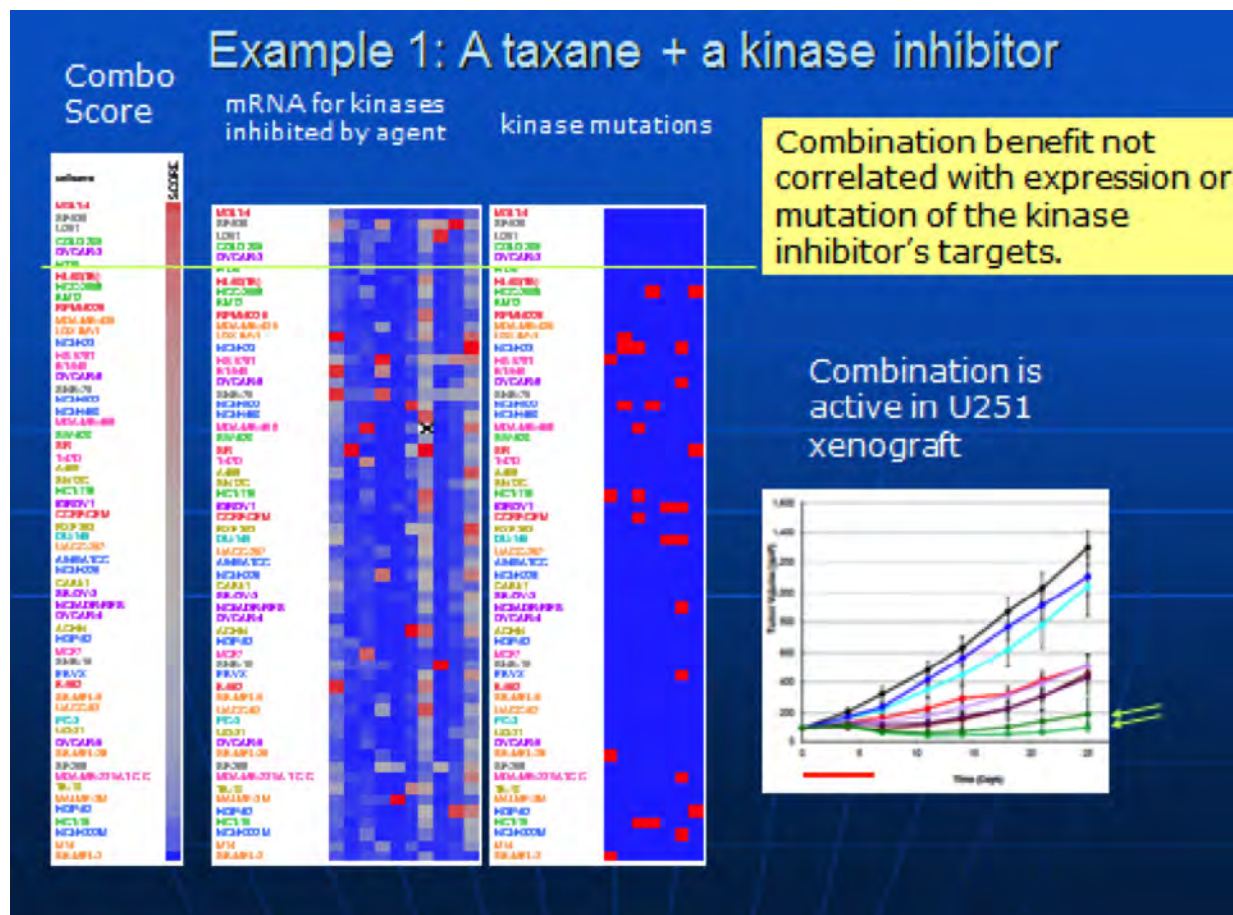
Beyond cell culture, enhanced activity has been demonstrated for a combination in the U251 xenograft model. Further, initial comparisons indicate that the enhanced benefit is not attributable to the primary targets of the agents.

Upon completion of quality control checks and peer review, this new repository of data will be made available to the public on [DTP's website](#). The extramural cancer research community will have unrestricted access to the data, and their analyses can give rise to new insights into potential drug combinations to target or avoid. Availability of the new data could expedite translational work and perhaps even hasten the start of human clinical studies.

STRUCTURE AND FUNCTION

DTP's mission is to facilitate the discovery and preclinical development of novel therapeutic agents and imaging tools. Created by Congress in 1955 as the Cancer Chemotherapy National Service Center, DTP serves as a vital resource for the acquisition of preclinical information and the distribution of research materials, including Internet-accessible data and tools, vialled and plated compounds, tumor cells, cell extracts, and animals, as well as bulk and formulated drugs for IND-directed studies.

Through its uniquely governmental role in providing resources and support to academic investigators and the



ENHANCED ACTIVITY IN VIVO FOR THE COMBINATION OF AN ACTIVE TAXANE AND AN INACTIVE KINASE INHIBITOR.

Note that the enhanced activity relative to single-agent taxane appears to be separate from the primary targets of the kinase inhibitor.

private sector, DTP has facilitated the discovery and development of more than half of the anticancer therapeutics on the market today. Although many academic and private-industry laboratories are also focused on drug discovery, barriers are presented by financial and technical burdens, as well as lack of funding and infrastructure, that may keep promising therapeutic agents from being developed and reaching patients. DTP helps to overcome barriers to the development of therapeutic agents by providing the resources and leadership necessary to pursue high-risk projects aimed at unmet medical needs. The management and oversight of a large research grant portfolio, worldwide distribution services for data and research materials, and a robust in-house and contract-based drug discovery and development infrastructure are organized under nine highly interactive branches.

In addition to providing reagents and services to researchers, DTP is an active participant in the **NCI Experimental Therapeutics (NExT) program**. NExT establishes the drug discovery and development pipeline under a single, well-documented system of peer review and governance. Through participation on working groups and committees and providing contract-based resources of approved projects, DTP staff support the **Chemical Biology Consortium (CBC)**, which is the early discovery engine for the NExT initiative, as well as development-stage projects.

PROGRAM ACCOMPLISHMENTS

GRANTS AND CONTRACT OPERATIONS BRANCH

The Grants and Contracts Operations Branch (GCOB) managed slightly more than 500 funded extramural investigator-initiated grants each year during 2011 and 2012 and counseled hundreds of unsuccessful applicants. Although the overall NCI success rate for R01s in fiscal year 2012 was the lowest in history, at 14.4%, the GCOB portfolio held fairly steady for all funding mechanisms from 2011 (547 grants) to 2012 (542 grants), perhaps due to the increased interest in translational research. GCOB grants focus on preclinical research that accelerates the discovery, development, and evaluation of agents to treat cancer. GCOB grantees have had substantial input into the discovery of new agents from both natural and synthetic sources and have provided new

concepts of drug treatment, new strategies to overcome drug resistance, rationales for drug combinations, and mechanistic understanding of how drugs function. They have also participated in the co-development of drugs and biomarkers to support the new era of precision medicine with its emphasis on shutting down targets and pathways that drive tumors.

GCOB History

GCOB was created in 1986 to manage the biochemistry and pharmacology grants portfolio and provide administrative assistance for drug discovery and development contracts within DTP. Management of the grant portfolio became more labor intensive with the implementation of the American Recovery and Reinvestment Act of 2009, which led to a bold idea to re-invigorate science supported by the National Institutes of Health (NIH) with grant supplements and 2-year awards in emerging scientific areas, such as the genetic sequencing of tumors. In 2010, NCI management decided to reserve more funds for awards outside a more limited payline, a shift that has provided NCI program staff with more input to funding decisions.

GCOB grants support research with therapeutic intent, including chemistry, natural products, mechanisms of drug action, and pharmacology-toxicology. Areas of emerging emphasis made possible by conceptual and technological advances include the following:

- Computer-aided drug design with greater reliance on structural data
- New synthetic techniques, such as fragment-based chemistry
- Biosynthesis of natural products
- Targeted drug delivery
- Nanotechnology
- High-throughput screening
- Cancer stem cells
- Drug studies covering diverse targets, mechanisms, and processes, such as angiogenesis, metastasis, role of the extracellular matrix, apoptosis, autophagy, cell signaling, DNA repair, and cancer cell metabolism



GCOB Accomplishments

Drugs. NCI's investment in natural-products research continues to pay off in the development of new anticancer agents. In addition to the drugs that were directly supported by DTP efforts (see "Overview"), the following treatments were based on natural products licensed from GCOB grantees and recently received marketing status from FDA:

- **Adcretris (brentuximab vedotin); Seattle Genetics:** This antibody–drug conjugate was approved in 2011 for the treatment of Hodgkin lymphoma and anaplastic large-cell lymphoma. The “warhead” is the antimetabolic agent monomethyl auristatin E, and the antibody is a chimeric monoclonal antibody that targets CD30, a cell membrane protein.
- **Kyprolis (carfilzomib); Onyx Pharmaceuticals:** The natural product YU-101 was modified to increase its solubility by the addition of a morpholine ring. This proteasome inhibitor with irreversible binding properties was approved for the treatment of multiple myeloma in 2012.

Initiatives. GCOB Program Directors participated in the development of several initiatives and continue to serve as contact persons for the following:

- **Nanoscience and Nanotechnology in Biology and Medicine (R01) (PA-11-148) and a companion initiative for R21 awards (PA-11-149):** These initiatives encourage applications for cutting-edge nanoscience and nanotechnology that can lead to breakthroughs in the diagnosis, treatment, and management of diseases.
- **International Cooperative Biodiversity Groups program:** This program is managed by the Fogarty International Center with advice and funding from several NIH institutes and agency partners, such as the National Science Foundation. It is a unique effort to address the interdependent issues of drug discovery from natural products, biodiversity conservation, and sustainable economic growth.
- **Solicitation of Assays for High-Throughput Screening to Discover Chemical Probes (R01) (PAR-12-058), a companion initiative for R21 awards (PAR-12-059), and a related PAR focusing on the discovery of chemical probes, Solicitation of Validated Hits for the Discovery of In Vivo Chemical Probes (R01) (PAR-12-060):** These screening initiatives stimulate research on assays that

provide new insight into important disease targets and processes; the later initiative focuses on the discovery and development of novel, small molecules that will inform studies of disease mechanisms.

- **Biomechanisms of Peripheral Nerve Damage by Anticancer Therapy (R01) (PA-12-082) and its companion initiative for R21 awards (PA-12-083):** This initiative encourages research on developing a better molecular understanding of peripheral nerve damage caused by anticancer treatments to allow the rational development of agents to prevent or treat its occurrence.

Other Staff Activities. In addition to informing investigators with possible drug discovery programs about the NExT program, reviewing manuscripts, and serving on NCI grant training panels, GCOB staff members were invited to chair sessions and make presentations at international meetings, serve on a scientific review panel for the Veterans Administration, teach a course for the Foundation for Advanced Education in the Sciences, serve as a Science Officer for the NIH Molecular Libraries Program, and participate on the committee to identify the most promising MERIT awardees.

GCOB Future Plans

GCOB plans to continue to support the best translational research based on peer review and clinical need, conduct portfolio analysis to identify gaps for new initiatives, catalyze interactions among scientists, educate the scientific community on peer review and grant policy changes, inform grantees about Division of Cancer Treatment and Diagnosis (DCTD) drug development services such as NExT, and organize workshops. GCOB also plans to assist colleagues in the Cancer Treatment Evaluation Program (CTEP) as they implement a new network for early clinical trials that involves asking important scientific questions and acquiring more information about the properties of a patient's tumor, including the genetic sequence, in order to match tumor targets and new drugs with less emphasis on type of cancer. Greater use of biomarkers and imaging is expected to preselect patients for trials and to monitor them for emergence of drug resistance and the need to make adjustments in treatment strategies.

MOLECULAR PHARMACOLOGY BRANCH

The Molecular Pharmacology Branch (MPB) is responsible for developing and conducting screens to identify improved therapies for recalcitrant, rare, and neglected cancers and participating as needed in the NExT discovery program.

NCI-60 Cell Line Screen

The NCI-60 cell line screen provides an initial evaluation of potential anticancer agents. The screen includes cell lines representing nine cancer types: leukemia, melanoma, and lung, colon, brain, ovary, breast, prostate, and kidney cancer. The aim of the screen is to identify, for further evaluation, synthetic compounds and natural-product samples and combinations showing selective growth inhibition or cell killing of particular tumor cell lines. The NCI-60 cell lines are very well characterized biologically and molecularly. More than 200 peer-reviewed papers have been published on the NCI-60 cell line panel since 2008. Although the majority of these reports (45%) are in the areas of medicinal chemistry, drug response, and compound studies, many (24%) center on gene expression, genomics, and development of gene signatures. Other prominent topics include mutation analyses (7%), proteomics (6%), development of bioinformatics methods (4%), biomarkers (4%), microRNAs (3%), metabolomics, epigenetics, and pathways analyses (1% each).

DURING FISCAL YEAR 2012, THE NCI-60 CELL LINE SCREEN LABORATORY:

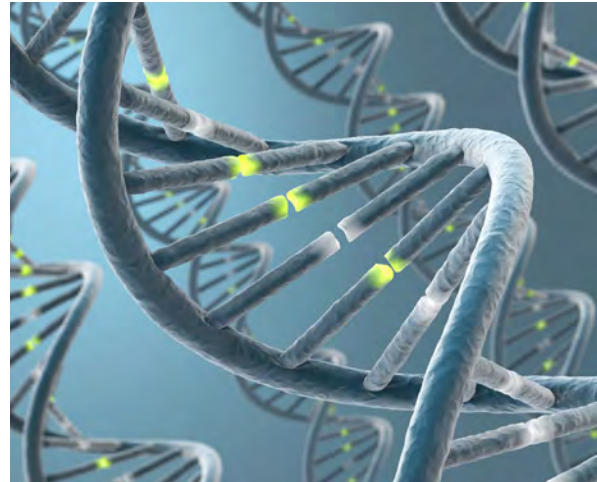
- Tested 8,118 new synthetic compounds and 5,094 natural products in the one-dose assay
- Tested 1,922 synthetic compounds, 739 natural products, and 808 retests in the five-dose assay
- Performed 216 combination drug assays
- Provided cells for use by other DTP support laboratories
- Provided cells to Dr. Yves Pommier to measure the enzymatic activity of TDP1 and TDP2

As an additional service to the extramural research community, the NCI-60 cell line screening laboratory prepared frozen cell pellets for each line in the NCI-60 panel at the request of the NCI-60 Molecular Targets Committee. The frozen cell pellets are supplied to investigators whose submitted proposals have been approved to provide further information about this diverse cell panel. The laboratory used more than 5,000 flasks to provide 48–52 frozen cell pellet vials for each cell line.

Target Validation and Screening Laboratory

The Target Validation and Screening Laboratory (TVSL) is dedicated to anticancer drug discovery and support of the NExT Program. TVSL has developed in-house expertise, automation, instrumentation, and information technology infrastructure to carry out screening campaigns with a diverse array of molecularly and cell-based assay technologies applied to large chemical libraries. TVSL has assembled and is characterizing disease-based cell line panels focused on challenging cancers for response to standard and investigational anticancer agents to uncover previously unrecognized sensitivities and potential new targets for therapeutic intervention in these cancers. The laboratory has also developed the infrastructure and instrumentation for a flow cytometry laboratory, utilizing a BD Biosciences FACSAria III flow cytometer with the capacity to operate a sophisticated cell-sorting facility.

During 2012, 89 sarcoma cell lines were acquired, expanded in culture, tested for mycoplasma and human pathogen contamination, and profiled with Identifiler, and stocks were deposited in the DCTD tumor cell repository. More than 60 sarcoma lines were screened for inhibition with the Approved Oncology Drug library. Screening of the same sarcoma lines with more than 350 investigational agents was initiated in November 2012. A total of 88 small-cell lung cancer (SCLC) cell lines were acquired, and approximately 40 lines were expanded in culture, tested for mycoplasma and human pathogen contamination, and profiled using Identifiler, and stocks were deposited in the repository. The data generated from the sarcoma and SCLC screens are being processed with the CambridgeSoft suite of database tools, which TVSL recently acquired in collaboration with the DTP's Information Technology Branch. The laboratory developed a label-free binding assay on the Octet platform to monitor the interaction of c-Myc with its binding partner Max for a NExT project.



Laboratory of Functional Genomics

The Laboratory of Functional Genomics (LFG) provides gene-based assays and genomics expertise; coordinates and analyzes profiling and sequencing efforts; and provides technical support, including gene expression by TaqMan real-time polymerase chain reaction (PCR), reporter gene assays, multiplexing gene assays, and recombinant DNA and RNA interference experiments. LFG assists in efforts to widely disseminate information and tools relating to nucleic acid characterization, allowing for facile exploration of the data and, potentially, identification of disease-specific targets.

Alveolar soft-part sarcoma (ASPS) is a rare tumor for which the DCTD has an ongoing clinical trial. Evaluation of genes in patient tumor biopsies both before and after treatment with cediranib, a novel vascular endothelial growth factor receptor (VEGFR) inhibitor, indicated a coherent and significant modulation of genes related to angiogenesis and inflammation. One of the most strongly downregulated genes was ESM1 (endocan), a proteolytic glycan that is expressed in the endothelium but has been identified in patient tumors and associated with a poor response. Nucleic acid extraction was completed in approximately 60 sarcoma cell lines. Samples were characterized for expression profiles with the Affymetrix EXON ST1 gene expression array and Nanostring microRNA (miRNA) arrays.

Initial analyses of the sarcoma exon array and miRNA data indicate that expression varies primarily by disease subtype. For instance, Ewing sarcoma overexpressed genes including PRKCB, NPY5R and NPY1R, and ITM2A, as well as adren-

ergic receptors B1, B3, and A1D, whereas ACTC1, IGF2, and CHRNA1 were dysregulated in rhabdomyosarcoma. Predicted associations between gene and miRNA expression included CSF1 with miR-128, thioredoxin reductase with miR-324-5p, MDM4 with miR-152, and PODXL with miR-199a-5p, suggesting potential regulatory relationships that might be exploited as cancer targets. The laboratory identified an miRNA that was correlated with differential expression of the MET gene between the Ewing sarcoma and osteosarcoma samples.

LFG has applied the Seahorse XF24 extracellular flux analyzer to the quantification of kinetic, real-time, physiological changes in cellular bioenergetics by measuring mitochondrial respiration and glycolysis in a microplate format in sarcoma and SCLC lines. Initial results with this technology showed that sarcoma and SCLC cell lines exhibit differential bioenergetic profiles that can be associated with their ability to survive metabolic insult.

Tumor Microenvironment Laboratory

The Tumor Microenvironment Laboratory (TML) provides support in the characterization of sarcomas and SCLC and in the identification of novel therapeutic targets of the tumor microenvironment in the context of these two diseases. TML also provides support to clinical trials and the NExT program.

The TML laboratory performed endpoint testing to evaluate hypoxia-inducible factor 1-alpha (HIF-1 α) messenger RNA

DMG PROJECT HIGHLIGHTS

- DMG developed three assays: STAT3/STAT1 luciferase reporter assays, a DNA ELISA assay, and a fluorescence polarization assay. DMG tested more than 50 compounds for the STAT3 project in 2012.
- DMG conducted a comprehensive MERTK receptor phosphosite analysis after treatment with pervanadate or GAS6 (quantitative proteomics). DMG established the effective concentration and time of GAS6 and pervanadate treatment that is required to induce the phosphorylation of MERTK in both 697 and BT12 cells by Western blot. Next, DMG developed an effective immunoprecipitation protocol to enrich for the low-abundant membrane protein MERTK from the 697 cells. A MERTK “standard,” recombinant MERTK, was expressed and purified in HEK293T cells. This standard was used to develop protocols for mass spectroscopic analysis, as well as for optimization of immunoprecipitation and enrichment. Mass spectroscopic analysis of native MERTK after pervanadate treatment has shown a significant increase in tyrosine phosphorylation in the autophosphorylation domain.
- Mechanistic studies for NSC 750854, a compound found to have structural homology with several well-characterized inhibitors of protein synthesis, revealed rapid activation of the EIF2 α kinase GCN2 (a sensor of amino acid deprivation) after treatment.
- Mechanistic studies of oxyphenisatin (NSC 59814; the active form of NSC 59687, a stimulant laxative) demonstrated that treatment is associated with acute nutrient depletion, inhibition of protein synthesis, and transient endoplasmic reticulum stress.

(mRNA) copy number in biopsies before and after treatment in support of protocols 10-C-0113 and 11-C-0042. The laboratory developed the assay and applied it to testing patient biopsies to evaluate HIF-1 α and B2M mRNA copy number. In addition, expression of three to six HIF-dependent genes was evaluated to correlate HIF-1 α mRNA changes following treatment with changes in its function.

TML evaluated signaling pathways and cell surface receptors in 14 sarcoma lines and normal cells (mesenchymal stem cells, osteoblasts, myoblasts, fibroblasts, and chondroblasts) to use in comparison experiments, and 10 SCLC lines. Evaluation entailed the use of the Proteome Profiler Human Phospho-Kinase Array Kit and the Proteome Profiler Human Phospho-RTK Array Kit. HIF-1 α protein expression and VEGF, CA9, and PDK1 mRNA expression was evaluated in 27 cell lines treated for 24–48 hours under normoxic or hypoxic conditions (1% O₂). VEGFR1, VEGFR2, and VEGFR3 expression was evaluated by flow cytometry in 30 cell lines. Metabolic profiling of mitochondrial functions was performed in normal cells and in seven non-soft-tissue sarcomas, and glycolytic profiling of six non-soft-tissue sarcoma lines was performed using the Seahorse XF24 instrument.

TML analyzed 45 human sarcoma cell lines for the expression of IL-11Ra and IL-11. IL-11Ra protein, secreted IL-11, and IL-11 mRNA were expressed at high levels in nearly all osteosarcoma, rhabdomyosarcoma, fibrosarcoma, and Ewing sarcoma cell lines. IL-11 shRNA decreased cell proliferation but did not affect the cell cycle or apoptosis.

Drug Mechanism Group

The Drug Mechanism Group (DMG) is responsible for determining mechanism(s) of action and identifying potential surrogate markers of drug activity for selected compounds by using microarray- and proteomic-based platforms and performing assays for the NExT drug discovery program. The proteomics technology includes quantitative, subcellular, chemical, and two-dimensional polyacrylamide gel electrophoresis proteomics. Validation technology includes cell-based assays, enzymatic assays, enzyme-linked immunosorbent assay (ELISA), flow cytometry, quantitative real-time PCR, Western blot analysis, immunohistochemistry, and various microbiologically based assays, such as transient or stable transfection assays.



Translational Science Laboratory

The Translational Science Laboratory (TSL) contributes broadly to collaborative projects. For example, TSL regularly performs detailed cell-based studies, including experiments with endothelial cells to assess their antiangiogenic potential and with cancer and normal cells to assess the potential for a therapeutic benefit that can contribute to the evaluation of various natural-product and synthetic compounds. In collaboration with the BTB, TSL processed more than 2,000 xenograft tissues by snap freezing, formalin fixation, and isolation of RNA and DNA.

TSL also carried out a detailed combination study with 6-MP and dasatinib in p53 wild-type (MCF-7, H460, A498) and p53 mutant (MDA-MB-468, H23, 786-O) breast, lung, and renal cell lines. In other projects, PKM-1 and -2 in sarcoma, and metabolic inhibitors in SCLC, were examined.

BIOLOGICAL TESTING BRANCH

The Biological Testing Branch (BTB) provides oversight and technical direction to support the preclinical development of new chemotherapeutic agents. To accomplish this, BTB is responsible for:

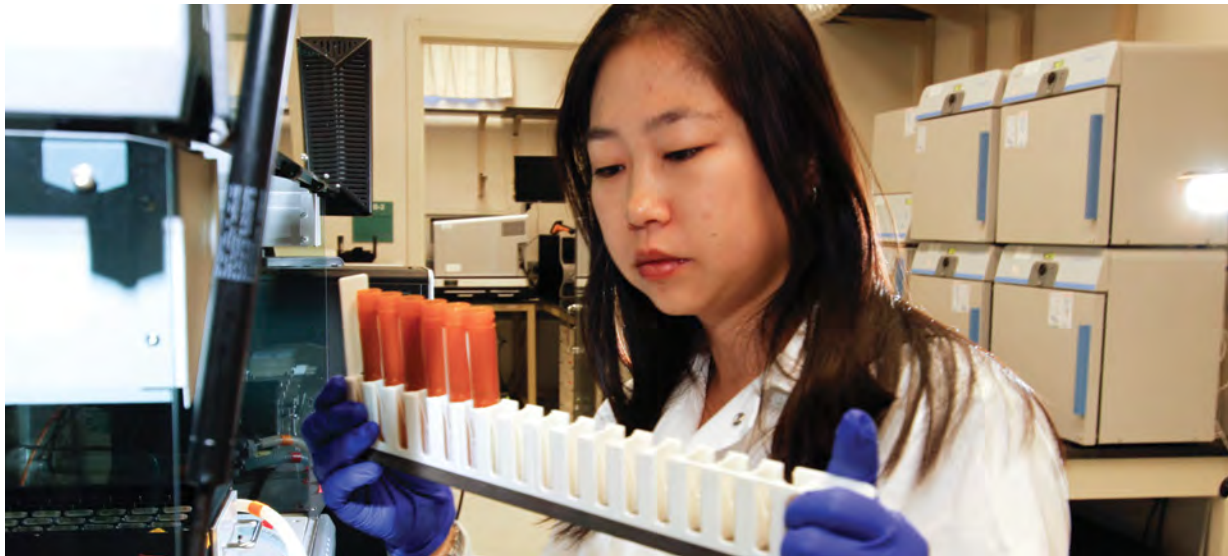
- Planning, directing, and managing a program to screen compounds for evidence of preclinical efficacy in rodent models
- Developing new in vitro and in vivo screening models
- Conducting in vitro combination screening assays to identify potentially beneficial drug combinations
- Providing preclinical support to the pharmacodynamic assay development and validation effort
- Defining the mechanisms of action for new experimental agents under development by DTP
- Providing preclinical and clinical pharmacokinetic support to the DCTD drug development effort
- Producing, providing quality control for, and distributing genetically and biologically defined rodents to NCI, NIH, and the grantee community
- Maintaining a repository of experimental animal and human tumor cell lines for use in research performed by the program and other qualified investigators

BTB Accomplishments and Ongoing Activities

BTB has assessed more than 300 synthetic molecules, 317 natural product extracts, and 10 unique vehicle formulations for determination of maximum tolerated dose in preparation for in vivo efficacy studies. It has conducted more than 190 hollow-fiber assays with more than 672 unique new molecules or natural product extracts for in vivo activity. Of these, 80 met the standard criteria for activity and referral for subcutaneous xenograft testing. BTB has also conducted 736 xenograft studies assessing antitumor activity of small-molecule and natural product extracts and 112 combination xenograft studies. These represent more than 50 unique human tumor xenograft models. The branch has conducted 157 xenograft studies in support of multiple pharmacodynamic assay development and validation projects. These 157 studies generated in excess of 45,350 samples for analysis. These studies supported the following projects:

- Methylation inhibition assay
- γ -H2AX assay
- c-Met assay
- HIF1 α assay
- Mer kinase assay
- Indole-3-carbinol (I3C) project
- 4'-Thio-deoxycytidine (TdCyd) project
- 750854 and 59687 projects
- Poly(ADP ribose) polymerase (PARP) inhibitors project
- Multiplex immunofluorescence assay
- Calf intestinal alkaline phosphatase assay
- Topoisomerase 1 complex assay
- Apoptosis panel for multiple agents

BTB prepares and ships 300–350 orders annually, representing a distribution of more than 2,000 vials of cells, tumor fragments, and cell pellets each year. The branch has prepared mRNA array samples collected at passages 1, 4, and 10 from serially passaged tumor material from more than 40 unique human tumor xenografts.



COLLABORATIVE EFFORTS BETWEEN BTB AND THE PHARMACODYNAMICS PROGRAM

BTB provided the preclinical animal model support for the development and validation of numerous clinical assays, using the methods it established for collecting and stabilizing tumor biopsies for subsequent analysis. These assays and projects included the methylation inhibition assay, the γ -H2AX assay, the c-Met assay, the HIF1 α assay, the Mer kinase assay, the I3C project, the TdCyd project, the PARP inhibitors project, the multiplex immunofluorescence assay, the calf intestinal alkaline phosphatase assay, the topoisomerase 1 complex assay, and the apoptosis panel for multiple agents.

During 2011–2012, the BTB Animal Production Program distributed more than 1.5 million mice and rats to various grantees. The program continues to operate with no biosecurity breaks in the state-of-the-art facility it has occupied since early 2009. The Animal Production Program successfully performed cryogenic preservation of the remaining nine strains and stocks of mice and rats (30 completed in 2011–2012). Through this effort, the Animal Production Program eliminated 11 low-demand strains and stocks that will now be supplied on an as-needed basis via embryo recovery.

BTB Collaborative Project: Alveolar Soft-Part Sarcoma Model

BTB developed an *in vitro* and *in vivo* model of ASPS, the first successful establishment of an ASPS tumor in mice after implantation of fresh human tumor tissues. This tumor can be serially passaged in mice while maintaining its genotypic and phenotypic characteristics. The tumor provided cellular material for *in vitro* studies, including establishing an ASPS human tumor cell line. A therapeutic trial demonstrated that antiangiogenic therapies (bevacizumab and topotecan) can suppress growth of the xenografted tumors.



DRUG SYNTHESIS AND CHEMISTRY BRANCH

The Drug Synthesis and Chemistry Branch (DSCB) supports the discovery and development of novel anticancer agents by:

- Worldwide scientific liaison activities with academic and industrial colleagues to stimulate the acquisition of a diverse set of synthetic compounds, natural products, and combinatorial libraries for in vitro cancer screening
- Management of the storage, inventory, documentation, and distribution of samples for research purposes
- Synthesis of cold and radiolabeled compounds for in vitro and in vivo studies

DSCB Accomplishments and Ongoing Activities

External Synthesis Contracts	<ul style="list-style-type: none">• Supports NExT Initiatives and the Biological Evaluation Committee• Synthesis of benchmark clinical and preclinical candidates
Chemical Repository	<ul style="list-style-type: none">• Manages new compounds submitted by extramural researchers• Distribution of compounds for external research activities
Laboratory of Synthetic Chemistry	<ul style="list-style-type: none">• Supports CBC discovery initiative• Synthesis of benchmark compounds• Internal supplier of new compounds through vigorous medicinal chemistry program

DSCB RESOURCES

Year	Compounds Shipped	Plates Shipped*	New Compounds (NSCs)
2005	11,753	3,470	2,972
2006	12,418	7,329	2,391
2007	19,964	4,742	3,194
2008	25,842	3,223	2,716
2009	28,830	5,649	2,469
2010	44,200	2,899	3,603
2011	29,451	3,314	7,596
2012	27,842	3,034	8,488

DISTRIBUTION AND PROCUREMENT SUMMARIES, 2005–2012

*Plates include structural diversity set, mechanistic diversity set, natural products set, combination set, approved oncology drugs set, and random plates of open compounds.

The significant increase in Nomenclature Standards Committee (NSC) numbers assigned in 2011 and 2012 (relative to 2005–2010) can be traced to the incorporation of specialized agent sets (including the Pharmakon 1600 collection, GSK published kinase inhibitor set, Roche kinase inhibitor set, Medicines for Malaria Venture collection—consistent with DSCB’s commitment to acquire diverse sets of synthetic compounds), as well as the registration of novel agents associated with the NExT discovery program.

ACQUISITION OF INVESTIGATIONAL AND APPROVED AGENTS, 2011–2012

ACTIVITY	NUMBER
External-contract synthesis of investigational agents	99
External-contract synthesis for BEC	25
DSCB synthesis (including LSC) for NExT	316
Purchased approved and investigational drug agents	434
Synthesized radiolabeled agents	3
LSC synthesis of investigational agents	7
Total compounds delivered:	884

BEC = Biological Evaluation Committee;
LSC = Laboratory of Synthetic Chemistry.

DSCB acquired a total of 884 compounds during 2011–2012 for the drug acquisition initiative (acquisition of benchmark clinical and preclinical candidates), NExT projects, and the Biological Evaluation Committee program.

DSCB NExT Program Contribution. Laboratory resources within DSCB (including the Laboratory of Synthetic Chemistry) were applied to two approved NExT projects during 2011–2012 (c-myc and I3C). Several advances were made in the I3C project, including the design of a novel class of I3C derivatives distinct from the indole series associated with the lead molecule, NSC 743380. Several compounds synthesized within this new chemotype display significant improvements to cell potency and breadth of cell line coverage relative to NSC 743380.

Drug Tracker and Sarcoma Screen Web Applications.

During 2011–2012, DSCB began an initiative to develop and execute both internal and public-facing Web applications to allow for the extraction, visualization, and analysis of NCI-60 cell line data and sarcoma cell line data for the acquired approved and investigational drugs. The first phase of this initiative is on target, and Web applications for both datasets are due to be unveiled in 2013.

DSCB Future Plans

- Continue to design and execute strategies to increase the quality, quantity, and diversity of compound submissions to the NCI compound collection, with the goal of improving the overall quality of the collection (with regard to molecular properties and pathway diversity)
- Continue to design and implement strategies for extraction, visualization, and analysis of data (experimental and virtual) for NSC compounds that allow for the identification of trends and formation of hypotheses necessary for rapid and efficient project progression
- Continue to execute a vigorous DSCB medicinal chemistry program aimed at the design and synthesis of targeted anticancer agents
- Support the CBC initiative by management and oversight of CBC discovery projects as they proceed through program *Stage Gates* and provide input and guidance with regard to the selection of projects
- Support DTP combination study initiative through the acquisition and synthesis of marketed clinical and preclinical anticancer benchmark agents and candidates
- Continue the development and execution of the Drug Tracker and sarcoma cell line screen Web applications

NATURAL PRODUCTS BRANCH

Accomplishments

Natural Products Repository Program. The Natural Products Repository is the largest storehouse of natural products in the world, housing nearly 170,000 extracts from more than 70,000 plants, more than 10,000 marine organisms collected from more than 25 countries, and more than 30,000 extracts of diverse bacteria and fungi. The Natural Products Repository Program was initiated by NPB in 1991 to maximize the



potential of the plant, microbial, and marine invertebrate extracts derived from the raw materials that were collected by NPB collection contractors. From 1996, these extracts have been made available to organizations and investigators interested in exploring their potential in any disease related to NIH interests. Materials are provided for only the costs of shipment. Rather than providing vials of extracts, the program provides 96-well plates of dried extracts of all sources and types to Natural Products Repository recipients, followed by provision of more material in the case of positive results from initial screening.

Year	Vials	Plates	Extracts*	Cultures
2009	7,540	7,000	623,540	1
2010	79	79	10,137†	
2011	1,326	1,326	43,402	4
2012	2,119	2,119	119,499	4

NUMBERS OF SHIPMENTS MADE BY NPB TO NON-DCTD INVESTIGATORS AND COLLABORATORS, 2009–PRESENT

* The extract total is calculated from [(plates x 88) + vials].

†The 1600 Sanford-Burnham plates (equivalent to 155,000 extracts) were shipped in the second quarter of 2010, hence the low extract/plate count in that year.

In addition, a significant number of plates (more than 500 per year) are shipped to the NCI Center for Cancer Research (CCR) Molecular Targets Laboratory for their assays.

Marine Collection Program. NPB has one contract for murine sample collection, held by the Coral Reef Research Foundation (based in Palau but a U.S. nonprofit domiciled in California). This collection program operates in all waters of the globe, including the Arctic Ocean (from the Alaskan chain to north of Dutch Harbor), Californian waters, the Caribbean Sea, Puerto Rico and Curacao, the Pacific Ocean, and Australasian waters.

NPB successfully negotiated an agreement based on a Letter of Collection with the Government of the Northern Territory in Australia. This was the first agreement signed under a new law that was not with an academic group. This agreement is currently allowing a Coral Reef Research Foundation subcontractor to operate in Australian state waters with the

Australian Institute of Marine Sciences (equivalent to the U.S. National Oceanic and Atmospheric Administration) and thus obtain samples that were previously forbidden to U.S. investigators. A similar agreement is under discussion with the government of the Solomon Islands that should permit collections in the second quarter of 2013. Collections are still ongoing in the area of Palau.

Plant Collections of Opportunity. Although contracts for collections of plants have not been funded by NCI since 2004, NPB has been successful in finding other pathways to continue the acquisition of these materials.

Harvard Medical School Traditional Chinese Medicinal Plants. With the help of the DCTD Office of Cancer Complementary and Alternative Medicine, NPB negotiated with Harvard Medical School to save over 1,600 kilogram samples of medicinal plants from China. These plants had been collected under Traditional Chinese Medicine (TCM)–defined conditions from sites where the original plants were collected for the ancient TCM monographs approximately 1,000 years ago. Five-hundred-gram samples of each part of the collection have been ground, extracted, and tested in the single-dose NCI-60 cell line panel. For the few that passed the NPB standard assay criteria, five-dose NCI-60 assays were performed. Approximately 20 of these samples were initially selected for future work.

The data on these samples were compiled with the help of DCTD's Office of Cancer Complementary and Alternative Medicine and an expert on TCM at the FDA. The intention is to determine the methodologies used for the preparation of these samples under the original monograph, as all were supposed to have potential antitumor properties. These extracts (probably only a single extract per plant sample rather than the two used in NCI protocols) will then be reassayed in the NCI-60 cell line panel. A comparison of the two methods of extraction should be informative in designing further experiments in due course.

Pfizer Plant Collection. After more than a year of negotiations to obtain 80,000 plant extracts from the Pfizer collection, approval was finally given by Pfizer at the end of 2012. Accession of the samples is expected in 2013. All taxonomic data, sources, and methods of extraction will be provided by Pfizer at no cost other than shipment to the Frederick National Laboratory of Cancer Research.

Natural Products Support Group

NPSG extracts samples of natural products for testing in the NCI-60 cell line, provides a compound plating support service for all drugs and natural products entering the NCI-60 queue, and conducts discovery research to characterize and purify extracts showing promising screening results. These tasks include:

- Preparation of all samples (natural-product extracts or fractions, purified natural products, and synthetic compounds) for the one- and five-dose NCI-60 in vitro screens and the in vivo hollow-fiber and xenograft tests run by BTB
- Management and maintenance of in-house computerized systems, including the successful integration of two state-of-the-art Tecan robotic systems that materially improved the liquid handling systems and output. The output of this part of the NPSG can be seen in the quantity of the screening numbers reported on a weekly basis covering the NCI-60 cell line screens.
- Purification and identification of active materials from the various efforts of DCTD laboratories, as well as materials (both natural and synthetic) from within DCTD whose chemical structures require independent confirmation
- Isolation, curation, and subsequent growth of microbes isolated as a result of collaboration with the U.S. Department of Agriculture's Noxious Weeds Research Unit based on the Fort Detrick campus

NPSG has continued the reinvestigation of an old technique for antitumor drug discovery, the use of crude active extracts in two in vivo assays. As a result of close cooperation between the in vivo testing laboratories of BTB and NPSG, significant numbers of crude extracts from plant and marine sources that demonstrated activity against hollow-fiber assays in mice have been followed by xenografts in suitable mouse models. A number of both known and unknown agents have been identified after deconvolution of the active principles from these experiments. As a result of the number of extracts with inhibitory patterns similar to those of cardiac glycosides, a separate project involving this class of molecules is under consideration due to literature reports of nontraditional cardiac glycosides with potentially novel mechanisms of action that have recently advanced to early clinical trials in cardiology.

At present, 26 extracts have shown sufficient activity in xenografts to warrant identification of their active molecules, excluding cardiac glycosides and tubulin binders. Fractionation of these extracts by high-pressure liquid chromatography have narrowed the search for the active compounds, but none of these isolates have yet demonstrated sufficient intrinsic activity in their purified forms to warrant extension of testing. Further examination of active fractions in these extracts is the rate-limiting step in this project and is the highest priority for the next round of efforts.

Natural-Product Activities in Support of NExT

NPB recently collaborated with Ohio State University (OSU) on a project to develop purified extracts of silvestrol, a plant metabolite isolated from the Island of Borneo. A second major achievement was a very-large-scale effort to find inhibitors from natural-product extracts of the protein-protein interactions involved in 10 apoptotic protein targets in conjunction with the Sanford Burnham Research Institute, the Harbor Branch Oceanographic Institute, and the University of Minnesota.

Silvestrol. Silvestrol entered the DTP system from two sources. The first was the Sarawak Biodiversity Centre (SBC), a Malaysian research organization, which submitted the compound via a routine pure compound submission but under the wrong structure. The second source was as part of a National Cooperative Drug Discovery Group comprising the University of Illinois at Chicago, OSU, and Bristol-Meyers-Squibb. The compound from this second source was collected on the Indonesian side of the Malaysian-Indonesian frontier in northwestern Borneo. Bristol-Meyers-Squibb dropped the compound because SBC had an existing patent, but OSU continued working on the compound because it has a very interesting activity against acute lymphocytic leukemia, being a T-cell-sparing cytotoxin. NPSG successfully aided in purifying the compound from the Indonesian source.

Silvestrol demonstrated in vivo activity in hollow-fiber assays at DTP and in in vivo models of acute lymphocytic leukemia and chronic myelogenous leukemia at OSU. It also demonstrated in vitro efficacy against hepatocellular carcinoma cells at OSU. OSU has negotiated an agreement with SBC that allows the university to work with NCI (effectively, NPB and NPSG) under the NExT umbrella. SBC is fully aware of this collaboration and is satisfied with the arrangement. In



conjunction with the small engineering company Aphios, in Woburn, Massachusetts, NPB and NPSG have successfully extracted silvestrol from an initial sample of ground wood provided by SBC. This work was followed by a larger-scale series of experiments in which silvestrol was extracted by supercritical fluid extraction from a variety of plant parts provided by SBC. Attempts are being made to selectively enrich the first extraction material by using a more selective supercritical fluid extraction solvent. When successful, this will permit calculation of the amounts of raw materials required for provision of sufficient silvestrol to proceed through the drug development process. NPB and NPSG have also developed a water-miscible formulation showing extremely good bioavailability on intravenous (IV) administration, which led to a publication with OSU on the pharmacokinetics of silvestrol.

Burnham Research Institute. By the second quarter of 2010, NPB and NPSG had provided 1,600 96-well plates (155,000 extracts) to the Burnham Research Institute (later the Sanford Burnham Research Institute) in La Jolla, California, to determine whether they could be utilized in a high-throughput screen against 10 apoptotic protein targets. Because of the potential labor and time required to pull these plates from low-temperature storage in the Natural Products Repository (requiring many hours of work in -20°C freezers), an initial set containing examples of all six types of extract were provided for a pilot scale system. Researchers at Sanford Burnham were successful in establishing 1,536-well plate assays using crude extracts, the first time that this had ever been done. This work also included the natural-products group in NCI CCR.

After the initial pilot scale experiments proved successful, the 155,000 wells were provided as 96-well plates to the Sanford Burnham Research Institute in dry format. They were converted into 1,536-well formats by Sanford Burnham, and successful campaigns were run, leading to the identification of a small number (<50) of plant, marine, and microbe-sourced extracts. Although almost all plant and marine extracts could be provided from current stocks (no significant plant collections have been made since 2004), as mentioned previously, extracts from microbes (predominately fungi) would be a rate-limiting step because all would have to be grown in shake flasks. The microbiology and sample-processing groups within NPSG rose to the task and provided a series of up to 100-milligram-scale extracts in a series of campaigns with 17 carefully chosen extracts. NPB and NPSG are currently awaiting the final choices from the team to regrow up to five of these extracts in bulk, using shake flasks, and one in an 8-L bench-top fermentor.

Activation of Cryptic Biosynthetic Clusters

In recent years, it has become obvious from analyses of microbial genomes by various investigators worldwide that a significant number of potential secondary metabolites can be produced by biosynthetic clusters per microbe. These metabolites are not normally expressed under the culture conditions used. The microbiology component of NPSG has for many years collaborated with the U.S. Department of Agriculture's Noxious Weeds Research Group at Fort Detrick and have collected more than 30,000 cultures. These cultures are mainly fungi but also include a fair number of

actinomycetes. With help from NPSG chemists, more than 40 compounds have so far been identified. These compounds are derived from multiple cluster activation techniques and include novel analogs of spliceostatin, xanthocillin, and equisetin, as well as novel active agents against agricultural pests. The ultimate aim of this work is to be able to initially induce the activation of cryptic biosynthetic pathways and the production of previously unknown metabolites as potential lead structures for chemical modification and development into cancer treatment.

Acquisition and Analysis of Clinical Supplies— Mithramycin

NPSG and NPB were able to source two batches of ICH Q7-quality mithramycin A from an Israeli manufacturer and to provide the necessary quality control and quality assurance analyses. The materials were used as Active Pharmaceutical Ingredient and were formulated and used in two clinical trials sponsored by NCI CCR investigators.

BIOLOGICAL RESOURCES BRANCH

The Biological Resources Branch (BRB) supports research in biological therapies and provides resources to explore potential leads for the treatment of cancer and related conditions. Classes include recombinant proteins, monoclonal antibodies, genetically modified viruses, bacteria and mammalian cells, peptides, and oligonucleotides. These entities may function as cytokines, growth factors, vaccines, adjuvants, or other immune-modifying agents. For projects that have been approved by senior NCI management, BRB has a coordinated portfolio of research grants and contracts that represent the flexible utilization of all three legs of the discovery and development process:

1. Peer-reviewed, grant-supported, investigator-initiated discovery
2. Access to consistent and high-quality supplies of reliable reagents for detailed preclinical studies
3. Pilot-scale production capability for clinical-grade material for early-phase proof-of-concept safety studies



PREPARATION OF THE CGMP FILL STATION.

This small-scale automated filling machine is useful for the lots typically manufactured by BRB's Biopharmaceutical Development Program for products like recombinant human IL-5 or ch14.18 monoclonal antibody. Between 100 and 10,000 vials are filled and sealed in a single run. Validation studies for each vial and stopper size are typically performed at the 5,000-vial scale and must be repeated before vialing a clinical product if more than 1 year has elapsed since the last validation.

BRB Accomplishments and Ongoing Activities

Funded Grants in the Biologicals Portfolio. The BRB biologicals grants portfolio contains approximately 170 grants that support concept discovery and development in nonclinical models and laboratory studies conducted in parallel with ongoing clinical trials.

Preclinical Repository and the Biopharmaceutical Development Program. The Preclinical Repository was established in 1988 to acquire, usually by donation, and distribute qualified biological reagents to peer-reviewed academic investigators to enable more reliable model studies. The Biopharmaceutical Development Program (BDP) was established at the NCI Frederick campus in 1993 to manufacture biologicals at pilot scale for first-in-human, proof-of-concept studies. BDP products are used in preclinical development, phase 1 and 2 clinical studies, or selected phase 3 trials. Outside projects that are approved by senior NCI management are funded by interagency transfers to NCI if they are from a government source or by CRADAs if they come from a commercial partner.



BRB PRECLINICAL REPOSITORY

- The BRB Preclinical Repository houses more than 200 bulk cytokines, monoclonal antibodies, cytokine standards, and other highly sought research reagents. All are maintained under carefully controlled storage conditions.
- Since 1996, more than 68,000 vials of different reagents have been shipped domestically and internationally to over 3,000 scientists. The total number of shipments has increased from 1,000 to over 6,000 shipments per year.
- The initial repository inventory was significantly augmented with thousands of vials of cytokine standards from the United Kingdom's National Institute of Biological Standards and Control for distribution to U.S. investigators and 80,000 vials of recombinant human IL-2 from industry.
- Agents developed and manufactured under NCI-sponsored programs recently made available through the repository include ch14.18 and 1A7 monoclonal antibodies, Ad-CCL21 chemokine, MPL adjuvant, and IL-7, IL-12, and IL-15 cytokines.
- The 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 are retested or revalued by the BDP to generate high-quality reagents for research and development.



Technical expertise and specialized capabilities that are available to BRB and BDP support applications beyond cancer treatment for collaborations with other government programs, such as the National Institute of Allergy and Infectious Diseases (NIAID) and the U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID) for vaccine development in infectious diseases, and the National Institute of Diabetes and Digestive and Kidney Diseases for approaches to abort the autoimmune course of early type 1 diabetes. In addition, staff expertise is frequently tapped for advice or training by a range of programs outside DCTD that are involved in drug development:

- Service on grant and contract Source Evaluation Groups or Special Emphasis Panels for non-NCI initiatives
- Participation in steering committees for new NIH programs in infectious disease or nanotechnology applications
- In-plant training experience for senior staff of new biopharmaceutical programs and academic institutions in developing countries
- Technical expertise for site visits of new foreign production plants in NIH collaborations

THE BIOPHARMACEUTICAL DEVELOPMENT PROGRAM

Since 2008, BDP has released 76 clinical or toxicology lots in addition to numerous other GMP entities, such as master cell banks, control lots, diluents, 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; Chemistry, Manufacturing, and Control documents for IND applications; and post-filing technical and regulatory assistance. In addition to the projects discussed under “BRB Grant Programs—Selected Highlights,” following are some of the most prominent products produced during this interval.

ch14.18 Monoclonal Antibody

At present, ch14.18 monoclonal antibody is the highest-priority project for BDP. ch14.18 is an anti-disialoganglioside (GD2) antibody. GD2 is a surface antigen on neuroblastoma, osteosarcoma, glioblastoma, melanoma, and SCLC. It is also found on peripheral pain fibers. A family of antibodies against GD2+ was generated in the 1980s at the Scripps Institute. NCI-funded phase 1 and 2 studies explored the use of these agents singly and in combination, demonstrating modest activity in neuroblastoma as a single agent or in combination with IL-2 or GM-CSF.

The final results of an NCI-funded, randomized, controlled, phase 3 trial showed a 20% increase in progression-free survival at 2 years. These results were published in the *New England Journal of Medicine* in September 2010, marking a new standard of care for pediatric neuroblastoma.



CGMP DOWNSTREAM COLUMN PURIFICATION.

Chromatography at this scale is used to support multigram cGMP lots for projects like ch14.18 monoclonal antibody. Columns and resins at this scale are expensive, but the resin can be sterilized, recharged, and reused to purify the same product for a limited number of cycles, depending on validated process data. Three or four sequential columns with different separation methods (e.g., size, charge, affinity, and/or hydrophobicity) are typically used for purification of a cGMP product at BDP. A column of this size can purify about 25 g of ch14.18 antibody in a single pass.

After discussions with FDA, the control arm was closed and the phase 3 study continued to provide treatment access pending transfer of the product to a commercial entity.

In January 2010, the NCI advertised for a CRADA partner and selected a company to commercialize the antibody. In collaboration with NCI, the industry partner developed a commercial-scale production process and is preparing to file a Biologics License Application in 2013. In the interim, BDP has continued to manufacture sufficient antibody (over 18,000 vials) to support clinical development and ongoing clinical trials. Extramural investigators are currently exploring additional indications.

Hu14.18-IL-2 Fusion Protein

Hu14.18-IL-2 fusion protein is another agent in the same anti-GD2 family as ch14.18 antibody. In studies coordinated at the University of Wisconsin, this fusion protein is in phase 1/2 clinical trials in neuroblastoma and melanoma. The product has been in commercial development by EMD, although most of the clinical lots were actually manufactured at BDP. Under a CRADA, BDP is currently transferring its process and testing information to support validation of EMD's new commercial-scale process.



Recombinant Human IL-15

BDP has developed a process for clinical-grade manufacture of IL-15 in an *Escherichia coli* production system. Since 2009, BDP has produced six clinical lots and more than 9 g of GMP-grade IL-15. The FDA activated the initial IND in April 2010, and there are now five clinical investigations open:

1. CCR—IV bolus and continuous infusion for renal cell cancer and melanoma
2. University of Minnesota—Ex vivo and in vivo donor NK expansion for acute myeloid leukemia
3. CCR—IV bolus for Young tumor-infiltrating lymphocyte therapy in melanoma
4. Loyola University Chicago—Ex vivo expansion of engineered T cells for melanoma
5. Cancer Immunotherapy Trials Network—Multicenter trial in solid tumors using IL-15 applied subcutaneously

In addition to supplying the clinical investigations, BRB is providing IL-15 to NIAID for preclinical animal studies that support the use of IL-15 as an adjuvant in HIV vaccine formulation. NIAID plans to file an IND to assess the vaccine strategy in HIV-positive patients. BRB also supplies IL-15 to the preclinical repository for distribution to the research community. This material has been utilized in ex vivo applications for clinical research based on high quality and a published production process.

CGMP 80-L FERMENTATION OF RECOMBINANT HUMAN (RH)IL-15.

Production of rhIL-15 involves refolding, purification, and pooling of product derived from fermentation paste. Several fermentations in this 80-L fermentor at 50-L working volume are run for one 1-g lot of rhIL-15.

BRB Grant Programs—Selected Highlights

Significant events in the BRB grants portfolio since 2008 have included the following:

- A BRB grantee from University of Texas, MD Anderson, received the prestigious Presidential Early Career Award for Scientists and Engineers for research on the modulation of microglia and T-cell interactions in malignant glioma. The results of this work suggests potential immunomodulating approaches to treat malignant glioma.
- An NCI grantee, with grant support from BRB and CTEP, successfully utilized funding from the American Recovery and Reinvestment Act to hire two technicians and acquire laboratory equipment to support a research program in engineered T cells. In addition, the IL-15 in the BRB Preclinical Repository was demonstrated to be useful in expanding engineered T cells. Permission was obtained from FDA to use the repository IL-15 in a clinical investigation with melanoma patients, based on the quality of the reagent and a publication by BDP that describes the manufacture of the cytokine.
- In an adult leukemia project in the former Rapid Access to Intervention Development (RAID) program, a selective depletion reagent was developed in memory T cells for immune reconstitution after allogeneic stem cell transplant. The material, produced with support from the RAID program, is now in clinical trials at Yale University and the Fred Hutchinson Cancer Research Center in Seattle.

- In collaboration with the NCI NExT program, a BRB investigator from Duke University developed a novel strategy exploiting poliovirus biology for the treatment of brain tumors. The project is currently under clinical development using material manufactured by BDP.
- A BRB investigator was selected for funding under the highly competitive Special Translation Research Acceleration Project (STRAP) grant initiative for development of an autologous T-cell treatment targeting CD19 in patients with B-cell malignancies.
- A BRB grantee at the Wistar Institute has optimized the delivery of nanoparticles carrying small interfering RNA targeting tolerogenic mediators to regulatory dendritic cells, reprogramming them from immunosuppressive to immunostimulatory cells capable of promoting antitumor immunity. This approach will be tested in a clinical trial in ovarian cancer at the Methodist Hospital Research Institute.

TOXICOLOGY AND PHARMACOLOGY BRANCH

The Toxicology and Pharmacology Branch (TPB) provides essential toxicology and pharmacology data and expertise for drugs, biologics, and imaging agents in development for clinical trials. Most of the data is submitted to the FDA.

Background and Accomplishments

TPB generates and interprets the toxicology data necessary to file an IND application with the FDA and provides unique toxicology expertise to the extramural community, creating tailored preclinical strategies and study designs for safety assessment. TPB investigators guide studies by pharmacokinetics and pharmacodynamics, enabling the correlation of pharmacokinetics and pharmacodynamics with toxicity and establishing relationships among pharmacokinetics and pharmacodynamics, toxicity, and safety across species. In vitro toxicity data and/or studies are incorporated as appropriate, and toxicity is compared with that of accepted clinical agents as necessary. TPB scientists demonstrate the sequence and extent of adverse effects as they relate to dose and exposure, minimizing toxicity by changes in route and/or

dosing schedule and establishing safe operating parameters for clinical administration of promising new anticancer drug candidates. Potential toxicology and pharmacology hurdles for targets and chemical scaffolds are identified during the earliest stages of project development. Early and rapid in vitro or in vivo characterization of potential adverse effects or absorption, distribution, metabolism, and excretion (ADME) properties can define structure–activity relationships and guide chemical modifications. TPB contributes a unique body of knowledge to enhance mechanistic understanding of toxicities associated with anticancer agents. It plays a unique role for NCI by providing access to key preclinical findings to encourage and catalyze mechanistic investigation.

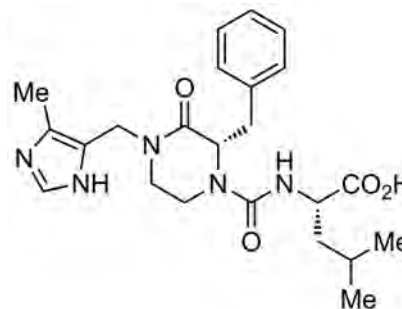
Investigative Toxicology Program

The goal of the Investigative Toxicology Program is to generate insights about the cellular toxicity of compounds and apply this insight to characterize and aid in the selection of drug candidates and introduce mechanism-based in vitro screens. The program provides investigative toxicology deliverables to the extramural scientific community by serving the immediate needs of the NExT portfolio. The program's services include:

- Surveying clinical needs for profiling early adverse effects for high-priority organ systems
- Providing data to describe biologically qualified pathways that are mediating mechanisms of toxicity for classes of approved agents
- Providing data that qualify semivalidated in vitro systems for screening opportunities

Screening Strategies based on mechanistic toxicology	Tools <ul style="list-style-type: none"> • Cell-based assays • Computer-based pathway modeling • Protein-based assays • In vivo studies
Solubility and early formulations	Tools <ul style="list-style-type: none"> • In vitro solubility and ADME assays • In silico assessment of ADME properties and compound characteristics
Cellular systems support and compound characterization	Tools <ul style="list-style-type: none"> • Tissue slice systems • Cell culture systems for toxicology and ADME • Bone marrow assay

INVESTIGATIVE TOXICOLOGY



GGTI - NSC 732082

The program offers a functional toxicogenomics data resource that provides mRNA assessments for the characterization of molecular changes in vital organs (heart, lung, liver, kidney, bone marrow) induced by marketed anticancer agents, investigational agents, and combinations. Most pre-clinical toxicology data generated to characterize investigative agents are unpublished and generally not available as a public data resource.

PHARMACEUTICAL RESOURCES BRANCH

The Pharmaceutical Resources Branch (PRB) provides comprehensive pharmaceutical services to various programs of DCTD and other parts of NCI and NIH. The primary objective of PRB is to supply high-quality chemical substances and formulated products in support of preclinical studies and human clinical trials. This objective is accomplished essentially through contract management activities. Most of the data generated are submitted to the FDA.

The major contract areas managed by PRB staff include:

- Chemical synthesis and large-scale GMP production
- Analytical services and quality control
- Pharmaceutical research and development for identifying dosage forms and novel formulations
- Clinical dosage form manufacturing and shelf life surveillance

PRB Ongoing Activities

Chemical Resources. PRB performs small-scale synthesis, including probe runs, process optimization, and large-scale GMP synthesis. These range from relatively short syntheses of one to two steps to complicated and challenging multistep syntheses involving 20 or more steps. These activities are supported by three chemical synthesis contracts.

Analytical. PRB develops validated assays to certify the purity, identity, and quality of test agents according to FDA guidelines and industry standards. For bulk chemical substances of all lots, the branch also prepares specifications for release for IND-directed current Good Laboratory Practice toxicology studies and for use in manufacturing clinical supplies.

Pharmaceutical Research and Development. PRB develops dosage forms suitable for use in human clinical trials and evaluates salts, non-aqueous solvents, and surfactants. Emphasis is given to newer techniques to improve solubility or stability (emulsions, prodrugs, and complexation). PRB scientists also evaluate dosage forms for chemical content, activity in rodent models whenever possible, and feasibility for manufacture on production scale. These activities are supported by three pharmaceutical research and development contracts.

CLINICAL SUPPLIES PROVIDED BY PRB FOR ONGOING TRIALS

- Z-Endoxifen
- PH-H71
- Fenretinide
- LMP-400
- DMS-612
- Safingol
- LMP-776
- 1-MT
- IPdR
- FdCyd/
THU
- SJG-136
- TRC102
- AFP-464

Pharmaceutical Production. Under a pharmaceutical production contract for parenteral drug products, including freeze-dried, emulsion, and liquid-filled dosage forms, PRB produces capsules and tablets for oral use, with the capability to produce creams and gels for topical use. Production is carried out with adherence to strict cGMP guidelines and regular inspection by the U.S. FDA, the United Kingdom Medicines and Healthcare Products Regulatory Agency (the U.K. equivalent of FDA), and other European regulatory authorities.

Shelf-Life Surveillance. PRB conducts a stability program for each clinical batch of drug to certify potency, degradation products, and other aspects as required. Testing schedules are carried out according to FDA and other guidelines.

PRB Accomplishments

PRB has produced clinical supplies and chemistry, manufacturing, and control data to support 10 INDs sponsored by DCTD and 6 INDs sponsored under the former NCI RAID mechanism. Several new clinical candidates are in advanced IND development stages. The branch has synthesized 96 distinct compounds ranging in batch sizes of grams to multi-kilograms, often manufacturing additional batches. PRB has also validated high-pressure liquid chromatographic methods that were developed for 45 distinct compounds in advanced development. A total of 185 individual lots underwent complete analytical assessment and were released for advanced preclinical studies (IND directed) and/or for use in preparing clinical dosage forms. In addition, PRB has prepared approximately 50 batches of parenteral dosage forms, including freeze-dried products, liquid-filled products,

nanosuspensions, and emulsions. Oral dosage forms (mostly capsules) of 13 distinct compounds have been prepared in multiple batches and multiple strengths to accommodate dosing needs in ongoing clinical trials. PRB conducted shelf-life studies at multiple points each year on an average of 80 distinct batches of drug products. It has also conducted pre-formulation and formulation work to identify the conditions required for preparing suitable and stable formulations. The results were transferred to the manufacturers of the clinical dosage forms for preparation of actual clinical supplies. PRB prepared several lots of GMP bulk drugs, performed quality-control release testing of these batches, developed formulations and/or new size configurations, and manufactured sterile injectable and capsule dosage forms as appropriate for each drug. It developed GMP synthetic process and analytical methods for the NExT ZW800-1 project; synthesized on gram scale and provided 70 investigational agents in support of preclinical combination studies; and monitored the shelf-life of 20 separate clinical batches and analyzed samples at 71 distinct time points.

INFORMATION TECHNOLOGY BRANCH

The Information Technology Branch (ITB) provides scientific computing support and development for DTP and other programs in DCTD. ITB staff work to understand the needs of DTP and other programs with regard to data capture, storage, searching, and analysis and to translate them into specific programming tasks. ITB efforts fall into two broad categories, internal and external. Internal efforts focus on infrastructure for DTP screening activities, including compound scheduling and shipping, experiment setup, data capture, report generation, and decision support and recording. External efforts focus on the DTP public Web pages and involve not only making DTP data available to the research community, but also making available DTP data analysis tools, such as COMPARE.

Accomplishments and Ongoing Activities

Support for Continued Development of Screening Program. Although the basic experimental protocol for the NCI-60 cell line screen is established, continuous changes in the details are implemented. A recent change instituted the combination screen in the NCI-60 cell lines, both at the Frederick National Laboratory for Cancer Research and at external contractors. ITB managed the needed changes in the shipping, data capture, reporting, and workflow systems.



ITB HISTORY

ITB was formed in 1989 to guide the implementation of computer resources for the NCI-60 cell line screen. Three developments led to an increased scope for its activities:

1. The COMPARE algorithm proved valuable for taking full advantage of screening data. In addition to capturing, recording, and reporting the data, ITB is actively involved in looking for ways to make better use of data.
2. DTP Web pages were developed to provide the research community with easy access to a large amount of chemical and biological data from DTP. Thus ITB's "customers" expanded from just DTP staff to the greater research community.
3. ITB assisted other DCTD programs as they started operations in Frederick.

Support for In Vivo Screening. Computer systems for assignment, data capture, and reporting for both the hollow-fiber and xenograft in vivo screens have been implemented to better integrate the data from these screens into the larger DTP dataset.

Support for Combination Studies. DTP has committed to a significant effort in looking at combinations of agents in the NCI-60 cell line screen, and ITB has created the computer systems to capture, store, and report the data generated. The screen design allows for testing of "rational" combinations of pathway-specific agents but also casts a wider net, allowing for the discovery of synergistic combinations that would not otherwise be predicted. In addition to studies in the full NCI-60 panel, a prescreen utilizes three cell lines, chosen from the NCI-60 cell lines, for the diversity of their molecular characteristics. Each new agent is tested in these three cell lines, in combination with a panel of approximately 85 FDA-approved oncology drugs and investigational agents. Promising combinations are then tested against the entire NCI-60 panel. Combinations with promising results in this prescreen are nominated to DTP and CTEP staff at meetings of the Biological Evaluation Committee and Data Review

Committee for combination testing in the NCI-60 cell line screen. Some of the active combinations are expected (e.g., mTOR inhibitor plus PI3 kinase inhibitor), whereas others are unexpected (e.g., vincristine plus epidermal growth factor receptor [EGFR] inhibitors).

Compound Submission. A Web-based submission form for researchers to submit their compounds to NCI for screening collects the information necessary to process these submissions. The online form also allows submitters to follow the progress of their compounds through screening and to access data as the assays are completed.

Molecular Targets. The NCI-60 cell line panel, utilized to screen for novel anticancer agents, has an ongoing program to molecularly characterize the cell lines. More than 300 laboratories worldwide have contributed to this effort, and the results are available for data mining through the DTP website. These projects have consisted of small-scale projects focusing on targets of interest to a particular laboratory as well as large-scale, genome-wide studies. These larger studies include the characterization of mRNA by microarrays (six platforms, five independent groups), high-density arrays of single-nucleotide polymorphisms (two platforms, three groups), characterization of microRNA (three independent laboratories), metabolomic data, and genome-wide DNA methylation. In addition, a project is in progress to sequence the exome of these cell lines.

Compound Order System. DTP's large repository of collected compounds is accessed via a Web interface that lets researchers request samples of individual compounds or request plated sets of compounds with an electronic Material Transfer Agreement that is automatically generated and routed, minimizing paperwork and processing time.

Website Development. ITB continues to maintain and develop the DTP Web pages. The purpose of this effort is to provide data generated from DTP's screening programs to the research community and to provide current information on accessing DTP resources and Web front ends to analysis tools such as COMPARE. The Website is popular with the research community and now receives more than 10,000 hits per day. Of the more 10,000 unique visitors per month, about 5% return at least 10 times per month.

PubChem. ITB was closely involved with the initial creation of the PubChem database; approximately one-third of the

initial structures and 100% of the initial bioassay data originated from DTP. ITB continues to update the DTP data in PubChem to provide an additional resource for the research community.

Interagency Agreement. An agreement between DTP and USAMRIID supports a molecular modeling team that is stronger than either institution could have developed independently, allowing collaborations on projects that are of interest to both (e.g., phosphatase inhibition).

Future Plans

The ITB chief has served on the Molecular Libraries Project Team since its inception. DTP has sent more than 4,000 compounds to the Molecular Library repository, and the first batch of these compounds has now been tested in nearly 200 assays. These compounds have also been through the NCI-60 screen, so there is an unprecedented opportunity to examine the detailed relationship of molecular activity to screening pattern of activity. In addition, the number of probe compounds created by the Molecular Library effort has risen to nearly 100. Efforts are under way to test these probe compounds in the NCI-60 cell line screen. Because many of the targets of these probes are cancer related, there should be a number of compounds that show interesting activity. It also will enrich the set of patterns known to be associated with a particular mechanism.

OFFICE OF THE ASSOCIATE DIRECTOR

DTP's Office of the Associate Director (OAD) coordinates special projects that cross branches in DTP and other programs in DCTD, such as the following:

- The COMBO drugs project is a joint DTP–CTEP effort that is supported by the DTP OAD and other DTP branches. BTB conducts studies in vivo, MPB conducts studies in cell culture, DSCB provides drug supply, ITB provides data management, and TPB provides external contractor management.
- The Pharmacokinetics Laboratory encompasses and connects the preclinical activities of DTP with ongoing clinical studies at the DCTD Developmental Therapeutics Clinic in the NIH Clinical Center. Samples from patients on protocols at the Clinical Center are sent to the Pharmacokinetics Laboratory for analysis of systemic exposure to the drug and its metabolites. For earlier-stage

projects, the Pharmacokinetics Laboratory investigates the metabolism of compounds in vitro and then conducts pharmacokinetics and metabolism 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.

SELECTED PUBLICATIONS

GRANTS AND CONTRACTS OPERATIONS BRANCH—GRANTEE PUBLICATIONS

Ferroptosis: an iron-dependent form of nonapoptotic cell death, Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, Morrison B 3rd, Stockwell BR. *Cell*, 2012;149(5):1060–1072.

<http://www.ncbi.nlm.nih.gov/pubmed/22632970>

- A unique, iron-dependent form of nonapoptotic death, called ferroptosis, was discovered during the study of erastin, a small molecule that is a selective inhibitor of oncogenic RAS.

Relative mitochondrial priming of myeloblasts and normal HSCs determines chemotherapeutic success in AML,

Vo TT, Ryan J, Carrasco R, Neuberger D, Rossi DJ, Stone RM, DeAngelo DJ, Frattini MG, Letai A. *Cell*, 2012;151(2):344–355.
<http://www.ncbi.nlm.nih.gov/pubmed/23063124>

- By taking a functional rather than a genetic approach, it was found that mitochondrial priming measured by BH3 profiling was a determinant of initial response to induction chemotherapy and thus may be useful as a clinical predictive biomarker.

Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma,

Provenzano PP, Cuevas C, Chang AE, Goel VK, Von Hoff DD, Hingorani SR. *Cancer Cell*, 2012;21(3):418–429.

<http://www.ncbi.nlm.nih.gov/pubmed/22439937>

- An animal model of pancreatic cancer was developed that mimics the stromal barrier that creates a drug-free sanctuary in human pancreatic cancer by creating extremely high interstitial fluid pressures (IFP) that induce vascular collapse. Hyaluronan, or hyaluronic acid, is the major determinant of high IFP. An infusion of enzyme



PEGPH20 ablates hyaluronic acid, normalizes IFP, remodels the stroma, and increases tumor responsiveness to chemotherapy, a strategy that has led to a clinical trial.

RNAi screen of the druggable genome identifies modulators of proteasome inhibitor sensitivity in myeloma including CDK5, Zhu YX, Tiedemann R, Shi C-X, Yin H, Schmidt JE, Bruins LA, Keats JJ, Braggio E, Sereduk C, Mousses S, Stewart AK. *Blood*, 2011;117(14):3847–3857.

<http://www.ncbi.nlm.nih.gov/pubmed/21289309>

- A small interfering RNA screen was used to find molecular targets that would cooperate with proteasome inhibitors in multiple myeloma. After identifying CDK5, small-molecule CDK5 inhibitors were demonstrated to synergize with bortezomib to induce cytotoxicity of primary myeloma cells and cell lines. These findings have led to a clinical trial of MC088, a CDK5 inhibitor, which will be followed by a combination trial with bortezomib.

Effect of KRAS oncogene substitutions on protein behavior: implications for signaling and clinical outcome, Ihle NT, Byers LA, Kim ES, Saintigny P, Lee JJ, Blumenschein GR, Tsao A, Liu S, Larsen JE, Wang J, Diao L, Coombes KR, Chen L, Zhang S, Abdelmelek MR, Tang X, Papadimitrakopoulou V, Minna JD, Lippman SM, Hong WK, Herbst RS, Wistuba II, Heymach JV, Powis G. *Journal of the National Cancer Institute*, 2012;104(3):228–239.

<http://www.ncbi.nlm.nih.gov/pubmed/22247021>

- KRAS mutations were examined in a series of patient lung samples and found that not all mutant KRAS proteins affect patient survival or downstream signaling in a similar way. The heterogeneous behavior of mutant KRAS proteins implies that the specific KRAS mutant expressed by the tumor must be taken into account in selection of patient therapies.

MOLECULAR PHARMACOLOGY BRANCH

The “survivin suppressants” NSC 80467 and YM155 induce a DNA damage response, Glaros TG, Stockwin LH, Mullendore ME, Smith B, Morrison BL, Newton DL. *Cancer Chemotherapy and Pharmacology*, 2012;70(1):207–212.

<http://www.ncbi.nlm.nih.gov/pubmed/22526412>

- Data from this study provide the first evidence that NSC 80467 and YM155 are DNA-damaging agents where suppression of survivin is a secondary event, probably a consequence of transcriptional repression.

Role of the VEGF/VEGFR axis in cancer biology and therapy, Rapisarda A, Melillo G. *Advances in Cancer Research*, 2012;114:237–267.

<http://www.ncbi.nlm.nih.gov/pubmed/22588059>

- This chapter discusses the role of the VEGF axis in tumor biology and highlights the clinical application of anti-VEGF therapies, elaborating on pitfalls and strategies to improve clinical outcome.

Overcoming disappointing results with antiangiogenic therapy by targeting hypoxia, Rapisarda A, Melillo G. *Nature Reviews Clinical Oncology*, 9(7):378–390.

<http://www.ncbi.nlm.nih.gov/pubmed/22525710>

- This review examines the evidence linking antiangiogenic agents and intratumor hypoxia by providing an overview of the preclinical and clinical data, focusing on the possibility of exploiting intratumor hypoxia as a means to improve the therapeutic response to antiangiogenic agents.

Identification of CBX3 and ABCA5 as putative biomarkers for tumor stem cells in osteosarcoma, Saini V, Hose CD, Monks A, Nagashima K, Han B, Newton DL, Millione A, Shah J, Hollingshead MG, Hite KM, Burkett MW, Delosh RM, Silvers TE, Scudiero DA, Shoemaker RH. *PLOS One*, 2012;7(8):e41401. Erratum in *PloS One*, 2012;7(11).

<http://www.ncbi.nlm.nih.gov/pubmed/22870217>

- Enhanced clonogenicity, tumorigenicity, and drug sensitivity were found in sphere cultures enriched with tumor stem cells as compared with monolayers. In addition, a number of osteosarcoma biomarker candidates were found that could be used in combination with already known markers.

CHEK2 genomic and proteomic analyses reveal genetic inactivation or endogenous activation across the 60 cell lines of the US National Cancer Institute, Zoppoli G, Solier S, Reinhold WC, Liu H, Connelly JW Jr, Monks A, Shoemaker RH, Abaan OD, Davis SR, Meltzer PS, Doroshow JH, Pommier Y. *Oncogene*, 2012;26(4):403–418. Erratum in *Oncogene*, 2012;31(4):535–536.

<http://www.ncbi.nlm.nih.gov/pubmed/21765476>

- This report provides information on the relationship between different genomic and proteomic parameters related to Chk2 in cancer cells and on the broad spectrum of variation in these parameters, using the NCI-60 cell line panel as a systems biology model.

Searching for molecular targets in sarcoma, Teicher BA. *Biochemical Pharmacology*, 2012;84(1):1–10.
<http://www.ncbi.nlm.nih.gov/pubmed/22387046>

- This commentary focuses on advances in sarcoma genomics that have the goal of identifying therapeutic targets and discovering new drugs.

Testing of the topoisomerase I inhibitor Genz-644282 by the pediatric preclinical testing program, Houghton PJ, Lock R, Carol H, Morton CL, Gorlick R, Kolb EA, Keir ST, Reynolds CP, Kang MH, Maris JM, Billups CA, Zhang MX, Madden SL, Teicher BA, Smith MA. *Pediatric Blood & Cancer*, 2012;58(2):200–209.
<http://www.ncbi.nlm.nih.gov/pubmed/21548007>

- Genz-644282, a novel non-camptothecin topoisomerase I poison that is in clinical development, was tested against the Pediatric Preclinical Testing Program in vitro panel to assess the dose–response relationship, and mRNA gene signatures predictive for Genz644282 response in vitro were applied to select 15 tumor models that were evaluated prospectively. Like other topoisomerase I poisons, Genz-644282 was highly active within a narrow dose range. How accurately these data will translate to clinical activity will depend upon the drug exposures that can be achieved in children treated with this agent.

Targeting HER2-positive cancer with dolastatin 15 derivatives conjugated to trastuzumab, novel antibody-drug conjugates, Gianolio DA, Rouleau C, Bauta WE, Lovett D, Cantrell WR, Recio III A, Wolstenholme-Hogg P, Busch M, Pan P, Stefano JE, Kramer HM, Goebel J, Krumbholz RD, Roth S, Schmid SM, Teicher BA. *Cancer Chemotherapy and Pharmacology*, 2012;70(3):439–449.
<http://www.ncbi.nlm.nih.gov/pubmed/22821053>

- This study showed that Dol15 tethered at the C-terminus may be a useful tubulin-targeting agent for conjugation at various antibody-reactive sites.

Targeting cancer metabolism, Teicher BA, Linehan WM, Helman LJ. *Clinical Cancer Research*, 2012;18(20):5537–5545.
<http://www.ncbi.nlm.nih.gov/pubmed/23071355>

- This *CCR Focus* section highlights aspects of cancer metabolism and renewed hope of taking advantage of altered cancer metabolism therapeutically.

The promise of antibody-drug conjugates, Teicher BA, Doroshow JH. *New England Journal of Medicine*, 2012;367(19):1847–1848.
<http://www.ncbi.nlm.nih.gov/pubmed/23134386>

- This editorial discusses the promise of antibody–drug conjugates as a potential major contributor to improved cancer therapy.

NATURAL PRODUCTS BRANCH

Induced production of N-formyl alkaloids from *Aspergillus fumigatus* by co-culture with *Streptomyces peucetius*, Zuck KM, Shipley S, Newman DJ. *Journal of Natural Products*, 2011;74(7):1653–1657.
<http://www.ncbi.nlm.nih.gov/pubmed/21667925>

- This paper reports on the induction of production of formyl xanthocillin analogues by co-culture of the fungus *Aspergillus fumigatus* with the bacteria *Streptomyces peucetius*. The structures of two new metabolites were determined, and cytotoxic activity of all the analogues was tested on the NCI-60 panel, with one of the compounds showing significant activity against several cell lines.

Characterization of silvestrol pharmacokinetics in mice using liquid chromatography–tandem mass spectrometry, Saradhi, UV, Gupta, SV, Chiu M, Wang J, Ling Y, Liu Z, Newman D J, Covey JM, Kinghorn, AD, Marcucci G, Lucas DM, Grever MR, Phelps MA, Chan KK. *AAPS Journal*, 2011;13(3):347–356.
<http://www.ncbi.nlm.nih.gov/pubmed/21499689>

- This paper reports on the development of a liquid chromatography–tandem mass spectrometry method that was capable of accurately measuring tissue levels of silvestrol in a mouse model.

Histone deacetylase inhibitors from *Burkholderia thailandensis*, Klausmeyer P, Shipley SM, Zuck KM, McCloud TG. *Journal of Natural Products*, 2011;74(10):2039–2044.
<http://www.ncbi.nlm.nih.gov/pubmed/21967146>

- The authors report on the isolation and identification of a new cytotoxic depsipeptide and its dimer from an extract of *Burkholderia thailandensis*.

Natural products as sources of new drugs over the 30 years from 1981 to 2010, Newman DJ, Cragg GM. *Journal of Natural Products*, 2012;75(3):311–335.
<http://www.ncbi.nlm.nih.gov/pubmed/22316239>



- This review, an updated and expanded version of prior reviews on natural products as new drug sources, highlights the significant number of natural product drugs or leads produced by microbes and/or microbial interactions.

The impact of the United Nations Convention on Biodiversity on natural products research, Cragg GM, Katz F, Newman DJ, Rosenthal J. *Natural Product Reports*, 2012;29(12):1407–1423.

<http://www.ncbi.nlm.nih.gov/pubmed/23037777>

- The authors discuss the experiences of NCI and the U.S. government–sponsored International Cooperative Biodiversity Groups program in the establishment of international agreements in the context of the Convention of Biological Diversity’s objectives of promoting fair and equitable collaboration with multiple parties in many countries. Included are specific lessons in developing such collaborations.

Anticancer Agents from Natural Products, 2nd ed, Cragg GM, Kingston DGI, Newman DJ. Boca Raton, FL: Taylor & Francis, 2012.

- This book summarizes the current status of research and development of the major classes of clinically used anticancer natural products, including their history, mechanisms of action, medicinal chemistry, synthesis, and clinical applications.

TOXICOLOGY AND PHARMACOLOGY BRANCH

Identification and elucidation of the biology of adverse events: the challenges of safety assessment and translational medicine, Turteltaub KW, Davis MA, Burns-Naas LA, Lawton MP, Clark AM, Reynolds JA. *Clinical Cancer Research*, 2011;17(21):6641–6645.

<http://www.ncbi.nlm.nih.gov/pubmed/22046025>

- This Special Report reviews how the application of systems biology methods to the evaluation of toxicities in oncology treatments can accelerate the introduction of safe and effective new anticancer drugs.

Preclinical pharmacokinetic, toxicological and biomarker evaluation of SR16157, a novel dual-acting steroid sulfatase inhibitor and selective estrogen receptor modulator, Rausch L, Green C, Steinmetz K, Levalley S, Catz P, Zaveri N,

Schweikart K, Tomaszewski J, Mirsalis J. *Cancer Chemotherapy and Pharmacology*, 2011;67(6):1341–1352.

<http://www.ncbi.nlm.nih.gov/pubmed/20737149>

- This in vivo preclinical study was carried out to determine the pharmacokinetics and toxicokinetics of SR16157, a promising agent for the endocrine therapy of breast cancer, as well as to investigate a potential biomarker for use in clinical trials involving this agent.

Plasma pharmacokinetics and oral bioavailability of the 3,4,5,6-tetrahydrouridine (THU) prodrug, triacetyl-THU (taTHU), in mice. Beumer JH, Eiseman JL, Gilbert JA, Holleran JL, Yellow-Duke AE, Clausen DM, D’Argenio DZ, Ames MM, Hershberger PA, Parise RA, Bai L, Covey JM, Egorin MJ. *Cancer Chemotherapy and Pharmacology*, 2011;67(2):421–430.

<http://www.ncbi.nlm.nih.gov/pubmed/20443002>

- Because the preclinical evaluation and clinical use of 3,4,5,6-tetrahydrouridine (THU), a potent CD inhibitor, are limited by its low (20%) oral bioavailability, the authors characterized the pharmacokinetics of THU after the administration to mice of the more lipophilic prodrug triacetyl-THU (taTHU). The resulting data, which showed the higher (30%) oral bioavailability of taTHU, will support the clinical studies of taTHU.

Attenuation of neurovirulence, biodistribution, and shedding of a poliovirus:rhinovirus chimera after intrathalamic inoculation in *Macaca fascicularis*, Dobrikova EY, Goetz C, Walters RW, Lawson SK, Peggens JO, Muszynski K, Ruppel S, Poole K, Giardina SL, Vela EM, Estep JE, Gromeier M. *Journal of Virology*, 2012;86(5):2750–2759.

<http://www.ncbi.nlm.nih.gov/pubmed/22171271>

- This study demonstrated the safety of the prototype oncolytic poliovirus recombinant, PVS-RIPO, and its inducement of neutralizing antibody responses against poliovirus serotype 1 after intrathalamic inoculation of long-tailed macaque monkeys (*Macaca fascicularis*).

A new generation of serotype chimeric infectivity-enhanced conditionally replicative adenovirals: the safety profile of Ad5/3-Δ24 in advance of a phase I clinical trial in ovarian cancer patients, Kim KH, Ryan MJ, Estep JE, Brock M, Miniard BM, Thomas L, Rudge TJ, Peggens JO, Broadt TL, Wang M, Preuss MA, Siegal GP, Hemminki A, Harris RD, Aurigemma R, Curiel DT, Alvarez RD. *Human Gene Therapy*, 2011;22(7):821–828.

<http://www.ncbi.nlm.nih.gov/pubmed/21171861>

- This study, which evaluated the safety of intraperitoneal Ad5/3-Δ24 in advance of a phase I clinical trial in gynecologic cancers, found no specific histopathologic changes attributable to virus administration in Syrian hamster cohorts.

Short-term toxicity study of ST-20 (NSC-741804) by oral gavage in Sprague-Dawley rats, Terse PS, Johnson JD, Hawk MA, Ritchie GD, Ryan MJ, Vasconcelos DY, Contos DA, Perrine SP, Peggins JO, Tomaszewski JE. *Toxicologic Pathology*, 2011;39(4):614–622.

<http://www.ncbi.nlm.nih.gov/pubmed/21558467>

- This subchronic oral toxicity study conducted in Sprague-Dawley rats found that toxicity produced by a 15-day oral administration of ST-20 was reversible upon a 14-day recovery period and determined the no-observable-adverse-effect level of this agent.

in vitro exposure of precision-cut lung slices to 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole lysylamide dihydrochloride (NSC 710305, Phortress) increases inflammatory cytokine content and tissue damage, Behring HP, Furniss MJ, Davis M, Tomaszewski JE, Parchment RE. *Toxicological Sciences*, 2012;131(2):470–479.

<http://www.ncbi.nlm.nih.gov/pubmed/23143926>

- The authors used an ex vivo precision-cut lung slice (PCLS) model to search for concentration-dependent effects of NSC 710305 on cytokine content, protein content, and immunological and histological endpoints, finding that the concentration- and time-dependent inflammatory response of PCLS to NSC 710305 preceded relevant tissue damage by a few days.

Formation of active products of benzaldehyde dimethane sulfonate (NSC 281612, DMS612) in human blood and plasma and their activity against renal cell carcinoma lines, Parise RA, Anyang BN, Eiseman JL, Egorin MJ, Covey JM, Beumer JH. *Cancer Chemotherapy and Pharmacology*, 2012;71(1):73–83.

<http://www.ncbi.nlm.nih.gov/pubmed/23053264>

- This paper describes a liquid chromatography–mass spectrometry assay developed to detect and quantitate benzaldehyde dimethane sulfonate and its metabolites and decomposition products in support of clinical trials.

Preclinical pharmacology of novel indolecarboxamide ML-970, an investigative anticancer agent, Rayburn E, Wang W, Li M, Zhang X, Xu H, Li H, Qin JJ, Jia L, Covey J, Lee M, Zhang R. *Cancer Chemotherapy and Pharmacology*, 2012;69(6):1423–1431.

<http://www.ncbi.nlm.nih.gov/pubmed/22367116>

- This study was conducted to define the pharmacological properties of ML-970 (AS-I-145; NSC 716970), an indolecarboxamide synthesized as a less toxic analog of CC-1065 and duocarmycin, a natural product that binds the A-T-rich DNA minor groove and alkylates DNA.

Effects of tetrahydrouridine on pharmacokinetics and pharmacodynamics of oral decitabine, Lavelle D, Vaitkus K, Ling Y, Ruiz MA, Mahfouz R, Ng KP, Negrotto S, Smith N, Terse P, Engelke KJ, Covey J, Chan KK, Desimone J, Sauntharajah Y. *Blood*, 2012;119(5):1240–1247.

<http://www.ncbi.nlm.nih.gov/pubmed/22160381>

- This study found that combining oral tetrahydrouridine with oral decitabine changes the latter's pharmacology in a manner that may facilitate accessible noncytotoxic DNA methyltransferase 1–targeted therapy.

OFFICE OF THE ASSOCIATE DIRECTOR

Principles of pharmacokinetics, In: *Cancer Chemotherapy and Biotherapy, Fifth Edition*, Chabner BA, Longo DL (eds). Baltimore: Lippincott Williams & Wilkins, 2011:50–61.

- This chapter is part of the introductory section in a comprehensive reference on the preclinical and clinical pharmacology of anticancer agents.

Phase I trial of vandetanib and bevacizumab evaluating the VEGF and EGF signal transduction pathways in adults with solid tumours and lymphomas, Kummar S, Gutierrez ME, Chen A, Turkbey IB, Allen D, Horneffer YR, Juwara L, Cao L, Yu Y, Kim YS, Trepel J, Chen H, Choyke P, Melillo G, Murgu AJ, Collins J, Doroshow JH. *European Journal of Cancer*, 2011;47(7):997–1005.

<http://ncbi.nlm.nih.gov/pubmed/21247755>

- In this phase I study, the authors safely combined vandetanib, an investigational agent with activity against EGFR and VEGFR2, and bevacizumab, a monoclonal antibody against VEGF, demonstrated preliminary evidence of clinical activity, and conducted correlative studies demonstrating anti-angiogenic effect.



Phase I study of the synthetic triterpenoid, 2-cyano-3, 12-dioxolean-1, 9-dien-28-oic acid (CDDO), in advanced solid tumors, Speranza G, Gutierrez ME, Kummar, Strong JM, Parker RJ, Collins J, Yu Y, Cao L, Murgo AJ, Doroshow JH, Chen A. *Cancer Chemotherapy and Pharmacology*, 2012;69(2):431–438.

<http://ncbi.nlm.nih.gov/pubmed/21805353>

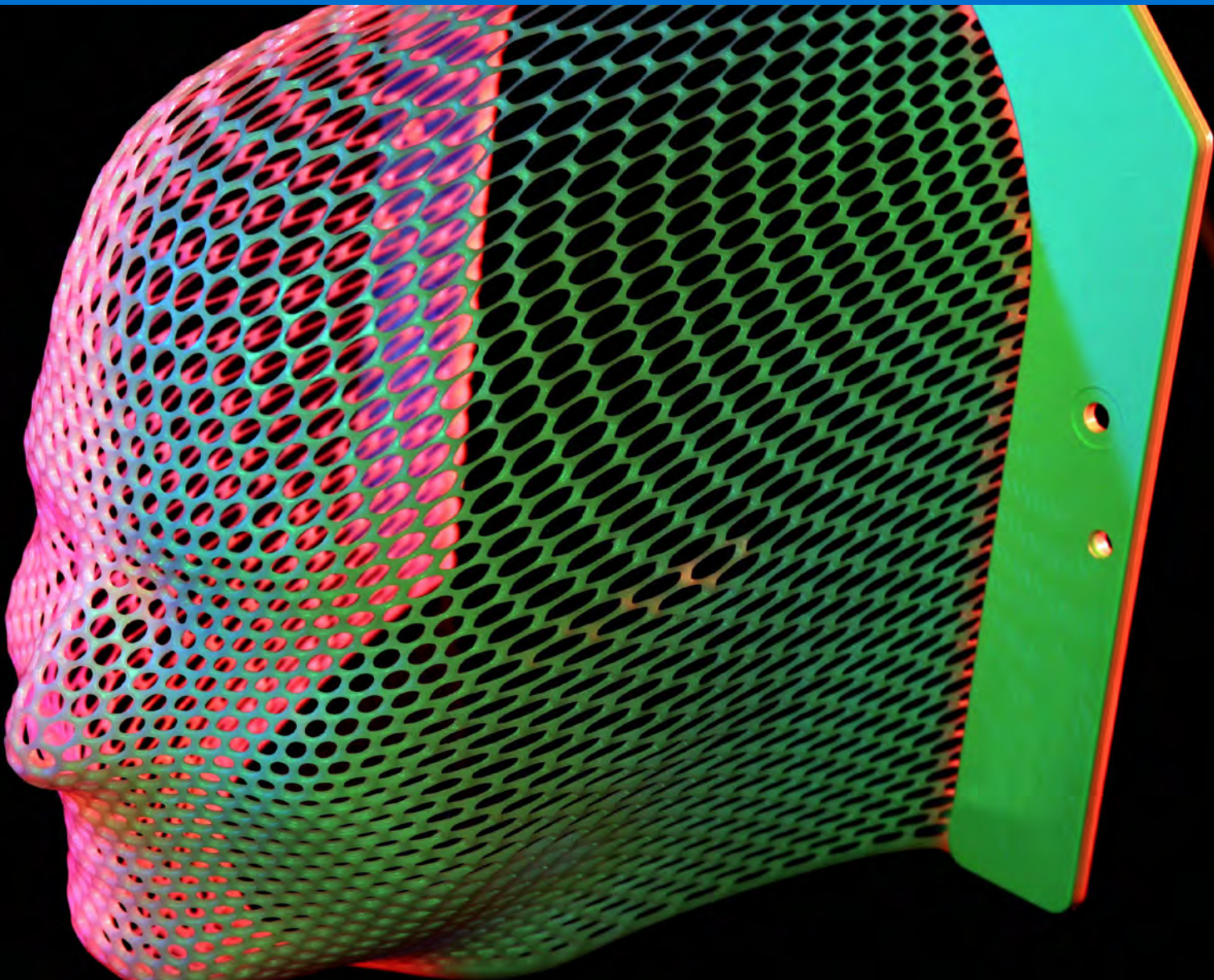
- This phase 1 dose-escalation study was conducted to determine the toxicity, maximum tolerated dose, and pharmacokinetics and pharmacodynamics of the triterpenoid 2-cyano-3,12-dioxolean-1,9-dien-28-oic acid (CDDO). A causal relationship of observed thromboembolic events to CDDO was considered possible but could not be established.

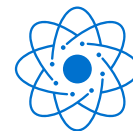
Phase 1 clinical trials, Collins JM. In: *Principles of Clinical Pharmacology, Third Edition*, Atkinson A (ed). Burlington, MA: Elsevier, 2012:541–546.

- This chapter discusses disease-specific considerations, including dose escalation and interspecies differences in drug metabolism, in this prominent reference book covering the pharmacologic principles underlying the individualization of patient therapy and contemporary drug development.

2012 PROGRAM ACCOMPLISHMENTS

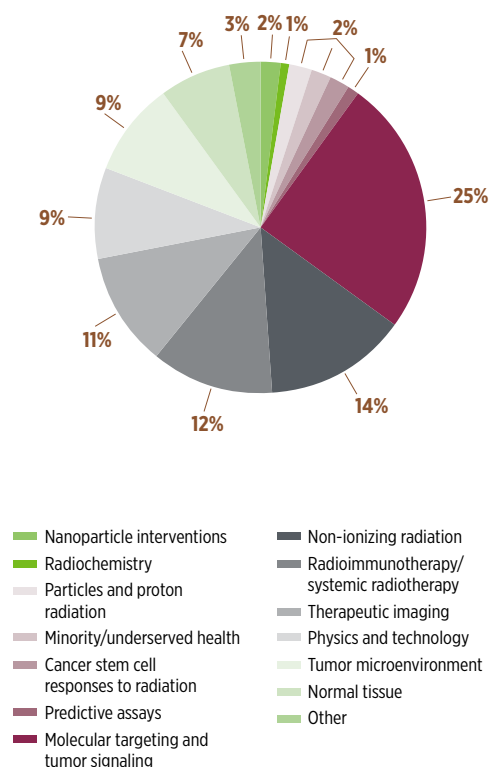
RADIATION RESEARCH PROGRAM





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, innovative technology, electronic data acquisition and analysis, image-guided therapy, multimodality cancer treatment, outreach to the underserved, and medical and societal response to the threats from nuclear and radiological disasters, potentially including terrorism. With its research base in basic biology and physics and clinical care that encompasses the entire spectrum of oncology, radiation oncology has a unique role in multidisciplinary translational science collaboration. Radiation therapy is used in more than half of patients during the course of their cancer treatment and is effective both as a curative modality and for palliation. The **Radiation Research Program (RRP)** is the sole program focused on therapeutic radiation sciences within the extramural programs of the National Cancer Institute (NCI).



PERCENT DISTRIBUTION OF 2012 GRANTS, BY RRP RESEARCH AREAS

As part of ongoing efforts to stimulate research in radiotherapy and radiation biology, the RRP supports basic, translational, and clinical research in the Division of Cancer Treatment and Diagnosis (DCTD) by:

- Providing expertise to investigators and potential grantees who perform cutting-edge research with radiation and other forms of energy
- Helping to lead the radiotherapy 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
- Developing unique models and capabilities to help and mentor medically underserved communities in the United States and worldwide to access cancer clinical trials
- Evaluating the effectiveness of radiation research being conducted by NCI grantees
- Advising the NCI-funded clinical trials groups and the Cancer Therapy Evaluation Program (CTEP) regarding scientific priorities and quality assurance in clinical studies with radiotherapy
- Providing laboratory support for preclinical evaluation of systemic agents that can be used with radiation (through the Molecular Radiation Therapeutics Branch on NCI's Frederick, Maryland, campus)
- Serving as the NCI's 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 the National Institute of Allergy and Infectious Diseases (NIAID) and the Office of the Assistant Secretary for Preparedness and Response within the Department of Health and Human Services

RRP coordinates its activities with other radiation research efforts at NCI, in particular the Division of Cancer Biology, the Division of Cancer Control and Population Sciences, the Center for Cancer Research's (CCR's) Radiation Oncology Branch and Radiation Biology Branch, and the Division of Cancer Epidemiology and Genetics, as well as the National Institutes of Health (NIH), other federal agencies, and national and international research organizations. RRP

C. NORMAN COLEMAN

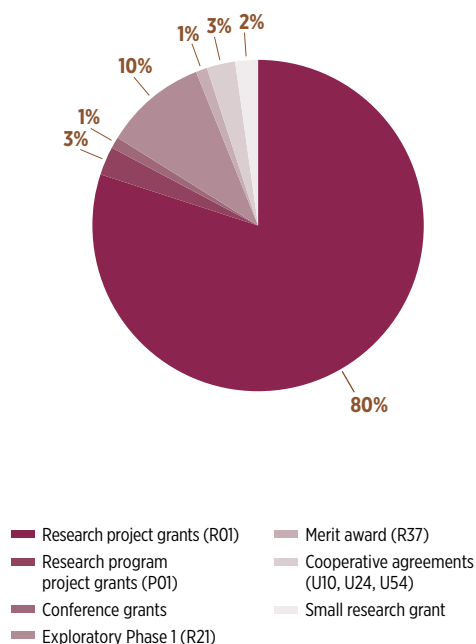
ASSOCIATE DIRECTOR



C. Norman Coleman, MD, is Associate Director for the Radiation Research Program (RRP), Senior Investigator in the Radiation Oncology Branch, and a Special Advisor to the NCI Director. He received his medical training at the Yale University School of Medicine. Dr. Coleman completed his internship and residency in internal medicine at the University of California, San Francisco; a fellowship in medical oncology at NCI; and a fellowship in radiation oncology at Stanford University. He is board certified in internal medicine, medical oncology, and radiation oncology. Dr. Coleman was a tenured faculty member in Radiology and Medicine at the Stanford University School of Medicine before joining Harvard Medical School in 1985 as the Alvan T. and Viola D. Fuller–American Cancer Society Professor and Chairman of the Joint Center for Radiation Therapy. In 1999, he became Director of NCI’s Radiation Oncology Sciences Program, and in addition to heading RRP, he served as Chief of the Center for Cancer Research’s Radiation Oncology Branch from 1999 until 2004. He has written extensively in his field and has won numerous awards, including the 2005 Gold Medal Award from the American Society for Therapeutic Radiation Oncology for his many scientific and professional contributions to the fields of radiation oncology and radiation biology. He is a Fellow of the American College of Physicians, the American College of Radiology, the American Society for Radiation Oncology, and the American Society of Clinical Oncology. In 2011 he received the Service to America Homeland Security Medal from the Partnership for Public Service. Since 2004, Dr. Coleman has been the Senior Medical Advisor and Team Leader of the Chemical, Biological, Radiological, and Nuclear Team in the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services.

serves as a focal point for extramural investigators who are concerned with clinically related radiation oncology and biology research.

The RRP research portfolio currently comprises approximately 175 awarded grants. The grant award mechanisms used by RRP and their distribution in terms of research support in 2012 are shown in the accompanying chart. The predominant mechanism is the individual research project grant (R01), followed by exploratory phase grants (R21).

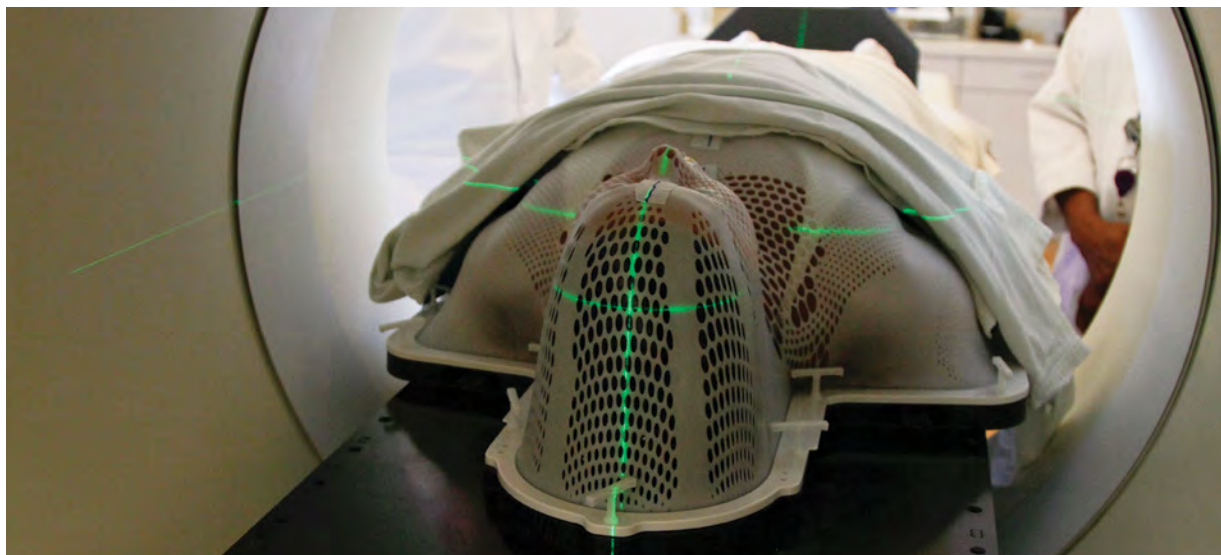
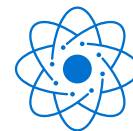


RRP 2012 RESEARCH FUNDS BY GRANT TYPE

STRUCTURE AND FUNCTION

RRP is divided into three branches:

1. Radiotherapy Development Branch
2. Clinical Radiation Oncology Branch
3. Molecular Radiation Therapeutics Branch



The primary responsibility of RRP is to the grantees and contractors of NCI and NIH. In fiscal year (FY) 2012, RRP administered 164 awarded grants, most through the Radiotherapy Development Branch. In addition to conducting grants management and related duties, RRP program 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

The research portfolio of the **Radiotherapy Development Branch (RDB)** encompasses a broad range of topics that includes:

- Development and implementation of advanced technologies for the production and delivery of radiation
- Radiation-inducible molecular changes in both tumor and normal tissues, including signaling and apoptosis
- Tumor biology and microenvironmental changes relating to radiation response
- Radiation sensitizers and protectors
- Normal tissue injury and treatment
- Systemic targeted radionuclide therapy, including radio-immunotherapy
- Non-ionizing radiation-based therapies such as photodynamic therapy and hyperthermia

RDB and the Clinical Radiation Oncology Branch collaboratively manage grants that deal with image-guided radiotherapy and particle therapies, as well as the physics of basic radiation track (beam) structure and radiation chemistry. RDB also collaborates with NCI's Center to Reduce Cancer Health Disparities, especially on issues relating to the accrual of minority populations to cancer clinical trials.

RDB is also involved in workshops highlighting the importance of biology in radiation therapy and has organized workshops on the tumor microenvironment, DNA repair (in collaboration with the Division of Cancer Biology), targeted radionuclide therapy and the role of immunity in radiation responses.

CLINICAL RADIATION ONCOLOGY BRANCH

The **Clinical Radiation Oncology Branch (CROB)** manages a grant portfolio of clinical and translational research in radiation oncology and nuclear medicine, as well as the technical and physical aspects of radiation research and the development of new therapeutic approaches. In addition to managing the RRP grant portfolio, CROB devotes a substantial effort to supporting NCI, NIH, the U.S. Department of Health and Human Services, and government-wide activities such as technology development and assessment and comparative effectiveness research. The branch works extensively with:

- DCTD partners, such as CTEP and the Cancer Imaging Program, assisting with their cooperative clinical trial groups and early-phase trials consortia

- The Coordinating Center for Clinical Trials, working with several of its steering committees and their task forces (e.g., subcommittees on head and neck, thoracic, breast, gastrointestinal, genitourinary, and gynecological malignancies; investigational drugs; and symptom management and quality of life)
- The National Cancer Informatics Program and the Center for Biomedical Informatics and Information Technology (CBIIT) in developing demonstration projects using radiation oncology as a platform
- NIAID in identifying opportunities for radiation countermeasure investigators to decrease treatment toxicity in cancer patients 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) in identifying needs and opportunities for postmarketing surveillance of devices cleared for use in radiation oncology, and in establishing endpoints and benchmarks for the approval/clearance of new drugs and devices for non-muscle-invasive bladder cancer
- The Agency for Healthcare Research and Quality and the National Academy of Sciences in identifying priorities and opportunities for comparative effectiveness research in cancer in general and in prostate cancer in particular
- DoD's Armed Forces Radiobiology and Research Institute (AFRRI) in exploring ways in which cancer clinical trials may help in licensing of countermeasures
- The Department of Veterans Affairs in 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 Radiation Therapy Oncology Group (RTOG)
- Professional societies, such as the Society of Nuclear Medicine and Molecular Imaging, the American Association for Physicists in Medicine, and the American Society for Radiation Oncology, to facilitate transition of the most promising, radiation-based, experimental therapies to clinical practice
- International organizations, such as the International Atomic Energy Agency, the International Agency for Research on Cancer, the World Health Organization,

and the Pan American Health Organization, in assisting countries and provinces with cancer control planning, especially with regard to human and other resources required for improving cancer detection and management using radiation therapy and allied treatments

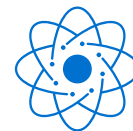
MOLECULAR RADIATION THERAPEUTICS BRANCH

The **Molecular Radiation Therapeutics Branch (MRTB)** is an RRP in-house laboratory program that serves as a focal point for collaborations with the Developmental Therapeutics Program (DTP) and CTEP within DCTD, investigators in the Radiation Biology Branch and the Radiation Oncology Branch within CCR, national cooperative groups (RTOG and NRG [the National Surgical Adjuvant Breast and Bowel Project, the Gynecologic Oncology Group, and RTOG] in the reorganization of the National Clinical Trials Consortium), and university and industry collaborators specifically addressing development needs in combined-modality therapy using radiation. MRTB focuses on the development of radiation modifiers for tumor sensitization, works with DTP to establish assays to better guide clinical trial designs, identifies putative radioresponsive targets, and studies mechanisms of actions of radiomodifiers. On the campus of the Frederick National Laboratory for Cancer Research (NCI-Frederick), MRTB works in coordination with DTP and with drug development activities and molecular imaging in DCTD and CCR. The MRTB also plays a major role in developing radiosensitizers as part of the NCI Experimental Therapeutics program (NExT).

Capabilities

The current capabilities of the MRTB laboratory at NCI-Frederick include:

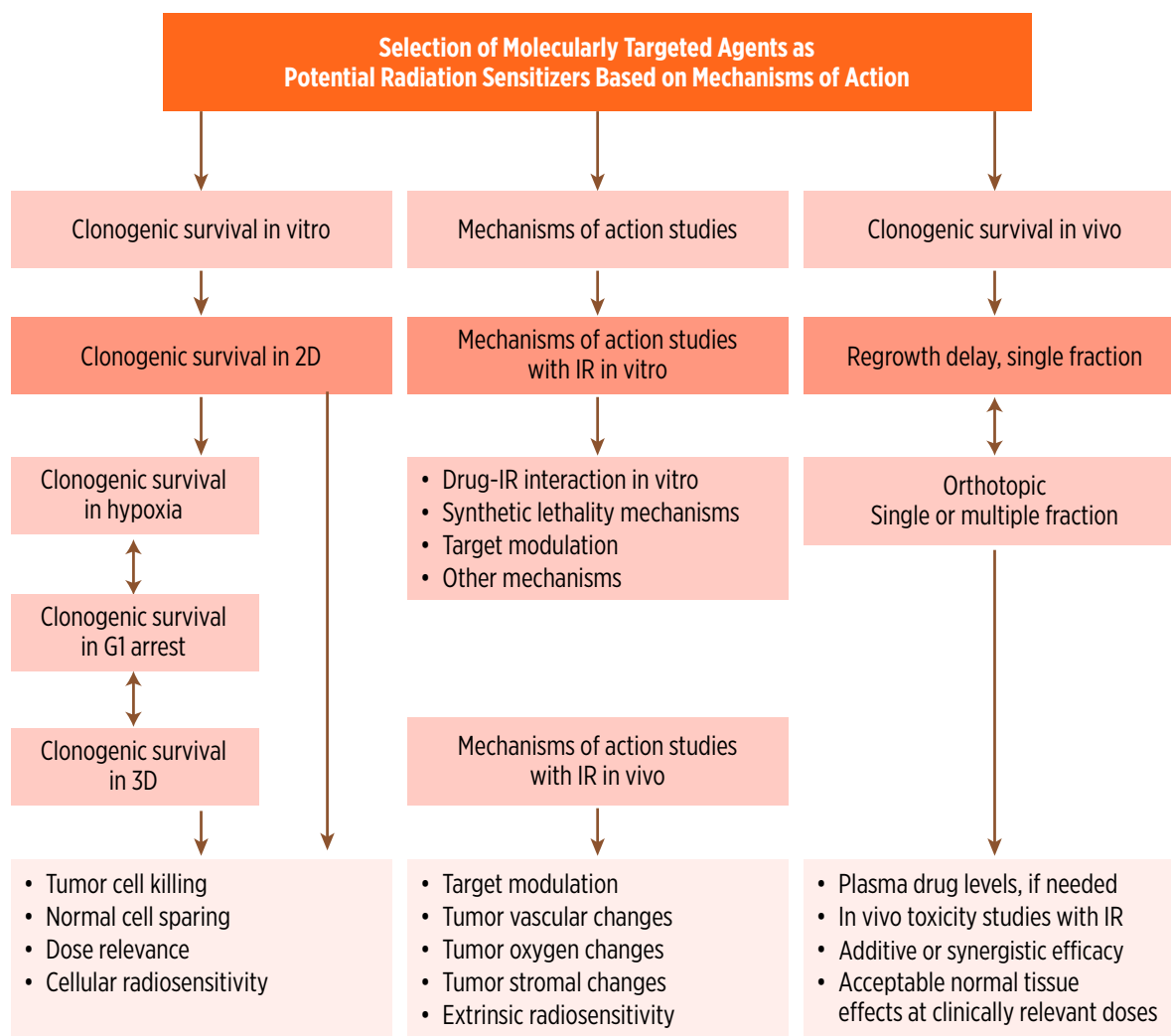
- Testing of anticancer agents with ionizing radiation, using an in vitro clonogenic assay in various human cancer and normal cell lines
- Evaluating potential radiation modifiers, using in vivo xenografts or orthotopic mouse models or genetically engineered mouse models
- Determining mechanisms of action of potential radiation modifiers, using a variety of molecular and biochemical approaches for biomarker development



In addition, MRTB partners with DTP's Biological Testing Branch and Screening Technologies Branch to further develop animal models that can be used in the fields of radiation biology and radiation oncology and to identify potential radiation modifiers from the initial screening phase. MRTB also actively collaborates with CTEP and the Investigational Drug Branch to proactively evaluate potential radiosensitizers. A part of preclinical as well as clinical trial investigations are achieved through established working groups under the MRTB umbrella based on diseased sites (breast-to-brain metastases; rectal, lung, and human papillomavirus-negative head and neck cancers; sarcoma; pancreatic cancer; hepatocellular carcinoma; and esophageal cancer).

Plans for Drug Development and Serving as a National Resource

The experimental paths for drug evaluation are shown below. These are designed to be efficient in throughput yet stringent enough to have good predictive accuracy of an agent's eventual clinical utility. MRTB serves the radiation biology and radiation oncology research communities by developing and disseminating optimized in vitro and in vivo assays (such as in vitro clonogenic assays and animal studies).

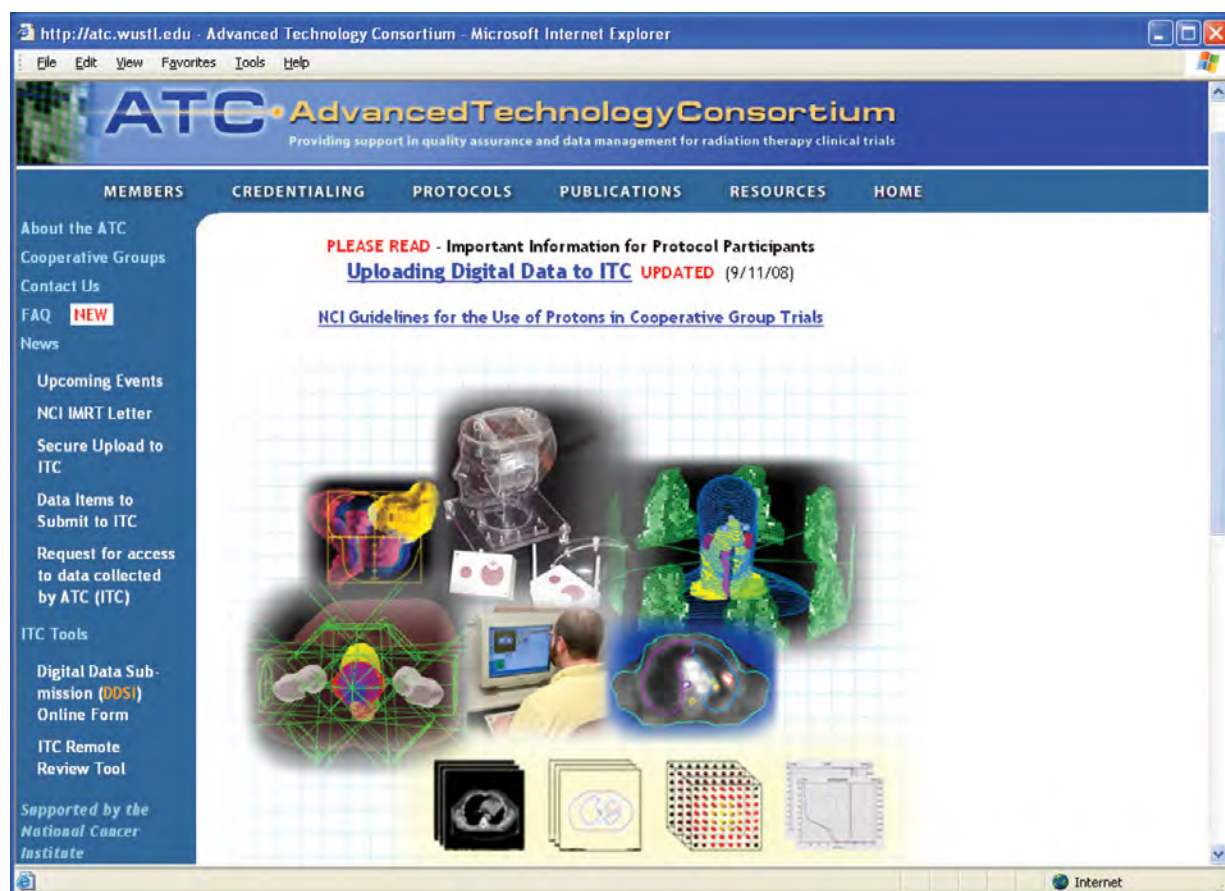


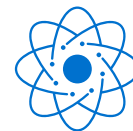
PROGRAM ACCOMPLISHMENTS

ADVANCED TECHNOLOGY CONSORTIUM

The *Advanced Technology Consortium (ATC)* (U24CA081647) capitalizes on the infrastructure and strengths of the nation's existing quality assurance programs—including the Image-Guided Therapy Center, RTOG, the Radiological Physics Center, and the Quality Assurance Review Center—to develop and maintain advanced medical informatics and quality assurance capabilities. These efforts provide an environment in which institutions can submit and Quality Assurance Centers can receive, share, and analyze volumetric multimodality imaging, treatment planning, and verification digital data. Specifically, the ATC:

- Maintains, manages, and improves electronic data submission of advanced technologies (three-dimensional conformal radiotherapy, intensity-modulated radiation therapy, stereotactic body radiotherapy, and brachytherapy), protocol credentialing and case data, archival storage, and remote quality assurance review process
- Develops novel, Web-based, remote-review tools to enhance the efficient and effective review of protocols by utilizing advanced modular-design technologies to promote the development of efficient tools and subsystems to achieve compatibility with existing software standards, including CBIIT
- Assists cooperative groups to develop and manage advanced-technology clinical trial protocols, including:





- Tumor/target volume and organ-at-risk definitions
- Credentialing requirements and evaluation criteria
- Electronic data submission requirements and instructions
- Quality assurance review procedures
- Serves as an educational resource to the nation's clinical trial cooperative groups and participating institutions for support of clinical trials on advanced-technology radiation therapy

RADIOBIOLOGY BIOTERRORISM RESEARCH AND TRAINING GROUP

The **Radiobiology Bioterrorism Research and Training Group (RABRAT)** is an informal working group of scientists in government agencies that are involved in radiation research, including the Low-Dose Radiation Research Program of the Department of Energy (DoE), the normal tissue medical countermeasures program of NIAID, radiation biology and biodosimetry of AFRRRI (DoD), space radiation (NASA), BARDA, and others (see below) interested in radiation sciences and preparedness for radiation accidents and terrorism events. The purpose of RABRAT is to help keep the agencies informed of ongoing activities, to avoid both gaps and duplication of effort, and to discuss training and educational opportunities. In addition to RRP staff, members include representatives of the U.S. Department of Health and Human Services, other NCI divisions (Division of Cancer Epidemiology and Genetics, Division of Cancer Biology, and Division of Cancer Prevention), other NIH Institutes (NIAID), and other government agencies (FDA, DoD, DoE, Environmental Protection Agency, NASA, Department of Homeland Security, and Emergency Assistance Center/Training Site). RABRAT meets three to four times per year.

CANCER DISPARITIES RESEARCH PARTNERSHIP

Cancer health disparities are exemplified by differences in cancer morbidity and mortality as a function of gender, ethnicity, and socioeconomic status. Health care institutions that provide cancer services to medically underserved, low-income, minority populations often are not linked effectively to the national cancer research enterprise and struggle to main-

tain state-of-the-art cancer care. RRP's **Cancer Disparities Research Partnership (CDRP)** program is a pilot program designed to test novel approaches toward reducing the negative consequences associated with cancer health disparities.

During the pilot U56 planning phase (2002–2008) of the Cancer Disparities Research Partnership program, six grantee institutions succeeded in establishing:

- Clinical trial research infrastructures at community-based institutions to facilitate the participation of targeted ethnic and minority, medically underserved, or low-income populations in the latest NCI-sponsored radiation oncology or combined modality treatment trials
- Mentoring partnerships with cancer centers and institutions with clinical trials expertise, and particularly, cancer centers experienced in clinical trials; these partnerships were facilitated by the provided telemedicine system (TELESYNERGY®)
- Community education and outreach activities and patient navigation program to facilitate patient recruitment and accrual into clinical trials

From these accomplishments, RRP succeeded in 2008 to reissue the CDRP program as a limited competition RFA (RFA-CA-09-502). In September 2009, three grantees (Rapid City Regional Hospital in Rapid City, South Dakota; Singing River Health System in Pascagoula, Mississippi; and New Hanover Regional Medical Center in Wilmington, North Carolina) received five-year funding, while the University of Pittsburgh Medical Center's McKeesport Hospital in McKeesport, Pennsylvania, received a two-year award. This final U54 implementation phase of the CDRP program (2009–2014) has provided the necessary time for the grantees to stabilize their existing clinical research infrastructure and modify or adopt new strategies to maximize the access, accrual, and participation of their minority and underserved populations onto all types of NCI-sponsored cancer clinical trials, including cancer prevention, symptom management and cancer control, surgical, medical, and radiation oncology. The successful CDRP grantees will apply for other NCI funding, especially the Division of Cancer Prevention's Community Clinical Oncology Program, in order to sustain established cancer disparities programs that address the needs of minority and underserved populations.

FUTURE INITIATIVES

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, the RRP approaches its entire portfolio and that of its potential collaborators as a complex 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 links and develop new links that can accelerate advances. Further, through its own in-house research and development (including the CCR), as well as workshops, program staff strive to lead the field into new areas of opportunity. The broad but highly interrelated fields are:

- Basic molecular and cell biology
- Complex tumor biology
- Systems biology
- Normal tissue injury
- Molecular imaging and image-guided therapy
- Stress biology
- Molecularly targeted therapeutics with radiation
- Therapeutic nuclear medicine
- Nuclear medicine
- Quality assurance for prospective clinical trials
- Electronic databases to facilitate comparative effectiveness research and international collaboration
- Accelerator physics
- Outreach to the underserved through technology and mentoring
- International collaboration for nuclear safety and terrorism response
- International oncology-based diplomacy

With a staff actively engaged in research planning and conduct through its MRTB, collaboration with CCR, NIAID, and the Assistant Secretary for Preparedness and Response's BARDA, RRP generates a strong level of enthusiasm, collaboration, and innovation among agencies, investigators, and partners. This leadership has helped to sustain a critical mass

of talent and enthusiasm within government (RABRAT), the new Radiation Education Initiative (see below), and a new means of bringing cancer advances to underserved populations worldwide using public-private partnerships such as the International Cancer Expert Corps.

INTERNATIONAL CANCER EXPERT CORPS

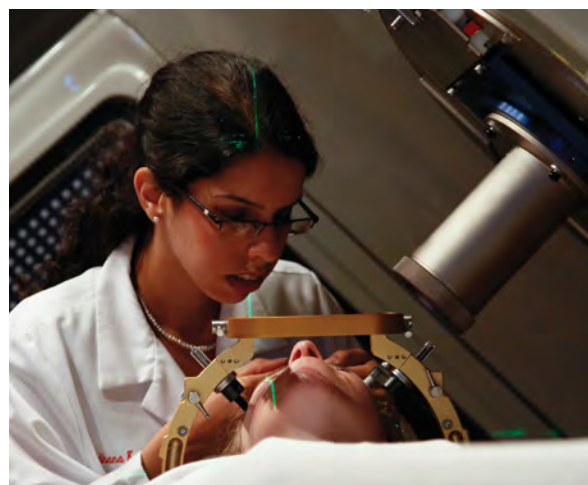
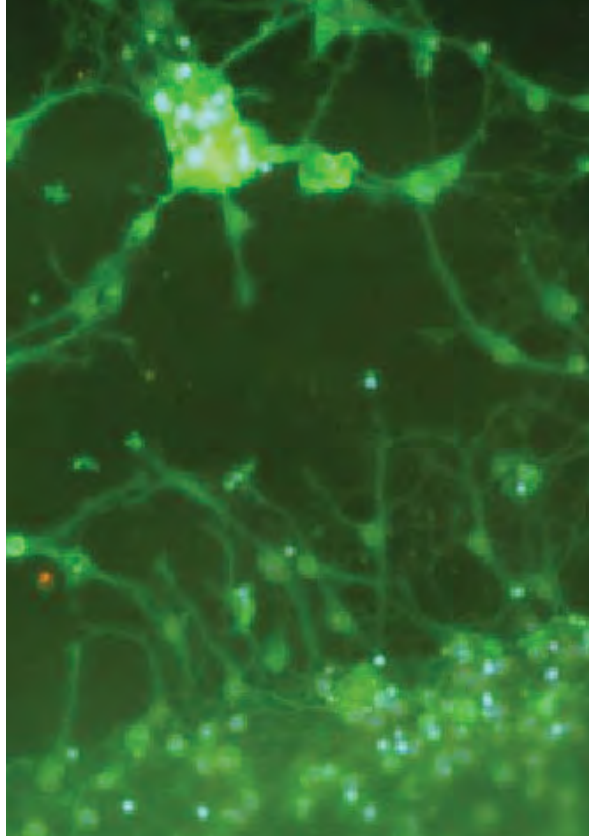
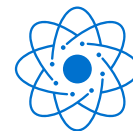
The **International Cancer Expert Corps (ICEC)** concept is being developed with advice and experts within NCI, particularly the Center for Global Health. ICEC will be a global, multi-national initiative with the goal of improving the quality of life of cancer patients (with direct applicability to other diseases) by bringing protocol-based treatment (and ultimately the possibility for participation in cancer clinical trials), education, and mentoring to underserved populations in the United States and worldwide. Given the need for radiation therapy and the experience of individuals in RRP in international and domestic programs related to cancer health disparities, the RRP plays a central role for NCI in developing mechanisms for a public-private partnership.

The ICEC will have three components:

1. **Associates:** Members of medical facilities and locations that serve underserved populations and are interested in participating and investing in improving the quality of care and life for their affected citizens
2. **Experts:** ICEC expert panels comprising international experts from a broad range of oncology disciplines and health care delivery services that provide mentoring for associates based on long-term, person-to-person connectivity
3. **Infrastructure:** Hubs (i.e., infrastructure) located worldwide to coordinate the associate-expert linkage so that their time is spent on mentoring and education. This will build on the TELESYNERGY® system developed by NIH and further refined by NCI.

To establish and support this endeavor, ICEC is working with a number of agencies and groups to develop mentor-mentee partnerships:

- American Society for Radiation Oncology
- International Network for Cancer Treatment and Research
- American Society of Clinical Oncology (ASCO)



- RTOG
- The World Health Organization's International Agency for Research on Cancer
- Union for International Cancer Control
- International Atomic Energy Agency

A number of international partners have already made commitments to participate.

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 newer-generation scientists from more focused specialties (such as molecular biology), in many cases, have not received the broad training that ensures success in radiation-related research. To this end, an effort is being made to enhance current training in the radiation sciences through the development of supplemental training courses that will incorporate radiobiology, radiation physics, and experimental methodology. The aim is to provide enhanced training in the radiation sciences at a national level. Support in preparing applications for training programs geared to radiation training is provided on request to extramural investigators, in collaboration with personnel in the Cancer Training Branch. In addition, RRP staff participate in the educational initiatives of national societies, including the American Society for Therapeutic

Radiation Oncology and the Radiation Research Society, and international groups, such as the European Society for Therapeutic Radiology and Oncology. Current proposals call for a one-week intensive course and the development, through this course, of Internet-based teaching tools that would be available globally.

TRANSLATING RADIATION TERRORISM COUNTERMEASURES TO THE ONCOLOGY CLINIC

Another initiative that is under way aims to translate the findings obtained by research on radiation terrorism countermeasures for use in clinical radiotherapy in order to decrease the adverse effects of cancer treatment. To this end, a workshop was held in 2010 to address this issue.

SELECTED PUBLICATIONS

GRANTEE PUBLICATIONS

Patient navigation for American Indians undergoing cancer treatment: utilization and impact on care delivery in a regional healthcare center, Guadagnolo BA, Boylan A, Sargent M, Koop D, Brunette D, Kanekar S, Shortbull V, Molloy K, Petereit DG. *Cancer*, 2011;117(12):2754–2761. <http://www.ncbi.nlm.nih.gov/pubmed/21656754>

- In this report, the impact of patient navigation services was associated with fewer treatment interruptions and higher rates of clinical trial enrollment in American Indian cancer patients compared with national reports.

Caspase 3-mediated stimulation of tumor cell repopulation during cancer radiotherapy, Huang Q, Li F, Liu X, Li W, Shi W, Liu FF, O'Sullivan B, He Z, Peng Y, Tan AC, Zhou L, Shen J, Han G, Wang XJ, Thorburn J, Thorburn A, Jimeno A, Raben D, Bedford JS, Li CY. *Nature Medicine*, 2011;17(7):860–866.

<http://www.ncbi.nlm.nih.gov/pubmed/21725296>

- Deficiency of caspase 3 in either tumor cells or tumor stroma caused substantial tumor sensitivity to radiotherapy in xenograft or mouse tumors. In human subjects with cancer, higher amounts of activated caspase 3 in tumor tissues are correlated with markedly increased rate of recurrence and death. Hence, this report proposes the existence of a cell death-induced tumor repopulation pathway in which caspase 3 has a major role.

Deep penetration of a PDT drug into tumors by noncovalent drug-gold nanoparticle conjugates, Cheng Y, Meyers JD, Broome AM, Kenney ME, Basilion JP, Burda C. *Journal of the American Chemical Society*, 2011;133(8):2583–2591.

<http://www.ncbi.nlm.nih.gov/pubmed/21294543>

- In this work, a noncovalent photodynamic therapy cancer drug-gold nanoparticle conjugate system demonstrated rapid drug release and deep penetration of drug into tumors within hours. This study suggests that noncovalent delivery via gold nanoparticles provides an attractive approach for cancer drugs to penetrate deep into the center of tumors.

Prospective study of health-related quality of life for children with brain tumors treated with proton radiotherapy, Kuhlthau KA, Pulsifer MB, Yeap BY, Rivera Morales D, Delahaye J, Hill KS, Ebb D, Abrams AN, Macdonald SM, Tarbell NJ, Yock TI. *Journal of Clinical Oncology*, 2012;30(17):2079–2086.

<http://www.ncbi.nlm.nih.gov/pubmed/22565004>

- This paper describes the first study to the authors' knowledge of health-related quality of life in a cohort of children with brain tumors treated with proton radiation. This prospective study demonstrates the effect of disease type and intensity of treatment quality-of-life.

SIRT3 is a mitochondrial tumor suppressor: a scientific tale that connects aberrant cellular ROS, the Warburg effect, and carcinogenesis, Haigis MC, Deng CX, Finley LW, Kim HS, Gius D. *Cancer Research*, 2012;72(10):2468–2472.

<http://www.ncbi.nlm.nih.gov/pubmed/22589271>

- This report demonstrated that murine tumors lacking Sirt3 exhibit abnormally high levels of reactive oxygen species (ROS) that directly induce genomic instability and increase HIF-1 α protein levels. The subsequent transcription of HIF α -dependent target genes results in cellular metabolic reprogramming and increased cellular glucose consumption. Based on these findings, it was concluded that mice lacking Sirt3 provide a model that mechanistically connects aberrant ROS, the Warburg effect, and carcinogenesis.

The HIF signaling pathway in osteoblasts directly modulates erythropoiesis through the production of EPO, Rankin EB, Wu C, Khatri R, Wilson TL, Andersen R, Araldi E, Rankin AL, Yuan J, Kuo CJ, Schipani E, Giaccia AJ. *Cell*, 2012;149(1):63–74.

<http://www.ncbi.nlm.nih.gov/pubmed/22464323>

- The findings of this paper reveal an unexpected role for osteoblasts in the production of erythropoietin and modulation of erythropoiesis. Furthermore, these studies demonstrate a molecular role for osteoblastic PHD/VHL/HIF signaling that can be targeted to elevate both hematopoietic stem cells and erythroid progenitors in the local hematopoietic microenvironment.

Synthesis and preclinical evaluation of bifunctional ligands for improved chelation chemistry of ⁹⁰Y and ¹⁷⁷Lu for targeted radioimmunotherapy, Kang CS, Sun X, Jia F, Song HA, Chen Y, Lewis M, Chong HS. *Bioconjugate Chemistry*, 2012;23(9):1775–1782.

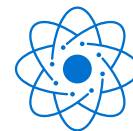
<http://www.ncbi.nlm.nih.gov/pubmed/22881720>

- This report describes a practical and high-yield synthesis of a bimodal bifunctional ligand, 3p-C-NETA-NCS, that possesses favorable in vitro and in vivo profiles, is an excellent bifunctional chelator that can be applied for targeted radionuclide therapy, and has the potential to replace DOTA and DTPA analogs in current clinical use.

STAFF PUBLICATIONS

Decreasing the adverse effects of cancer therapy: National Cancer Institute guidance for the clinical development of radiation injury mitigators, Movsas B, Vikram B, Hauer-Jensen M, Moulder JE, Basch E, Brown SL, Kachnic LA, Dicker AP, Coleman CN, Okunieff P. *Clinical Cancer Research*, 2011;17(2):222–228.

<http://www.ncbi.nlm.nih.gov/pubmed/21047979>



- This article, arising from an NCI- and NIAID-sponsored meeting in January 2010, presents an algorithm to guide clinical trials for radiation injury mitigators in patients receiving radiotherapy or radiochemotherapy. It reviews the mechanisms of radiation injury, the clinical problem, the preclinical and clinical development of candidate agents, and the design and conduct of clinical trials.

Decreasing the adverse effects of cancer therapy: an NCI workshop on the preclinical development of radiation injury mitigators/protectors. Ryan JL, Krishnan S, Movsas B, Coleman CN, Vikram B, Yoo SS. Radiation Research, 2011;176(5):688–691.

<http://www.ncbi.nlm.nih.gov/pubmed/21883022>

- The study of radiation mitigators/protectors for use in cancer treatment and management is complex, as they must reduce normal tissue toxicity without reducing tumor cell kill. The known toxicologic, pharmacokinetic, and mechanistic data for the proposed agent will direct investigators to the appropriate stage of preclinical development.

Normal tissue protection for improving radiotherapy: where are the gaps? Prasanna PG, Stone HB, Wong RS, Capala J, Bernhard EJ, Vikram B, Coleman CN. Translational Cancer Research, 2012;1(1):35–48.

<http://www.ncbi.nlm.nih.gov/pubmed/22866245>

- This review discusses examples of important adverse effects of radiotherapy (acute and intermediate to late occurring) when it is delivered either alone or in conjunction with chemotherapy, as well as important limitations in the current approaches of using radioprotectors and/or mitigators for improving radiation therapy. Further, it provides general concepts for drug development for improving radiation therapy.

Redesigning radiotherapy quality assurance: opportunities to develop an efficient, evidence-based system to support clinical trials: report of the National Cancer Institute Work Group on Radiotherapy Quality Assurance. Bekelman JE, Deye JA, Vikram B, Bentzen SM, Bruner D, Curran WJ Jr, Dignam J, Efstathiou JA, FitzGerald TJ, Hurkmans C, Ibbott GS, Lee JJ, Merchant TE, Michalski J, Palta JR, Simon R, Ten Haken RK, Timmerman R, Tunis S, Coleman CN, Purdy J. International Journal of Radiation Oncology, Biology, Physics, 2012;83(3):782–790.

<http://www.ncbi.nlm.nih.gov/pubmed/22425219>

- This is a recommendation report on radiotherapy quality assurance that can affect clinical trial accrual, cost, outcomes, and generalizability. To achieve maximum benefit, quality assurance programs must become more efficient and evidence based.

Public health oncology: a framework for progress in low- and middle-income countries, Love RR, Ginsburg OM, Coleman CN. Annals of Oncology, 2012;23(12):3040–3045.

<http://www.ncbi.nlm.nih.gov/pubmed/23087162>

- The authors propose an approach to address the increasing global cancer burden as a problem of public health oncology, or population-affecting cancer medicine. They then consider the major functional variables, models of international development efforts, and specific areas of interventions that are likely to successfully combat these mortality and case burdens.

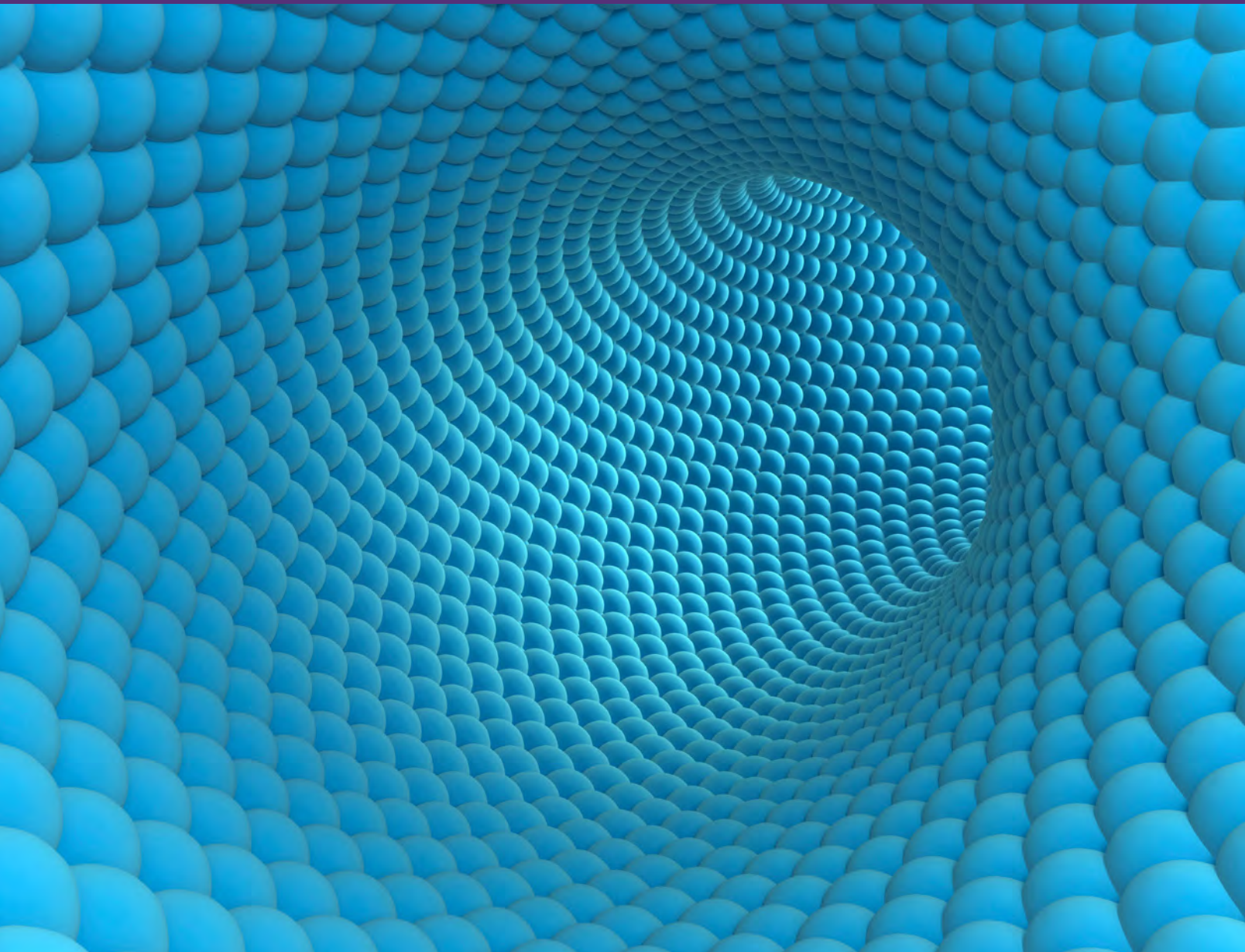
Emergency medical preparedness for radiological/nuclear incidents in the United States. Coleman CN, Lurie N. Journal of Radiological Protection, 2012;32(1):N27–N32.

<http://www.ncbi.nlm.nih.gov/pubmed/22395159>

- This report details key aspects of medical response planning for a radiation or nuclear accident, with the goal of providing planners and responders with just-in-time information and tools. The plans are based on the best available science, ranging from basic physics and radiation biology through diagnosis, medical countermeasures, medical management, and long-term follow-up, which requires extensive breadth of expertise.

2012 PROGRAM ACCOMPLISHMENTS

TRANSLATIONAL RESEARCH PROGRAM

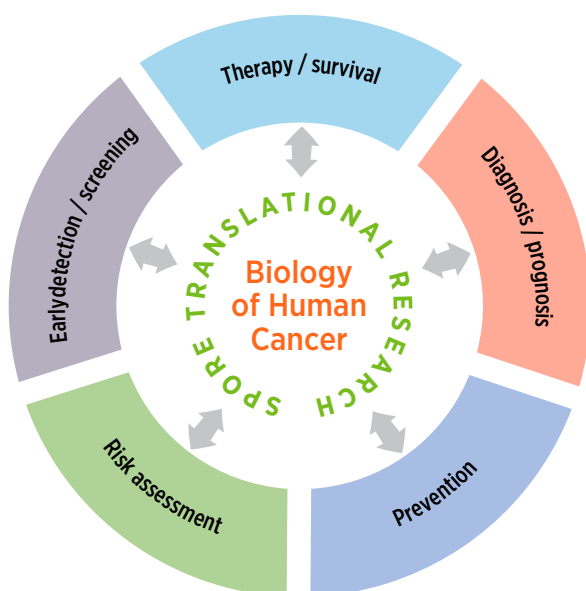




OVERVIEW

The **Translational Research Program (TRP)** of the Division of Cancer Treatment and Diagnosis (DCTD) is committed to reducing cancer incidence and mortality and improving survival and quality of life for cancer patients. TRP uses advances in basic sciences to develop new approaches for the prevention, diagnosis, and treatment of cancer by fostering interdisciplinary investigations and coordinating the resources of the National Cancer Institute (NCI) with those of academia, industry, and nonprofit organizations and foundations. These objectives are accomplished by:

- Supporting the **Specialized Programs of Research Excellence (SPOREs)** to translate novel scientific discoveries into clinical testing, including early-phase clinical trials
- Encouraging a multidirectional approach to translational research
- Promoting research in high-incidence as well as rare cancers
- Facilitating 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



TRP fosters a multidirectional approach to translational research by coordinating interdisciplinary investigations that are based on the biology of human cancer.

There are currently 56 SPOREs located at academic centers or consortia in 21 states across the United States, representing 17 organ sites and systems:

- Bladder
- Brain
- Breast
- Cervix
- Endometrium
- Gastrointestinal (GI)
- Head and neck
- Kidney
- Leukemia
- Lung
- Lymphoma
- Myeloma
- Ovarian
- Pancreatic
- Prostate
- Sarcoma
- Skin/melanoma

The SPOREs are a cornerstone of the NCI's efforts to promote collaborative, interdisciplinary translational research. In each individual SPORE, this goal is achieved by:

- Focusing on a specific organ site or a group of highly related cancers
- Supporting research projects that will 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 four diverse translational research projects per program and involving both basic and clinical or applied scientists in each research project
- Requiring a dedicated pathology and/or biospecimen 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 development program to promote the transition of early-stage or established investigators to translational cancer research in the proposed organ site
- Requiring collaboration among other SPOREs and across NCI-funded networks to promote translational advancement

Site	1992-1995	1996-1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Breast	4	6	6	9	9	9	9	10	8	10	11	10	10	8	6	6
Prostate	2	3	3	4	8	11	11	11	11	8	7	7	9	9	9	9
Lung	2	3	3	3	6	6	7	7	7	5	6	6	7	7	7	6
GI	1	2	2	2	2	4	4	5	4	4	5	5	5	6	7	4
Ovary			4	4	4	4	4	5	4	4	4	4	4	4	4	4
Bladder					1	1	1	1	1	1	1	1	1	1	0	1
Skin					1	2	2	3	3	3	3	5	3	4	3	4
Brain						2	2	4	4	4	3	4	2	2	4	3
Head & Neck						3	3	4	4	4	3	5	4	5	5	4
Lymphoma						2	2	3	3	3	3	4	4	4	5	4
Endometrial							1	1	1	1	1	0	1	2	2	1
Cervical							1	1	1	1	1	0	1	1	1	1
Kidney							1	1	1	1	1	0	1	1	1	1
Leukemia							1	1	1	1	1	1	2	2	2	2
Myeloma							1	1	1	1	1	1	1	2	2	2
Pancreas							3	3	3	3	3	2	2	3	3	3
Sarcoma														1	1	2
Total	9	14	18	22	31	44	53	61	57	54	54	55	57	62	61	53

SPORE ORGAN SITE DISTRIBUTION, 1992-2012*

*Excluding grants receiving interim funding.

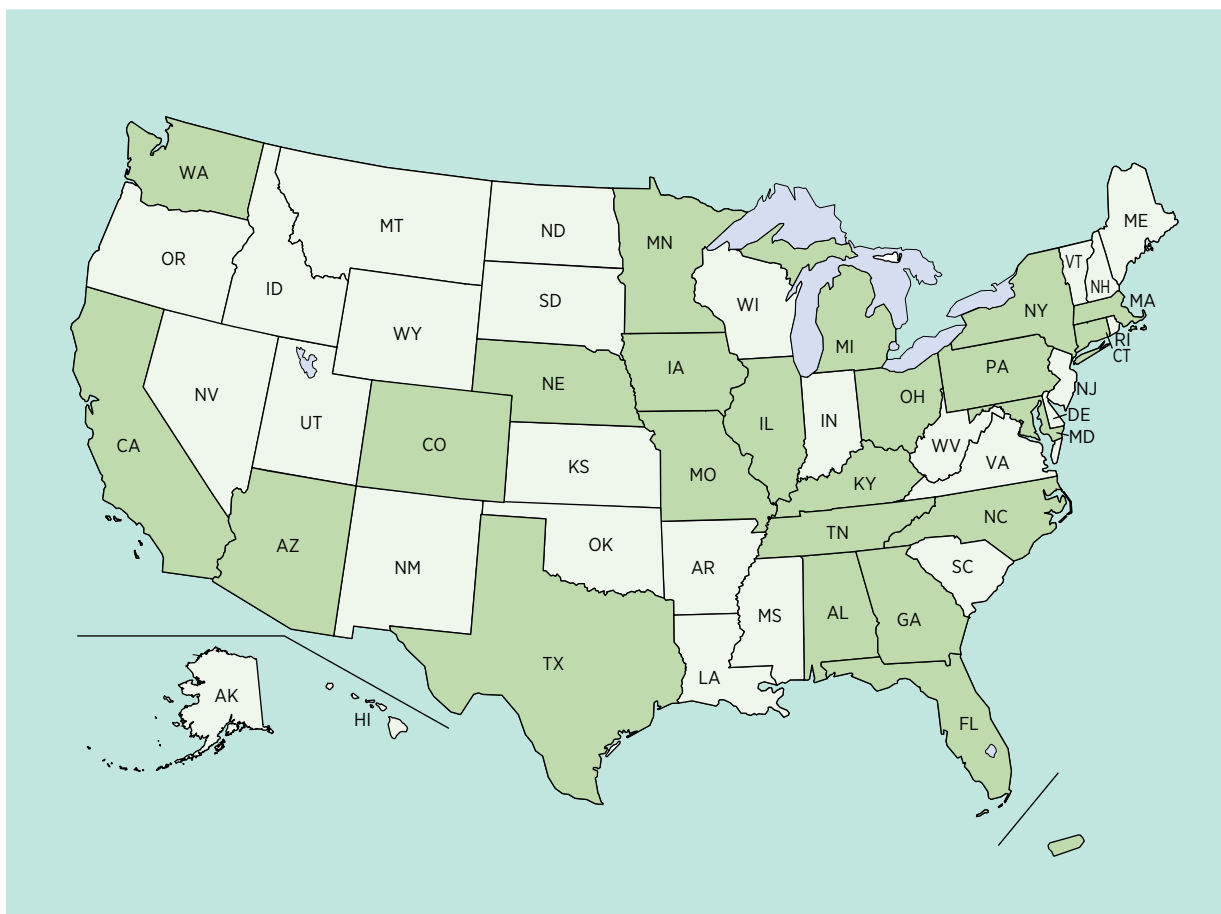
- Providing flexibility to SPORE investigators to realign resources and substitute research projects if translational objectives are not being met during the course of the funding period
- Encouraging the advice of patient advocates

In addition to SPORes, TRP managed grants entitled “Coordination of Clinical and Translational Research across the NCI” (2009 to present), part of the larger Grant Opportunities (GO) program funded by the American Recovery and Reinvestment Act of 2009, to support the collaborative efforts of translational scientists across various NCI programs and funding mechanisms.

BACKGROUND

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 cancer patients or populations at risk for cancer. TRP’s mission is accomplished by fostering broad interdisciplinary investigations that focus on bringing discoveries from the laboratory to the clinic and coordinating the resources of NCI with those of academia, industry, and nonprofit organizations and foundations to reduce cancer



STATES WITH ACTIVE SPORE GRANTS IN FISCAL YEAR 2012. A TOTAL OF 56 FUNDED SPORES ARE LOCATED IN 21 STATES WITHIN 31 INSTITUTIONS AND ONE CONSORTIUM

incidence, morbidity, and mortality; to extend survival; and to increase the quality of life of cancer patients. To that end, TRP engages in the following activities and initiatives:

- Planning, advising, coordinating, evaluating, and supporting the SPOREs, which use the P50 grant funding mechanism, to translate novel scientific discoveries from the laboratory and/or population studies to the clinic for testing in humans with cancer, to determine the biological basis for clinical observations, and to use specimens from clinical studies to determine correlations between biomarkers and outcomes in patients
- Encouraging and facilitating collaborations among the SPOREs, Cancer Centers, other NCI- and National Institutes of Health (NIH)-funded mechanisms and programs, and outside organizations to increase cross-fertilization of ideas, leverage resources, reduce duplication, and ensure access of resources to projects and investigators
- Establishing high-quality organ-specific tumor specimen banks to provide research resources for the cancer research community
- Maintaining the Developmental Research Program and the Career Development Program of the SPOREs to

TOBY T. HECHT

ASSOCIATE DIRECTOR



Toby T. Hecht earned a PhD in microbiology and immunology from the Albert Einstein College of Medicine studying the effect of virus infections on the expression of cell surface antigens. She conducted her postdoctoral research at Yale University in genetics and lymphocyte development before coming to NIH, where, among other accomplishments, she and her collaborators created a unique T-cell hybridoma to study the fine specificity of antigenic control of both proliferation and gamma-interferon production, as well as a Hodgkin lymphoma-specific monoclonal antibody that has been used in both human imaging and therapy trials. Dr. Hecht has worked for more than 30 years at NIH, 25 of which were spent at NCI in programmatic activities and biological agent development. She has also guided many projects (from conception to testing in the clinic) through the former NCI Rapid Access to Intervention Development (RAID) program, now known as the NCI Experimental Therapeutics (NExT) program. In 2008, Dr. Hecht was chosen to oversee the transition of the Organ Systems Branch, the program that administered the SPOREs, from the Office of the NCI Director to DCTD in order to fully integrate this program into the translational science activities of NCI. In 2011, she was made the permanent Associate Director of TRP.

promote high-risk and/or high-payoff projects and to ensure the development of promising researchers who are new to translational research

- Supporting research in high-incidence cancers as well as rare cancers
- Collaborating with patient advocates who support translational science in cancer

History

The organ-specific research programs at NCI trace their origins to the Breast Cancer Task Force of the 1960s. With the passage of the National Cancer Act of 1971, NCI established additional task forces for cancers of the bladder, prostate, and large bowel, and in 1976 for pancreatic cancer, through the National Organ Site Program, which was later reorganized into the Organ Systems Program and then the Organ Systems Branch.

In 2011, TRP staff issued new SPORE guidelines highlighting the collaborative character of SPOREs and including provisions that harmonize SPORE guidelines with those of Cooperative Groups (currently the NCI Clinical Trials Network) and Cancer Centers. For the first time, the terms of horizontal and vertical collaborations were introduced, the former relating to collaborations among groups on one level (laboratory studies, early-phase clinical trials, etc.) and the latter referring to hand-offs between stages along the translational research path, from discoveries to preclinical development to early- and late-phase clinical testing. TRP promoted collaborations by facilitating investigator-initiated interactions through meetings and teleconferences.

On July 28–29, 2011, more than 800 extramural and intramural researchers, patient advocates, industry representatives, and government officials convened in Washington, D.C., for the NCI Translational Science Meeting to explore the convergence of molecular information and clinical care. The meeting featured renowned cancer scientists presenting research in a variety of areas. TRP staff were instrumental in establishing the organization of the meeting, and SPORE grantees contributed substantially to its scientific content. The overarching goal of the meeting was to accelerate early translational cancer research by rapidly and efficiently moving the most promising new scientific discoveries from the laboratory into development and early-phase clinical testing in order to speed therapeutic benefit to patients.



TRP HISTORY

- 1991:** Congress appropriates funds for the NCI to establish the SPOREs through the P50 grant mechanism, which links laboratory studies with clinical research to rapidly translate basic research discoveries into clinical medicine.
- 1992:** NCI issues the first solicitation for applications and makes the first SPORE awards in three organ sites (breast, prostate, lung), followed by one award in GI cancer in 1993. The Organ Systems Branch in the Office of Centers, Training and Resources, in the Office of the NCI Director, is given the task of providing programmatic oversight of the SPORE program.
- 1995:** NCI expands the number of SPORE awards per organ site.
- 1999:** The Board of Scientific Advisors approves the expansion of the SPORE Program from 4 to 16 organ sites. The Executive Committee approves a supplemental program to support clinical trials.
- 2000:** The funding opportunity for SPOREs becomes a Program Announcement rather than specific Requests for Applications.
- 2002:** Progress for Patients, an Avon-NCI Award Program, is launched to fund innovative translational research in breast cancer.
- 2003:** The SPORE program undergoes a major expansion, to 61 grants, due to doubling of the NIH budget.
- 2007:** The Executive Committee approves the expansion of the SPORE program to all organ sites.
- 2008:** The Organ Systems Branch is transferred to DCTD and reorganized into TRP.
- 2009:** TRP issues the GO program “Coordination of Clinical/Translational Research Across the NCI” under the American Recovery and Reinvestment Act.

TRP organizers introduced a new social network, tsm3Linked, that enabled registered meeting participants to upload their abstracts and presentations, view the meeting schedule, and perform searches to identify potential collaborations. tsm3Linked was available for participants to use several weeks prior to the meeting, and NCI kept it open for 1 year after the meeting to foster scientific exchange among meeting participants.

Investigators associated with Hematological Malignancy SPOREs have met on several occasions since 2011 to discuss recent research results and potential future collaborations, including a Leukemia SPORE meeting in Houston, Texas, and a Lymphoma SPORE meeting in Atlanta, Georgia.

TRP also organized support for workshops to advance collaborative translational and clinical research in organ-specific cancers, in which investigators reached across funding mechanisms and institutions to attract the widest range of expertise. This effort was exemplified by the [NCI Prostate Cancer Genetics Workshop](#), which assembled leading researchers in the field to review the state of the science and to develop plans for a large new research consortium to study and translate genetic variants associated with prostate cancer aggressiveness, an important issue for clinical management of this disease. In September 2011, the NCI Workshop on Novel Neoadjuvant Therapy for Bladder Cancer brought together clinicians, scientists, and patient advocates to facilitate the development of new therapeutic agents for bladder cancer through biomarker-driven clinical trials. The clinical trials developed through this workshop included one trial for patients receiving neoadjuvant chemotherapy prior to cystectomy and another trial for patients managed with bladder preservation strategies. Leading basic scientists were engaged prospectively in the design of both trials as part of this unique collective effort to establish molecular-based therapy for bladder cancer.

In 2012, collaborative forums included the NCI Inter-Prostate SPORE Retreat at Northwestern University and the NCI Prostate SPORE Workshop on Contemporary Neoadjuvant Therapy for High-Risk Prostate Cancer, which was held in conjunction with the 2012 winter meeting of the Society of Urologic Oncology. Lung Cancer SPOREs and invited guests met in Pittsburgh, Pennsylvania, for a productive workshop featuring multiple collaborative projects in genomics, molecular diagnostics, and therapy. Investigators from the Skin/Melanoma SPOREs and other interested investigators met in

New Haven, Connecticut, to discuss current research and to forge new collaborative opportunities in both skin and non-skin melanoma research.

TRP is currently involved in two program announcements (PA-11-298 and PA-11-297) to promote innovative research across multiple disciplines for a better understanding of the biology, etiology, detection, prevention, and treatment of pancreatic cancer. In 2012, seven R03 grants and six R21 grants were funded with success rates of 39% and 8%, respectively.

In 2011 and 2012, TRP staff became actively involved in the conceptualization and management of the NCI Provocative Questions initiative. TRP Director Toby Hecht became the DCTD program representative for this effort, and several program directors were assigned applications that had been submitted in response to the request. The overall success rate of the first round at NCI was 7%; of those, about one-fifth ended up in DCTD.

NCI Program/Division	Grant
TRP/DCTD	<p>Predicting pancreatic cancer responses for a PARP inhibitor-based clinical trial – A randomized clinical trial to treat pancreatic cancer patients with standard chemotherapy drugs (irinotecan, cisplatin, bleomycin, and mitomycin C) with and without olaparib, a new poly(ADP ribose) polymerase (PARP) inhibitor</p> <p>Update: A phase 1 clinical trial has enrolled six patients on dose level one, and patients have shown stable disease or partial response. One patient is on the protocol after 15 months of therapy with partial response but with evidence of only minimal tumor burden. Toxicity has been manageable. Samples are being collected for correlative studies to test the predictive mutations.</p>
CTEP/DCTD	<p>Targeted Therapies for Childhood Acute Lymphoblastic Leukemia – A clinical study designed to identify high-risk patients who would benefit from Janus kinase (JAK) inhibitor therapy. JAK mutations are associated with high risk of relapse in children with acute lymphoblastic leukemia (ALL)</p> <p>Update: This research is ongoing; no findings have yet been reported.</p>
CDP/DCTD	<p>Translation of Predictive Rhabdomyosarcoma Biomarkers into Clinical Practice – Development of a new assay to stratify patients with low, intermediate, and high risk of childhood rhabdomyosarcoma to provide risk-tailored treatments</p> <p>Update: Data analysis and validation of the test are ongoing.</p>
CDP/DCTD	<p>Refining a Molecular Recursive Partitioning Analysis Model for Glioblastoma – Refinement of the existing glioblastoma classification models using new molecular, genetic, and epigenetic biomarkers to establish distinct prognostic groups of patients treated with radiation and temozolomide</p> <p>Update: The MD Anderson Cancer Center Brain SPORC participated in a multi-institute and international collaborative effort to develop regression analysis methods to correlate molecular results with the clinical outcome of glioblastoma.</p>
Cancer Biomarkers Research Group/DCP	<p>Validation of a Multi-Gene Test for Lung Cancer Risk – Establishment of a prospective cohort to test the validity of a new lung cancer risk assay that measures the activity of 14 key antioxidant, DNA repair, and transcription factor genes</p> <p>Update: Data analysis and validation of the test are ongoing.</p>



PROGRAM ACCOMPLISHMENTS

ORGAN-SPECIFIC CANCERS

Bladder Cancer

- **Novel DNA methylation biomarkers can detect bladder cancer in urine sediments.** Ten novel candidate genes from the most frequently hypermethylated genes were selected for the detection of bladder cancer in urine sediments. Using quantitative methylation-specific real-

time polymerase chain reaction, six methylation markers (MYO3A, CA10, SOX11, NKX6-2, PENK, and DBC1) were found to be most promising for detecting bladder cancer, providing a marker panel that detected bladder cancer with a high degree of accuracy.

- **Direct cytotoxicity produced by adenovirus-mediated interferon- α gene transfer in interferon-resistant cancer cells involves endoplasmic reticulum stress and caspase 4 activation.** This study centers on the direct bladder cancer cytotoxicity mediated by adenovirus interferon- α (Ad-IFN α), which has been shown to produce

NCI Program/Division	Grant
TRP/DCTD	<p>Biomarker Prediction of Gleason Upgrading in Prostate Cancer – Development of new biomarkers that can discriminate prostate cancer patients with pure Gleason grade (GG) 3 from those who have a mix of GG3 and GG4; the latter is not readily detectable in prostate biopsy samples</p> <p>Update: The key biomarkers were PTEN (by immunohistochemistry and fluorescence in situ hybridization), chromosome 8p loss (LPL) and 8q (MYC) gain, KI67, P53, P27, HIF1-α, GLUT-1, CA-IX, and a 22-gene genomic classifier developed by GenomeDX, using a 1.4 M feature oligonucleotide microarray. All biomarkers have been analyzed in GG3 tissue microarray cores from Gleason score 6 vs. Gleason score 7 prostatectomies, and preliminary analysis of the candidate gene biomarkers suggests a set of biomarkers that very strongly discriminate GG3 cores derived from Gleason score 7 tumors. The next step is to validate these results in Gleason score 3+3 biopsy cores from patients whose prostatectomy Gleason score remained 3+3 vs. those upgraded to 3+4 or 4+3.</p>
TRP/DCTD	<p>Proteasome/HDAC Inhibition in Leukemia/MDS; Phase 1 Trial and Correlative Studies – A clinical trial of the histone deacetylase inhibitor (HDAC) belinostat (PXD-101) and the proteasome inhibitor bortezomib in patients with refractory acute myeloid leukemia, ALL, chronic myelogenous leukemia blast crisis, and high-risk myelodysplastic syndromes (MDS)</p> <p>Update: Findings indicate that the regimen is well tolerated and shows evidence of activity.</p>
Lung and Upper Aerodigestive Cancer Research Group/DCP	<p>Clinical Evaluation of a Bioadhesive Gel for Oral Cancer Chemoprevention – An assessment of the chemopreventive efficacy of dried black raspberries on microscopic oral epithelial dysplastic lesions</p> <p>Update: Oral cancer chemoprevention trial data implied that patient-specific differences in local retention and metabolism of freeze-dried components of black raspberries affected therapeutic responsiveness.</p>
TRP/DCTD	<p>Defining the Importance of Immunity to NY-ESO-1 in Melanoma Therapy and Prognosis – Validation of the clinical benefits of antibodies that block cytotoxic T-lymphocyte-associated antigen 4 for melanoma patients with preexisting or induced immunity to cancer- and testis-specific antigen NY-ESO-1</p> <p>Update: Investigators showed in two separate cohorts from Memorial Sloan-Kettering Cancer Center and Yale that about one-fifth of melanoma patients treated with ipilimumab had antibody responses to NY-ESO-1, which may have predictive value for ipilimumab treatment. In addition, a melanoma patient treated with ipilimumab and radiotherapy showed antibody response to NY-ESO-1 antigen; shrinkage of tumor was noticed as “abscopal effect” (a phenomenon in which tumor regression is noticed at a site distant from the irradiated site).</p>

COORDINATION OF CLINICAL/TRANSLATIONAL RESEARCH (GO GRANTS) ACROSS NCI

CDP = Cancer Diagnosis Program (DCTD); CTEP = Cancer Therapy Evaluation Program (DCTD); DCP = Division of Cancer Prevention (NCI).

marked regression of human bladder cancer. Results show that caspase 4 activation is an early molecular event following Ad-IFN α transfection of cancer cells, an observation confirmed in exfoliated bladder cancer cells from a patient undergoing intravesical Ad-IFN α /SYN3 treatment. Data indicate that Ad-IFN α -mediated activation of caspase 4 signals downstream activation of caspase 3 and that this in turn is an effector of subsequent cell death in bladder cancer cells.

Brain Tumors

- **Oncolytic virus therapy includes multiple approaches for glioblastoma.** Patients with glioblastoma multiforme (GBM), the most common primary brain tumor, have a median survival of slightly more than 1 year. Because it rarely metastasizes, GBM is a good candidate for local delivery of gene and virus therapies. Four types of oncolytic virus therapies are under investigation in the Brain SPORE programs, including an engineered adenovirus, Delta 24-RGD; two herpes simplex viruses (HSVs), $\Delta\gamma_1$ 134.5 HSV and HSV-M032, which expresses interleukin (IL)-12; and two types of measles viruses. The latter virus type has been engineered to express markers that can monitor virus replication and tumor localization by noninvasive imaging and/or to import sodium iodide isotopes, including uptake of a radioactive isotope, ^{131}I , which can augment the cell-killing effect of viruses. Phase 1 trials have shown virus expansion within the tumor and effective killing of tumor cells. Collaborations with the NCI Experimental Therapeutics (NExT) program are assisting the translation of these virus products into clinical trials by supporting the production of pharmaceutical-grade viruses, such as adenovirus Delta-24-RGD, HSV M032, and HSV C134. The NExT program assists in regulatory compliance, filing of Investigational New Drug applications, toxicological testing, and Good Manufacturing Practice production of the products.
- **Noninvasive diagnostic tool measures presence of 2-hydroxyglutarate in IDH-1–mutated low-grade glioma.** A noninvasive diagnostic imaging technology for brain cancer, based on a unique genetic mutation in gliomas, is being developed. The technique uses magnetic resonance spectroscopy (MRS) to detect 2-hydroxyglutarate (2HG), which accumulates in gliomas harboring mutations in *IDH1* and *IDH2*. The molecule 2HG is a surrogate marker of brain tumor progression as identified by MRS and can identify tumors carrying the mutations,

distinguish different glioma subtypes, and detect recurrences without the need for repeated biopsy or surgery. This work characterizes the parameters for ex vivo spectroscopic measurements of tissue samples from patients with grade II glioma. A parallel effort addresses identical technology to detect 2HG in vivo in glioma patients.

- **Genomics meets epigenomics: a link between DNA methylation, IDH mutation, and survival in brain tumor patients.** The genetic mutation in *IDH* gene loci was found to be associated with a distinct DNA methylation profile of CpG loci in a study of histological subtypes of glioma brain tissues. In addition, patients with the *IDH* mutation showed improved survival compared with those with wild-type *IDH* when investigators adjusted for age and grade-specific tumor histology. The results raise a proposed mechanism that links multiple markers for glioma: epigenetics (hypermethylation), genetics (*IDH* mutation), and metabolites (levels of 2HG).

Breast Cancer

- **Loss of Rho GDI α enhances metastasis and resistance to tamoxifen.** Guanine dissociation inhibitor- α (GDI α) was shown to be expressed at lower levels in estrogen receptor- α (ER α)-positive tumors that recurred during tamoxifen treatment than in ER α -positive, tamoxifen-sensitive primary tumors. Loss of Rho GDI α enhanced metastasis and resistance to tamoxifen via effects on both ER α and metastasis-associated protein MTA2 in models of ER α -positive breast cancer and in tumors of tamoxifen-treated patients.
- **Assessment of kinome activity allows rational design of combination therapies in cancer.** Using a quantitative proteomics approach, investigators assessed kinome activity in response to MEK inhibition in triple-negative breast cancer cells and in a genetically engineered mouse model (GEMM). The inhibitor-induced receptor tyrosine kinases profile suggested a kinase inhibitor combination therapy that produced tumor apoptosis and regression in GEMMs where single agents were ineffective.
- **Sustained and complete inhibition of HER3 and its output to phosphatidylinositol 3-kinase (PI3K)/Akt are required for the optimal antitumor effect of therapeutic inhibitors of the HER2 oncogene.** These studies suggest that, because of HER3-mediated compensation, current clinical inhibitors of HER2 and PI3K/Akt will not completely block the PI3K pathway. Therapeutic inhibi-



tors of HER3 should be used in combination with HER2 inhibitors and PI3K pathway inhibitors in patients with HER2- and PI3K-dependent cancers.

- **The presence of ER β enhances the sensitivity of breast cancer cells to the anti-estrogenic effects of endoxifen, a tamoxifen metabolite, through the molecular actions of ER α / β heterodimers.** These findings underscore the need to further elucidate the role of ER β in the biology and treatment of breast cancer and suggest that the importance of pharmacologic variation in endoxifen concentrations may differ according to ER β expression.
- **IGF-1R/InsR tyrosine kinase inhibitors hold promise as antitumor agents in combination with hormonal therapies in hormone-sensitive breast cancer.** Using a model of postmenopausal, estrogen-dependent breast cancer, investigators studied the antitumor effects of insulin-like growth factor (IGF)-1R/InsR tyrosine kinase inhibitors alone and in combination with letrozole or tamoxifen. Cooperative cell cycle arrest, decreased proliferation, and enhanced promotion of apoptosis may contribute to antitumor effects to be gauged in future clinical investigations justified by these findings.

Cervical Cancer

- **Next generation of hybrid L1/L2 human papillomavirus (HPV) capsomers provide protection from wide range of HPVs.** To design the next generation of human HPV vaccines, capsomers were produced in bacteria with HPV type 16 L1 peptide alone or linked with residues 13–47 of HPV-18, HPV-31, and HPV-45 L2 in tandem. In addition



to HPV-16, the latter capsomer provided complete protection against HPV challenge in an experimental mouse model.

Endometrial Cancer

- **PTEN protein loss and other PI3K pathway aberrations are frequent in endometrioid endometrial cancer, while KRAS is mutated in endometrioid tumors.** Taken together, the PI3K pathway represents a critical driver of endometrial cancer pathogenesis and a novel therapeutic target. KRAS mutations activate events independently of PI3K aberrations.

Gastrointestinal Cancers

- **Pan-ErbB-negative regulator Lrig1, a stem cell marker, functions as a tumor suppressor.** Investigators performed linkage mapping on tamoxifen-inducible *Lrig1-CreERT2/+* transgenic mice and revealed that Lrig1 marked intestinal stem cells. Analysis by fluorescence-activated cell sorting showed that 2.4% and 4.8% of total cells expressed Lrig1 in small intestine and colon, respectively. These transgenic mice showed advanced adenomas when *Apc* was lost in Lrig1+ intestinal cells. Western blot analysis of intestinal crypts of transgenic mice showed that genetic ablation of Lrig1 resulted in increased ErbB1-3 protein levels, phosphorylation of Erk1/2, and duodenal adenomas. The data identified Lrig1 as a functional marker of mostly quiescent and long-lived intestinal stem cells that worked as a tumor suppressor under homeostatic conditions, which was maintained by ErbB signaling, and whose loss may contribute to neoplasia.

- **Genomic sequencing of colorectal adenocarcinomas identified *VTI1A-TCF7L2* fusion.** Chromosomal rearrangements were studied by whole-genome sequencing of tumors from nine colorectal cancer patients with matched adjacent nontumor tissues. On average, 75 somatic rearrangements were noticed in a single tumor. A recurrent fusion of *VTI1A* and *TCF7L2* genes was found in 3% of colorectal cancer cases, and 11 encoded rearrangements predicted in-frame fusion proteins. The *VTI1A-TCF7L2* fusion protein lacked the amino-terminal of TCF4 (transcriptional factor), which binds β -catenin. The discovery of recurrent *VTI1A-TCF7L2* fusion in colorectal cancers highlights the functional importance of genomic rearrangements and other oncogenic events.
- **Molecular evolution of acquired resistance to targeted epidermal growth factor receptor (EGFR) blockade in colorectal cancer.** The authors studied the development of acquired resistance in patients receiving monotherapy with panitumumab (anti-EGFR antibody). Thirty-eight percent of patients whose tumors were wild type developed mutations in *KRAS*, and mutant *KRAS* DNA was detectable in serum samples. Mutations appeared between 5 and 6 months after treatment. The data suggest that EGFR blockade resulted in the emergence of *KRAS* mutations, a mediator of acquired resistance, and that these mutations could be detected in a noninvasive manner.
- **Aspirin use, tumor *PIK3CA* mutation, and survival in colorectal cancer.** The authors studied the effect of aspirin on survival and prognosis in patients with colorectal cancer who had mutated versus wild-type *PIK3CA* cancers. Tumor tissue data, information on aspirin use, survival data, and presence or absence of *PIK3CA* mutation were evaluated in 964 patients with colon or rectal cancer. The study revealed superior colorectal cancer-specific and overall survival in patients with mutated *PIK3CA* who regularly used aspirin after diagnosis of the disease. In contrast, regular use of aspirin was not beneficial in patients with wild-type *PIK3CA* cancer. The data suggest that mutation in *PIK3CA* may serve as a predictive biomarker for adjuvant aspirin therapy in patients with colorectal cancer.

Head and Neck Cancer

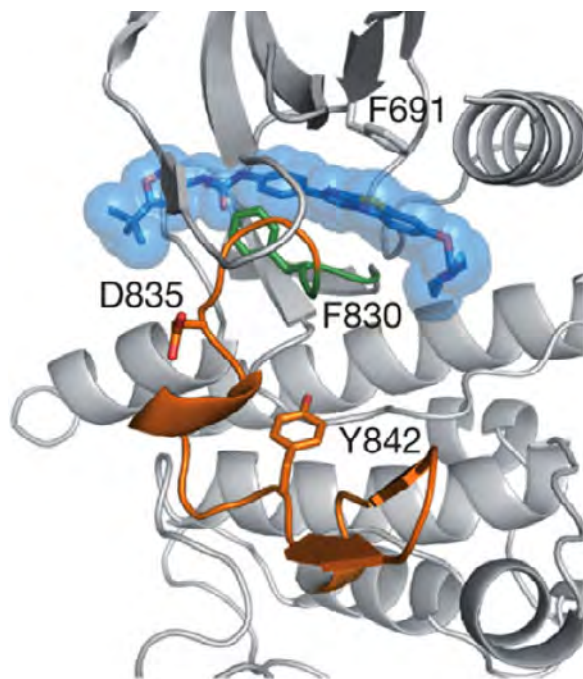
- **Sequencing of head and neck squamous cell carcinoma reveals new mutations.** Two seminal papers with the involvement of the three Head and Neck Cancer SPORES broadened our understanding of genomic changes in the

disease. A whole-genome sequencing analysis revealed that HPV-positive tumors had fewer mutations than did HPV-negative tumors. Both studies confirmed known mutations and identified previously unknown mutations in tumor specimens. Some of the newly detected changes imply that the gene *NOTCH1* has a tumor-suppressive rather than an oncogenic function.

- **Combination treatment with pemetrexed and bevacizumab shows promising outcomes in patients with recurrent or metastatic head and neck cancer.** In a phase 2 clinical trial of 37 patients, the addition of bevacizumab, a tumor blood vessel development inhibitor, to pemetrexed, an antimetabolite drug, had a beneficial effect in patients whose disease was not responsive to other therapies. The overall response rate was 30%, including 5% complete response, and the disease control rate was 86%. Although serious toxicity was observed in some patients, this effect may have been related to the natural history of the disease.
- **Genetic variants of a signaling pathway predict second primary tumor and/or recurrence risk and response to chemoprevention in head and neck cancer.** Head and Neck Cancer SPORE investigators created risk models based on epidemiology, clinical, and genetic data from 440 patients by focusing on the PI3K/PTEN/AKT/mTOR cellular signaling pathway. Twenty-two genetic loci were associated with increased risk of second primary tumor and/or recurrence, and six were also associated with a significant benefit following chemoprevention with 13-cis-retinoic acid. The study helps to identify individuals with a high-risk and/or high-benefit profile and provides a step toward personalized chemoprevention for patients with head and neck squamous cell carcinoma.

Leukemia

- **Validation of *FLT3-ITD* as a therapeutic target for acute myelogenous leukemia and identification of mutations that confer therapeutic resistance.** An internal duplication in the *FLT3* gene, resulting in the *FLT3-IDT* mutant, activates this kinase and is indicative of poor prognosis in patients with acute myelogenous leukemia. This study reports the identification of recurring point mutations in *FLT3-IDT* isolated from leukemia patients that confer resistance to the investigational *FLT3* inhibitor AC220. The data suggest that *FLT3-IDT* is a driver lesion and points to the need for new agents with the ability to inhibit the resistant forms of *FLT3-IDT*.



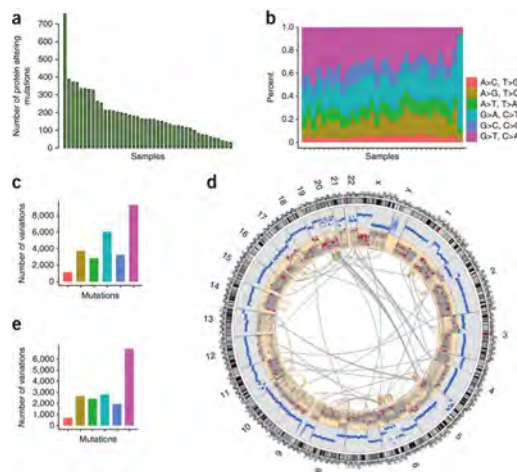
DOCKING MODEL SHOWING THE FLT3 KINASE DOMAIN BOUND TO ITS INHIBITOR AC220 (BLUE). THE ACTIVATION LOOP AND A REGION THAT CONFERS AC220 RESISTANCE ARE HIGHLIGHTED IN ORANGE AND GREEN, RESPECTIVELY.

- **Predictive biomarker identified for chronic lymphocytic leukemia.** This study demonstrates that loss of methylation of a single dinucleotide in the ZAP-70 promoter is highly predictive of poor prognosis in patients with chronic lymphocytic leukemia. In particular, this biomarker predicts diminished response to ibrutinib, an exciting new agent currently being evaluated for leukemia and lymphoma. As a result of this work, ZAP-70 methylation will now be prospectively assessed in clinical trials with ibrutinib.

Lung Cancers

- **Comprehensive genomic analysis of adenocarcinoma and small-cell carcinoma of the lung reveals new potential targets for therapeutic interventions.** Lung Cancer SPORE investigators continued in defining the genomic traits of lung adenocarcinoma with the use of massively parallel sequencing. In addition to known mutated genes, this study identified recurrent somatic mutations in the

splicing factor gene *U2AF1* and truncating mutations affecting *RBM10* and *ARID1A* genes. Mutation signatures grouped the sample set into distinct clusters that correlated with smoking history and alterations of reported lung adenocarcinoma genes. In a separate study, three Lung Cancer SPOREs, in collaboration with a commercial partner, published the first comprehensive genomic analysis of small-cell lung cancer. The authors identified 22 significantly mutated genes, including several members of the SOX family of genes and RLF-MYCL1 fusion. Functional studies confirmed the changes in SOX2 and MYCL1 as driver mutations for small-cell lung cancer that could be exploited in the future for therapy of this deadly disease.



SMALL-CELL LUNG CANCER (SCLC) SOMATIC MUTATIONS.

(a) Histogram of the number of mutations in each primary tumor sample. (b) Base-level transitions and transversions in each SCLC sample shown in a. (c) Average number of transitions and transversions in the SCLC samples based on the exome sequencing data. (d) Whole genome of an SCLC sample shown as a Circos plot. Copy-number changes measured using sequencing reads are shown in blue. Somatic nonsynonymous, splice-site, and stop-gain mutations are shown as red dots. Other somatic mutations are depicted as gray dots. Intrachromosomal (orange lines) and interchromosomal (gray lines) rearrangements are also shown. (e) Average number of transitions and transversions in the whole-genome sequence of an SCLC sample. Colors in c and e correspond to those defined in b.

- **Discovery of new genomic alterations in non-small-cell lung cancer broadens its treatment opportunities.** Systematic exploration of the genetic outfit in non-small-cell lung cancer tumors led to additional discoveries of previously unknown lesions. A Lung Cancer SPORE recently

released two studies, one of which described a new fusion between the *KIF5B* and *RET* genes and showed that cells bearing the oncogenic fusion are sensitive to multikinase inhibitors that inhibit RET. The second study presented as-yet-unrecognized insertion mutations of EGFR that sensitized tumors to treatment by its inhibitors. Another SPORE identified and successfully targeted *ROS1* gene fusions present in a subset of patients with non-small-cell lung cancer.

- **New mechanisms of drug resistance in anaplastic lymphoma kinase (ALK)-rearranged lung cancers are revealed.** The initial enthusiasm raised by remarkable responses to therapy in patients with lung cancer positive for ALK has been weakened by the development of tumor resistance to the treatment. Four Lung Cancer SPOREs led the effort in elucidating different forms of resistance to crizotinib and related agents. They identified new, secondary mutations in the EML4-ALK fusion gene as well as changes in other genes (KIT amplification, increased EGFR autophosphorylation, and KRAS mutations). One patient developed a treatment-resistant ALK-gene fusion-negative tumor with no detectable alternative driver mutation. The findings provide new therapy targets in these patients.
- **Preclinical models guide new designs for lung cancer therapy.** Investigators explored ways to interfere genetically and pharmacologically with ATM and MET kinase pathways and thus to induce malignant cells to die. The study identified new means of tumor control relevant to a major tumor suppressor gene, *p53*. Another study by the Dana Farber-Harvard Cancer Center SPORE developed animal models that will allow the testing of drugs that are active against common drug-resistant tumors. The model is specifically suitable for the evaluation of combination treatment.

Lymphoma

- **Loss of PRDM1 expression is an important pathogenetic mechanism for natural killer cell lymphoma (NKCL).** This study demonstrated that a significant percentage of patients with NKCL have either *PRDM1* gene mutations or promoter methylation that reduces the expression of *PRDM1*. In addition, *PRDM1* was shown to be a tumor suppressor gene that appears to be involved in natural killer cell homeostasis. The observation that disruption of this homeostatic control via *PRDM1* is involved in the development of NKCL suggests that further study of this mechanism could reveal new therapeutic opportunities for this disease.
- **Elevated free light chains in serum serve as a prognostic biomarker for multiple lymphoma types.** These studies report that elevated levels of free immunoglobulin light chains (both kappa and lambda types) in serum indicate inferior event-free and overall survival for patients with diffuse large B-cell lymphoma and Hodgkin lymphoma. An assay to detect free immunoglobulin light chains in serum could potentially help fill the need for additional prognostic biomarkers in lymphoma patients to better identify those who are likely to relapse after therapies or whose disease does not achieve remission.
- **Development of an immunotherapy approach for Epstein-Barr virus (EBV)-negative lymphoma.** As part of a strategy to develop a new therapy for EBV-negative lymphoma, investigators have developed an approach to obtain a lymphoma patient's cytotoxic T cells and train these T cells to recognize an array of nonvirus tumor-specific antigens. Using multiple tumor-specific antigens and including pro-survival and pro-proliferative cytokines, investigators generated autologous T cells that targeted self antigens. Obtaining reactivity against self antigens had previously been a stumbling block to this type of approach. These studies support the future use of such autologous cytotoxic T cells for the treatment of patients with EBV-negative lymphoma.

Myeloma

- **New insights into mechanisms for bortezomib resistance may lead to enhanced combination therapies for multiple myeloma.** This study describes the generation of myeloma cell lines selected to become resistant to the proteasome inhibitor bortezomib. Bortezomib resistance was subsequently found to require upregulation of IGF-1 signaling. Accordingly, an IGF-1 receptor inhibitor rendered this cell line, as well as bortezomib-resistant patient samples carried in mice as xenografts, sensitive to bortezomib. This study therefore provides a rationale for combining bortezomib with IGF-1 receptor inhibitors in order to overcome, or possibly prevent, bortezomib resistance.
- **P5091, a small-molecule inhibitor of deubiquitylating enzyme USP7, induces apoptosis in multiple myeloma cells and overcomes resistance to bortezomib.** This



study describes the identification and preclinical characterization of P5091, a USP7 inhibitor that is a possible new therapeutic agent for myeloma. This agent induces apoptosis in myeloma cells that have become resistant to the proteasome inhibitor bortezomib. In animal models, P5091 inhibits tumor growth, is well tolerated, and synergizes with other myeloma drugs such as lenalidomide, HDAC inhibitors, and dexamethasone. These data therefore support clinical evaluation of this new agent.

- **Lenalidomide maintenance therapy, initiated after hematopoietic stem cell transplantation, results in a significantly longer time to progression and improved overall survival among patients with myeloma.** This randomized clinical trial was carried out to investigate whether lenalidomide maintenance therapy prolongs the time to disease progression after stem cell transplantation in patients with multiple myeloma. Although lenalidomide was associated with more toxicity and second cancers, the time to progression for the lenalidomide-treated patients was lengthened to 46 months compared with 27 months for the control group.

Ovarian Cancer

- **Cancer microenvironment plays role in tumor cell behavior.** Markers within the microenvironment originating in blood vessels, macrophages, and cancer-associated fibroblasts may regulate tumor cell behavior. Two Notch ligands, delta-like ligand 4 (Dll4) and Jagged1, are overexpressed in ovarian cancers in both tumor and endothelial stromal compartments and are increased by vascular endothelial growth factor pathways. Targeting Dll4 or Jagged-1 by small interfering RNA in combination with anti-angiogenic agents may improve outcome of ovarian cancer treatment.
- **New Initiatives in diagnostics: bionanotechnology.** Screening patients for ovarian cancer can be achieved in 30 minutes with blood from a finger stick and laboratory-on-a-chip nanotechnology. Cancer antigen 125 (CA-125), a known marker, is being used for assay development of this nanotechnology, which can be expanded as additional biomarkers are identified. Rapid screening of ovarian biomarkers allows cost-effective, same-visit follow-up with transvaginal ultrasound for monitoring the progression or remission of ovarian cancer and may support improved survival rates through early intervention.

- **Decreasing platelets affects microenvironmental paracrine loop to reduce ovarian tumor growth.** Many cancer patients are known to have increased platelet numbers, a condition known as paraneoplastic thrombocytosis, but the mechanisms underlying the development of this condition has not been understood. Using mouse models and patient tissues, investigators have unraveled complex biological processes that link tumor-derived IL-6 to increased synthesis of thrombopoietin in the liver. This in turn was found to increase platelet production in bone marrow and in circulation, leading to tumor growth in the ovarian microenvironment. Anti-IL-6 treatments in mouse models and in patients in a phase 1/2 study showed reduction in platelets, and the mouse studies went on to show reduced ovarian tumor growth.

Pancreatic Cancer

- **KRAS is required for initiation, maintenance, and metastasis of pancreatic cancer.** To understand the mechanistic role of KRAS in pancreatic cancer, investigators showed that oncogenic KRAS played a key role in the early stages of tumor development, during tumor maintenance, and in metastasis of pancreatic cancer in transgenic mice. Induction of *KRAS* reversibly altered the normal epithelial differentiation, which led to precancerous lesions. Inactivation of *KRAS* either in established precursor lesions or during progression to cancer led to regression of the lesions. The data suggest that *KRAS* is required at all stages of pancreatic carcinogenesis and that targeting *KRAS* or its downstream signaling pathway could have a therapeutic effect, but prolonged use could result in acquired resistance in pancreatic cancer.
- **Computational modeling of pancreatic cancer reveals kinetics of metastasis.** Investigators used a stochastic mathematical model to study the progression and metastasis of pancreatic cancer, using a comprehensive database of 228 cancer patients along with autopsies from 101 subjects. They considered various parameters, including size of tumor, total number of cancer cells, the effect of therapies, resection of tumor, and survival time of patients. With the help of the model, they predicted mutation rate, metastasis rate, epigenetic alteration, and risk of harboring metastasis. The predicted data were validated with the autopsy patient data with an accurate fit. Furthermore, prediction of survival times with an adjuvant cohort provided an excellent fit with the growth kinetics obtained from autopsy database. Thus, the interdisciplinary model

provided insight into the dynamics of pancreatic cancer and its metastasis, opening the door for more effective therapeutic interventions.

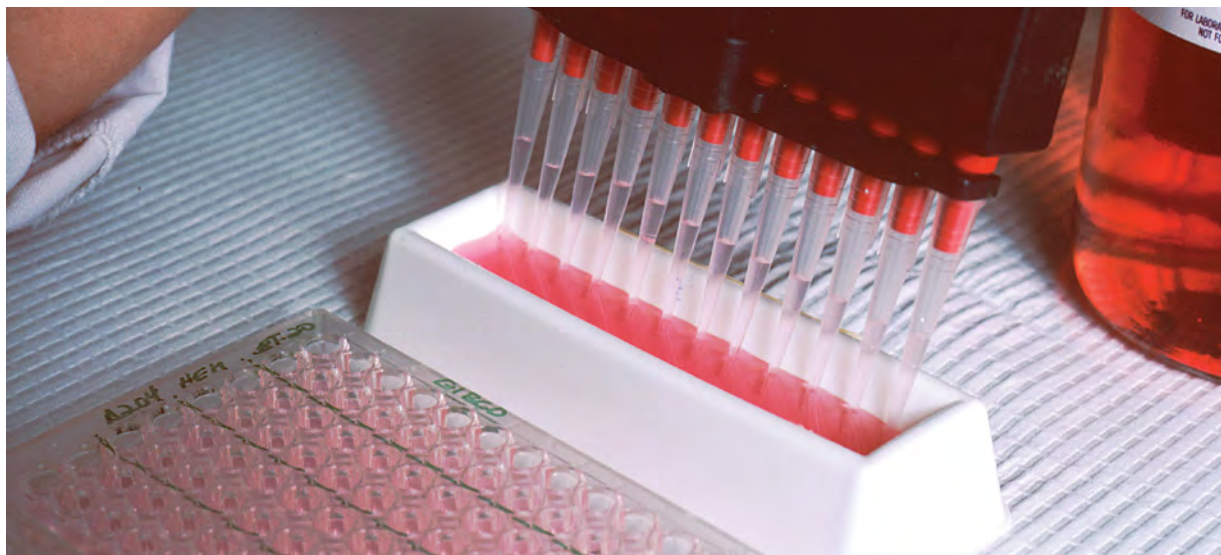
- **Deubiquitinase *USP9X* suppresses pancreatic ductal adenocarcinoma.** Two SPOREs used *Sleeping Beauty* transposon-mediated insertional mutagenesis in a mouse model of pancreatic cancer and identified 20 genes that cooperated with *KRAS* to accelerate tumorigenesis and promote progression. Of all the mutated genes, X-linked deubiquitinase, *USP9X*, was inactivated in more than 50% of tumors. Although *USP9X* has been attributed as a pro-survival gene in human neoplasia, the current study found that loss of *USP9X* enhanced transformation and protected pancreatic cancer from anoikis, a form of programmed cell death. Investigators proposed that *USP9X* is a major tumor suppressor gene with prognostic and therapeutic relevance in pancreatic ductal adenocarcinoma.
- **A phase 2 study of granulocyte macrophage–colony-stimulating factor–based adjuvant immunotherapy yields promising results.** Investigators used granulocyte macrophage–colony-stimulating factor (GM-CSF)–secreting cells in a single-institution–based, phase 2 study of 60 patients after resection of pancreatic adenocarcinoma. The immunotherapy (irradiated GM-CSF–transfected, allogeneic, whole-cell tumor lines) was followed by radiation and chemotherapy. Patients who remained disease free by computed tomography scanning were given additional regimens of immunotherapy. The immunotherapy was well tolerated and the overall survival compared favorably with published data, ranging from 15 to 20 months. The postimmunotherapy mesothelin-specific CD8+ T-cell response was associated with prolonged disease-free survival in HLA-A1+ and HLA-A2+ patients.

Prostate Cancer

- **Molecular characterization of localized prostate cancer enables the development of novel biomarkers and therapy.** Exome sequencing with primary prostate cancers identified recurrent SPOP, FOXA1, and MED12 mutations in prostate cancer. SPOP was the most frequently mutated gene; mutations involving the SPOP substrate-binding cleft were identified in 6–15% of tumors across multiple independent cohorts. Thus, SPOP mutations may define a new molecular subtype of prostate cancer. Notably, prostate cancers with mutant SPOP lacked ETS family gene rearrangements, which is

characteristic of most prostate cancers. Another study identified SPINK1 as an extracellular therapeutic target for an aggressive subtype of prostate cancer, with mutually exclusive outlier expression of ERG and ETV1. Using preclinical models, this study demonstrated the therapeutic potential of monoclonal antibody to SPINK1. It also showed that SPINK1 mediates its oncogenic effects in part through EGFR and that a monoclonal antibody to EGFR shows activity in SPINK1+ prostate cancer.

- **Molecular characterization of castration-resistant prostate cancer identifies new mechanisms of resistance to treatment and points to new potential treatment strategies.** The study of distinct transcriptional programs mediated by the ligand-dependent full-length androgen receptor (AR) and its splice variants in castration-resistant prostate cancer showed that the suppression of the canonical full-length AR (AR-FL) led to increased expression of constitutively active AR splice variants (AR-Vs). In vitro studies showed distinctive transcriptional programs mediated by AR-FL and AR-Vs, the latter associated with elevated cell cycle gene expression. These findings support an adaptive shift toward AR-V-mediated signaling in tumors as an important mechanism of resistance to therapies for castration-resistant prostate cancer that target the AR-FL. The results also point to AR-V signaling as an important potential target to overcome resistance to therapy for this cancer. Other studies showed that the loss of PTEN plays a key role in regulating the growth of castration-resistant prostate cancer and that PTEN loss suppresses androgen-responsive gene expressions by modulating the activity of AR transcription factors. PTEN loss or PI3K activation represents one of the most frequent genetic alterations found in human prostate tissue, and cross-talk between PI3K and AR pathways was identified as a mechanism of the development of castration-resistant prostate cancer. This new molecular understanding of the etiology of this cancer is leading to the development of effective new treatments using combined pharmacologic inhibition of PI3K and AR signaling, which results in near-complete prostate cancer regression in animal models. EZH2 was found to express its oncogenic function through co-activation of critical transcription factors, including AR, providing another new avenue of therapy for metastatic, hormone-refractory prostate cancer. The tumor microenvironment was also found to contribute to resistance to prostate cancer therapy. Using a genome-wide analysis of transcriptional responses to genotoxic



cancer therapeutics, investigators identified a spectrum of secreted proteins derived from the tumor microenvironment that included WNT16B, whose expression in the prostate tumor microenvironment attenuated the effects of cytotoxic chemotherapy, promoting tumor cell survival and disease progression.

- **Development of novel treatments for prostate cancer leads to promising preclinical results.** Administration of conditionally replicating adenovirus vectors expressing the sodium iodide symporter resulted in robust iodine radionucleotide uptake and tumor cytolysis in AR-expressing cells. This radiovirotherapy of xenografts resulted in very significant extension of survival. OGX-011, an antisense drug that targets clusterin, potentiated the efficiency of Hsp90 inhibitors by suppressing the heat shock response in castration-resistant prostate cancer, leading to an 80% inhibition of tumor growth with prolonged survival. These preclinical findings demonstrate that Hsp90 inhibitor-induced activation of the heat shock response and clusterin can be attenuated by antisense treatment, leading to delayed progression of castration-resistant prostate cancer.
- **Molecular profiling of an individual's lethal castration-resistant prostate cancer identifies key drivers of a person's clonal disease, enabling more precise treatments.** Integrated exome-based profiling of the mutational landscape of metastatic tumors from patients with castration-resistant prostate cancer identified a diverse series of potential driver mutations and copy number alterations in both known and novel genes, including *FOXA1*. This study also confirmed the clonal nature

of metastatic disease. The integrative genomics dataset provides a useful resource for the study of determinants of lethal prostate cancer as well as mechanisms of resistance to therapy. A report on a pilot effort to implement biomarker-based personalized oncology through integrative high-throughput sequencing described how tumors of individual patients with advanced refractory cancer were extensively evaluated with whole-genome sequencing and transcriptome sequencing (RNA-Seq) to identify potentially informative and actionable mutations. Several mutations, including structural rearrangements, copy number alterations, point mutations, and gene expression alterations, were found. A multidisciplinary Sequencing Tumor Board deliberated on the clinical interpretation to recommend treatments based on the clinical and molecular information. This pilot study demonstrates the feasibility of using integrative high-throughput sequencing to tailor treatment selection for individual patients.

Renal Cancer

- **Genetic and functional studies implicate HIF-1 α as a 14q kidney cancer suppressor gene.** Deletion of 14q is common in kidney cancers. This study identified focal homozygous deletions of the HIF-1 α locus on 14q in clear-cell carcinoma and found that all somatic HIF-1 α mutations that were identified in kidney cancers resulted in a loss of function. The results of this study show that HIF-1 α has the credentials of a kidney cancer suppressor gene and that its loss of function portends a poor prognosis.

Sarcoma

- **Novel gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites and in solitary fibrous tumor/hemangiopericytoma.**

The Sarcoma SPORE discovered a new gene fusion product (WWTR1-CAMTA1) that is present in rare tumors called epithelioid hemangioendothelioma. The lesion occurs in specimens from bones, soft tissue, and visceral locations such as lung and liver. This finding has the potential to improve the diagnostics in histologically uncertain cases.

Skin Cancer

- **Combination of MEK and PI3K inhibition enhances uveal melanoma cell death in a mutant *GNAQ*- and *GNA11*-dependent manner.** In a preclinical study using uveal melanoma cell lines, it was shown that inhibition of either MEK or PI3K alone resulted in modest apoptotic cell death. However, inhibition of both MEK and PI3K resulted in strong induction of apoptosis, which was most pronounced in *GNAQ*-mutant cells and was also evident in the majority of *GNA11*-mutant cells.
- **Tumor microenvironment elicits innate resistance to RAF inhibitors through secretion of hepatocyte growth factor.** Investigators studied the tumor microenvironment to understand the mechanisms underlying innate drug resistance. In a co-culture system, 23 stromal cell types were assayed for their ability to influence the innate resistance of a cancer cell line to 35 anticancer drugs. Immunohistochemical and proteomic analyses showed a significant correlation between innate resistance and the secretion of hepatocyte growth factor by stromal cells. RAF inhibition, combined with the inhibition of either HGF or MET, resulted in reversal of drug resistance in BRAF-mutant melanoma.
- **Proinvasion metastasis drivers in melanoma are oncogenes.** Investigators integrated genetically engineered mouse models, comparative oncogenomics, and functional genomics and identified six genes that were capable of driving invasion and transformation in early-stage melanomas. Of the identified genes, one proinvasion oncogene, ACP5, was involved in metastasis and was also a prognostic biomarker in human primary melanomas.
- **Exome sequencing identifies RAC1 mutations in melanoma.** Investigators characterized the mutational landscape by exome sequencing of 147 melanomas and

identified a recurrent ultraviolet-signature, somatic RAC1 mutation (RAC1^{P29S}) in 9.1% of sun-exposed melanomas. RAC1 was the third most frequent activating mutation after BRAF and NRAS in the cohort of sun-exposed melanomas. Biochemical, functional, and crystallographic studies of RAC1^{P29S} showed that the mutation affected conformational changes, which resulted in increased binding of the protein to downstream effectors and promoted melanocyte proliferation and migration. The data suggest that pharmacological inhibition of RAC1 might be of therapeutic benefit in the treatment of melanomas.

PROGRAM COLLABORATIONS

Collaborations and partnerships are essential for success in translational research. Over the years, TRP program staff and SPORE teams reached beyond their programs and grants to partner with other government programs, foundations, and industry to move discoveries into early-phase clinical testing. Highlighted here are recent projects that illustrate the range of collaborations and partnerships driven by SPOREs.

The Cancer Genome Atlas

The Cancer Genome Atlas (TCGA) is a comprehensive and coordinated effort to accelerate understanding of the molecular basis of cancer through genome analysis. SPOREs donated more than 1,600 tumor samples and contributed to the data analysis in various types of cancer. Listed here are recent published studies that included SPORE investigators:

- Comprehensive Molecular Portraits of Human Breast Tumors
- Association of BRCA1 and BRCA2 Mutations with Survival, Chemotherapy Sensitivity, and Gene Mutator Phenotype in Patients with Ovarian Cancer
- Identification of a CpG Island Methylator Phenotype that Defines a Distinct Subgroup of Glioma

Other Collaborative Genomic Studies

Genomic analysis of somatic mutations in diffuse large B-cell lymphoma. Investigators associated with the University of Iowa Lymphoma SPORE (Principal Investigator [PI], George Weiner) have collaborated with scientists at the Broad Institute to carry out genome-wide identification of somatic mutations in diffuse large B-cell lymphoma



(DLBCL), using whole-exome sequencing. In addition to recurrent mutations in genes already known to play a role in this disease, mutations in several genes not previously associated with DLBCL were identified. For example, the data suggest that *KRAS*, *BRAF*, and *NOTCH1* are likely drivers of DLBCL in some patients. These new data provide new insights into lymphomagenesis that may point toward new therapeutic strategies for this disease.

Early Detection Research Network. In an effort to improve early detection and diagnosis of cancer, SPOREs created a multifaceted partnership with investigators in the Early Detection Research Network (EDRN) of the NCI Division of Cancer Prevention. The Lung Cancer Biomarkers Working Group, created by SPORE and EDRN investigators with support from NCI staff, established a collection of well-characterized plasma and serum reference sets from patients with early lesions. These sets are available nationwide to scientists for independent qualification of their assays.

The Case Western GI SPORE (PI, Sanford Markowitz) is evaluating the accuracy and clinical efficacy of stool DNA testing (methylation of vimentin) in a population-based screening study for early detection of advanced adenomas. Investigators have established a significant collaboration with the EDRN Clinical Validation Center at the University of Michigan (PI, Dean Brenner, also PI of the GI SPORE) and with the EDRN Biomarker Reference Laboratory at the University of Maryland (PI, Sanford Stass). In this collaboration, the Clinical Validation Center will provide initial steps in processing of stool samples from study participants and chemical readout of fecal immunochemical testing, and the Biomarker Reference Laboratory will provide methylated vimentin assay of stool DNA in a setting that is compliant with the Clinical Laboratory Improvement Amendments.

Department of Defense. Prostate Cancer SPOREs have a partnership with the Prostate Cancer Clinical Trials Consortium (PCCTC), which is sponsored by the U.S. Department of Defense. The PCCTC endeavors to design, implement, and complete hypothesis-driven phase 1 and 2 trials of novel agents and combination treatments that could prolong the lives of patients with prostate cancer. A majority of PCCTC PIs are also leaders of clinical research projects in one of the Prostate Cancer SPOREs, and nearly all the Prostate Cancer SPORE institutions are members of the consortium. Many of the Prostate Cancer SPORE clinical trials are now being conducted interinstitutionally through the PCCTC infrastructure.

Office of HIV and AIDS Malignancy. The extended survival of HIV-positive patients as a result of advanced therapies leads to an increased incidence of disease-related malignancies. In collaboration with NCI's Office of HIV and AIDS Malignancy, projects were launched to explore the character of HIV-related lymphoma, lung, and head and neck cancers.

One project is conducting a retrospective study followed by a prospective collection of tumor and blood samples at all five Head and Neck Cancer SPORE Centers. These samples are being collected to obtain the fresh specimens that are necessary for the assessment of changes in functional immune markers in HIV-positive and -negative patients with head and neck cancers who are undergoing current therapies.

Lymphoma SPOREs focus on characterization of the AIDS lymphoma genome, identification of environmental factors and autoantigens in the pathogenesis of HIV-positive and -negative lymphomas, plasma markers in AIDS lymphoma, and treatment of HIV Hodgkin disease.

Lung Cancer SPOREs are exploring the clinical and molecular differences between tumors from HIV-positive lung cancer patients and matched HIV-negative lung cancer control subjects by performing high-throughput genome analyses. These SPOREs are investigating new genetic epidemiology markers associated with the development of lung cancer in HIV-positive patients. They study the role of viral cofactors that characterize the increased risk of lung cancer in these patients.

NIH Office of Research on Women's Health. The Research Enhancement Award Program in the NIH Office of Research on Women's Health (ORWH) provides transitional funding awards for highly meritorious grant submissions on women's health research that have just missed the funding paylines established by NIH institutions and centers. ORWH selects qualified applications on a competitive basis. In fiscal year 2009, ORWH and TRP co-funded the Washington University SPORE in Endometrial Cancer (PI, Paul Goodfellow).

National Institute of Neurological Disorders and Stroke and National Institute of Dental and Craniofacial Research. Other NIH institutes consistently express interest in supporting SPORE applications that match institutional research priorities and hold promise in reducing the burden of disease in their respective organ sites. In particular, the National Institute of Dental and Craniofacial Research

contributed one-third of the total cost for two Head and Neck Cancer SPOREs from 2011 to 2012 and fully funded one in the same period. In 2011–2012, the National Institute of Neurological Disorders and Stroke committed \$200,000 to the University of Alabama Brain SPORE to augment its research effort.

Collaboration with NCI Intramural Program. The scientific resources of the NCI intramural program allowed several SPOREs to build productive relationships with this part of NCI. The following recent examples represent this ongoing relationship.

The second Sarcoma SPORE was awarded in 2012 to the Sarcoma Alliance for Research Through Collaboration (SARC) consortium. This multi-institutional research group, under the leadership of Raphael Pollock, involves national and international team members and collaborators, including scientists from NCI. The four main projects focus on therapy and monitoring of various types of soft tissue sarcomas in adults and children.

The University of Texas MD Anderson Cancer Center Melanoma SPORE (PI, Elizabeth Grimm) collaborated with intramural programs of the National Human Genome Research Institute and NCI. Investigators identified somatic mutations in 68 genes with the help of exome sequencing of 14 matched normal and metastatic tumor DNAs. The study identified recurring genetic alterations in the *TRRAP* gene and revealed that *GRIN2A* (glutamine signaling pathway) was mutated in 33% of melanoma samples.

The Johns Hopkins GI Cancer SPORE, in collaboration with NCI's Division of Cancer Epidemiology and Genetics and the Mayo Clinic's Pancreatic Cancer SPORE, revealed a connection between pancreatic development and cancer risk. Investigators performed genome-wide association studies on 3,851 pancreatic cancer cases and 3,934 control participants pooled from 12 cohorts and 8 case-control studies. With the use of data mining, *NR5A2*, *HNF1A*, *HNF4G*, and *PDX1* genes were identified as critical for pancreatic development.

Collaboration with CTEP (Endoxifen). The Translational Research Program, the Cancer Therapy Evaluation Program (CTEP), and NExT supported preclinical and early clinical development of endoxifen, a derivative of tamoxifen, which has been used for many years to prevent and treat breast cancer. Despite a number of promising pharmaco-

logical properties of endoxifen, commercial development of this drug presents a unique set of challenges because, in the absence of intellectual-property ownership, potential sponsors cannot benefit from endoxifen patent protection. In 2011 and 2012, TRP and CTEP provided expert support and funding to characterize the preclinical pharmacology, toxicology, and metabolism of endoxifen and to initiate a phase 1 clinical trial in women with ER-positive breast cancer. These studies were conducted by the Mayo Clinic Breast Cancer SPORE and other Mayo Clinic investigators.

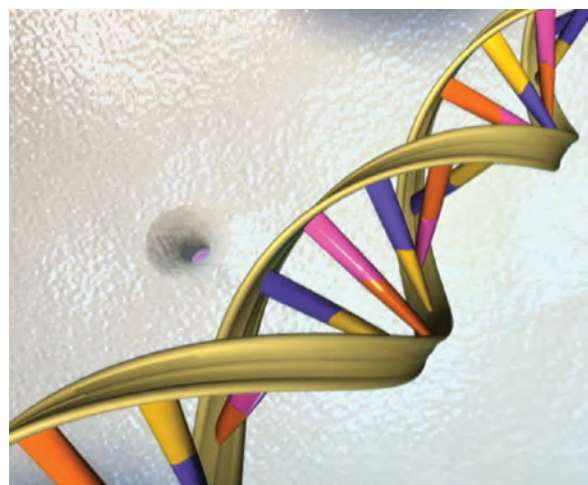
International Collaborations. As in the past, several SPORE projects reach out to collaborators abroad. For the past 2 years, several NIH institutes have provided funds to sponsor collaborative studies between U.S. and Chinese investigators. Program directors at TRP were involved in the solicitation and evaluation process, which resulted in the award of one supplement to the University of Pittsburgh Head and Neck Cancer SPORE (PI, Jennifer Grandis) within the TRP portfolio. The study, entitled "Genomic Analysis of Oncovirus-Associated Head and Neck Cancers in U.S. and Chinese Populations," aims to identify mutations in HPV- and Epstein-Barr virus-associated head and neck cancers in the United States and China and to characterize the driver and passenger mutations by using functional genomics.

Project 2 of the newly established SARC Sarcoma SPORE involves investigators in Germany who have access to additional patients with rare malignant peripheral nerve sheath tumors, along with corresponding unique animal models. The aim is to develop better treatment of the deadly disease.

The University of Alabama in Birmingham (UAB) Pancreatic SPORE (PI, Donald Buchsbaum) is collaborating with the United Kingdom's Cambridge Research Institute (PI, David Tuveson) to identify and target pathways of pancreatic cancer progression and metastasis.

The Mayo Clinic Ovarian SPORE (PI, Lynn Hartmann) involves a consortium agreement with Laval University in Quebec, Canada, for expertise and sample analysis from the phase 1/2 trial of topotecan and the poly(ADP ribose) polymerase (PARP) inhibitor ABT-888.

Jedd Wolchok at the Memorial-Sloan Kettering Institute is collaborating with the European Organisation for Research and Treatment of Cancer to understand the importance of NY-ESO-1 in immunotherapy for melanoma. Investigators



have access to specimens from a completed 900-patient trial of ipilimumab versus placebo as adjuvant therapy for stage 3 melanoma. The samples (serum and peripheral blood) from these patients are being collected to study the immune responses in these melanoma patients.

The Mayo Clinic Pancreatic Cancer SPORE (PI, Gloria Petersen), the UAB Pancreatic Cancer SPORE, and the Johns Hopkins University GI Cancer SPORE (PI, Scott Kern) collaborated globally on genomic analysis and identified mechanisms that were common among genomically diverse cancers. In a well-annotated clinical cohort of 142 patients of early (stages I and II) sporadic pancreatic ductal adenocarcinoma, they found potential involvement of axon guidance genes, particularly SLIT/ROBO signaling, in pancreatic carcinogenesis..

The Mayo Clinic Pancreatic Cancer SPORE, the University of North Carolina GI Cancer SPORE (PI, Joel Tepper), and the Vanderbilt University GI Cancer SPORE (PI, Robert Coffey) also collaborated with international partners. In mouse models, using genetic and pharmacological approaches, investigators showed that oncogenic *KRAS* upregulated *EGFR* expression and activation. Pharmacological inhibition or genetic ablation of *EGFR* or its ligand (*ADAM17*) eliminated *KRAS*-driven tumorigenesis.

Health Disparities. The NCI SPOREs support investigator-initiated basic and translational research in prevention, early detection, diagnosis, and treatment of organ-specific cancers. Basic and translational research projects focused on health disparities are interspersed in various SPORE

programs. For example, the University of North Carolina Breast Cancer SPORE (PI, Shelton Earp) supports the Carolina Breast Cancer Study, a population-based project to identify the determinants of racial health disparities. This study examines factors affecting risk, behavior, and prognosis within and across breast cancer subtypes, as well as between African American and non-African American women. In previous years, SPORE investigators demonstrated that young African American women had a higher prevalence of the poor-prognosis basal-like breast cancer and, conversely, a low prevalence of the good-prognosis luminal A subtype breast cancer. The University of North Carolina Breast Cancer SPORE currently funds gene expression profiling of tumors collected in phase 3 of the Carolina Breast Cancer Study to evaluate the difference in risk factor distribution by subtype. This research will provide a comprehensive picture of the biology and epidemiology of breast cancer and breast cancer disparities from risk to survival.

Investigators in the Dana Farber Cancer Center Myeloma SPORE (PI, Kenneth Anderson) are identifying genotypes that confer high risk for developing multiple myeloma, which is known to disproportionately affect African Americans and, to a lesser degree, Hispanics. DNA from 1,554 patient specimens indicated that the presence of a single-nucleotide polymorphism (SNP) was inversely associated with multiple myeloma in African Americans, whereas no association between this SNP and multiple myeloma risk was observed for whites. Identification of ethnic-specific genetic risk factors for multiple myeloma could facilitate screening approaches and inform subsequent treatment strategies.

The SPORE program also addresses the enrollment of minorities in clinical trials through collaborations with local community hospitals, organizations, and academic institutions serving racially and ethnically diverse populations. The Vanderbilt GI Cancer SPORE partners with a local minority medical college, Meharry Medical Center and Nashville General Hospital, and has increased minority accrual to clinical research through the placement of an oncologist in the community hospital. Finally, the Johns Hopkins GI Cancer SPORE is in partnership with Howard University and has been active in enrolling racially and ethnically diverse patients in clinical studies through outreach to faith-based communities and multicultural media.

Center to Reduce Cancer Health Disparities Minority Supplements. TRP has a long history of collaboration with NCI's Center to Reduce Cancer Health Disparities, where SPORE investigators have received additional funding to promote the careers of minority candidates and reduce cancer health disparities. In 2011, the University of Michigan GI Cancer SPORE and the University of Texas MD Anderson Cancer Center Melanoma SPORE received an administrative supplement and an award, respectively, to promote the training of minority candidates. In 2012, the University of Iowa Lymphoma SPORE received a supplement to support the career development of Evelena Ontiveros, an MD-PhD physician scientist of minority background who is investigating the relationship between vitamin D and prognosis in lymphoma. Research supplements to promote diversity in health-related research programs have also been awarded to the following SPOREs:

- University of Alabama at Birmingham Breast Cancer SPORE (PI, Kirby Bland)
- University of Chicago Breast Cancer SPORE (PI, Olufunmilayo Olopade)
- Johns Hopkins University Cervical Cancer SPORE (PI, Tzyy-Choou Wu)

NCI Translational Research Interactive Network. The TRP, together with the NCI Office of Communications and Education, created the NCI Translational Research Interactive Network, or NTRIN (pronounced "enter in"), a social media site that allowed researchers and administrators interested in cancer translational research to find one another online. The site included an opportunity for this community to discuss issues, exchange information, and establish collaborations.

NTRIN included groups, forums, a chat feature, and announcements that are directed to the community at large. The groups included organ-specific cancers, such as skin, prostate, and lung, as well as groups that span organ sites, such as biomarkers and immune response modifiers. A group for SPORE Administrators was also established to allow SPORE participants to discuss current and relevant information about managing their grants. They used the site to post forms, receive clarification on the grant mechanism, and share processes that worked for them. The site, with its 318 members, will be transitioned to another social medium platform in 2013.

Completed Collaborations:

- **Imatinib potentiates antitumor responses in GI stromal tumor.** The Memorial Sloan-Kettering Cancer Center Sarcoma SPORE (PI, Samuel Singer), in collaboration with a grant from NCI's Drug Development Program, showed that T cells are crucial to the antitumor effects of the drug imatinib in GI stromal tumor, and concomitant immunotherapy may further improve outcomes in human cancers treated with targeted agents.
- **Common breast cancer susceptibility loci are associated with triple-negative breast cancer.** The Triple-Negative Breast Cancer Consortium includes the Breast Cancer SPORES of the Mayo Clinic (PI, James Ingle) and the Harvard-Dana Farber Cancer Institute (PI, Eric Winer), the Fox Chase Cancer Center Ovarian Cancer SPORE (PI, Michael Seiden), and other participants from the United States, Europe, and Australia. The consortium investigated 22 common breast cancer susceptibility variants in 2,980 Caucasian women with triple-negative breast cancer and 4,978 healthy control subjects. Investigators identified six SNPs that were significantly associated with the risk of triple-negative breast cancer. Together, these results provide convincing evidence of genetic susceptibility for triple-negative breast cancer.
- **Vascular disrupting agent, DMXAA, enhances therapeutic HPV vaccine-induced cytotoxic T-lymphocyte responses and antitumor effects.** An international collaboration took place between the Obstetrics and Gynecology Hospital of Fudan University in Shanghai, China, and investigators in the Johns Hopkins University Cervical Cancer SPORE. These researchers tested the combination of a vascular disrupting agent with therapeutic HPV-16 E7 peptide-based vaccination for its ability

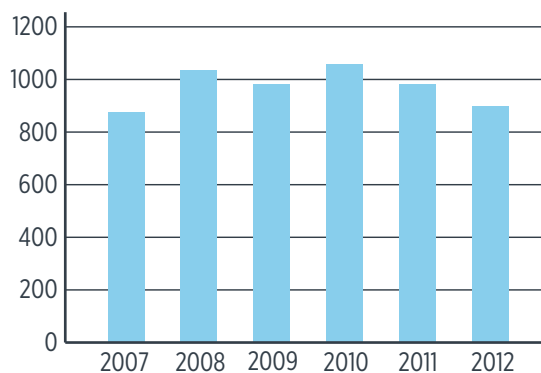


to generate E7-specific CD8+ T-cell immune responses and control E7-expressing tumors in a subcutaneous and a cervicovaginal tumor model. The combined treatment generated significantly stronger E7-specific CD8+ T-cell immune responses and antitumor effects than did treatment with vascular disruption or HPV peptide vaccination alone.

- **Early biomarker discovery for ovarian cancer: PLCO and beyond.** Ovarian cancers are typically asymptomatic until advanced disease presents with high fatality rates. Ovarian Cancer SPORE programs (MD Anderson Cancer Center, PI, Robert Bast; Fred Hutchinson Cancer Research Center, PI, Nicole Urban; and Brigham and Women's Hospital, PI, Daniel Cramer) have been part of a collaboration with EDRN, evaluating biomarkers for screening and early detection and cancer remission markers. CA-125 has been the established marker for screening for diagnosis and remission of ovarian cancer in the clinic. The ovarian cancer segment of the Prostate, Lung, Colon, and Ovarian Cancer Screening Trial (PLCO) investigated whether screening for CA-125 plus ultrasound could identify ovarian cancer at earlier stages or decrease mortality. Although no significant changes were found between patients who were screened and those who received usual care, the biospecimens collected from the study have been used to identify additional markers. The top-performing early detection markers were CA-125, human epididymis protein 4 (HE-4), CA-72.4, and CA-15.3. The expression of HE-4 could be used as a second-line screen for ovarian cancer and may predict its remission after surgery and chemotherapy at an earlier point than does CA-125. Although additional panels of biomarkers were evaluated, none could improve upon the performance of CA-125 in either the phase 2 or the phase 3 setting. Other markers, as well as algorithms for timing of expression, have also been explored.
- **Germline SNPs in brain tumors relate to risk and heterogeneity.** Ongoing collaborations between the Mayo Clinic (PI, Brian O'Neil) and the University of California San Francisco (PI, Mitchel Berger) Brain Tumor SPOREs enable access to large study populations from both SPOREs to identify and validate SNPs related to risk, survival, and brain tumor type. By using SNP genotyping of more than 2,600 tumors, specific germline alterations were linked to different morphologic subtypes and histologic grades. Polymorphisms in 8q24 were associated

with oligodendroglial gliomas but not with GBM, whereas SNPs within or near the TERT (5p15), CDKN2A/B (9p21), and RTEL1 (20q13) regions were most strongly associated with GBM. A closer investigation of SNPs at 8q24 found significance in the rs55705857 SNP that was associated with astrocytic tumors with mutated *IDH1* or *IDH2* but not with wild-type *IDH1/2*. Further studies are needed to explore whether this SNP may encode a microRNA. SNPs can be monitored as valuable genetic and epidemiological markers to understand the development of gliomas.

- **Germline mutations in *HOXB13* are concomitant with prostate cancer risk.** In an inter-institutional collaborative pursuit of the genetic factors contributing to familial risk of prostate cancer, linkage analysis in combination with targeted massive parallel sequencing identified a recurrent mutation in *HOXB13* to be associated with early-onset and hereditary prostate cancer. This *HOXB13* mutation is the first gene to show significantly increased risk of familial prostate cancer. Although it is a rare genetic lesion, it provides new insight into the molecular pathways involved in prostate carcinogenesis.



SPORE PUBLICATIONS FROM 2007 TO 2012

FUTURE INITIATIVES

Following are descriptions of TRP initiatives planned for future years:

- Increase translational cancer research in organ sites that are underrepresented in the NCI portfolio: pancreas, bladder, sarcoma, and head and neck
- Increase research in organ sites that represent recalcitrant cancers (not represented above) where additional translational research is warranted: liver, esophagus, stomach, brain, ovary, lung, and myeloma
- Change cancer patient care, based on validated scientific studies, toward a more personalized approach to risk assessment, early detection, prognosis of outcome, and prediction of treatment options, including efficacy and toxicity
- Advance studies on the dynamic relationship between tumors and cells/mediators in the microenvironment to translational science to make a difference in the diagnosis and treatment of cancer
- Advance the goals of translational research by facilitating collaborations between SPOREs and other NCI-funded mechanisms such that discoveries can move quickly and seamlessly along pathways from the laboratory to phase 1 and phase 2 trials and beyond, with strong correlative study support

SELECTED PUBLICATIONS

CLINICAL/TRANSLATIONAL RESEARCH (GO GRANTS)

NFKBIA deletion in glioblastomas, Bredel M, Scholtens DM, Yadav AK, Alvarez AA, Renfrow JJ, Chandler JP, Yu IL, Carro MS, Dai F, Tagge MJ, Ferrarese R, Bredel C, Phillips HS, Lukac PJ, Robe PA, Weyerbrock A, Vogel H, Dubner S, Mobley B, He X, Scheck AC, Sikic BI, Aldape KD, Chakravarti A, Harsh GR 4th. *New England Journal of Medicine*, 2011;364(7):627–637.

<http://www.ncbi.nlm.nih.gov/pubmed/21175304>

- The authors hypothesized that deletion of NFKBIA (encoding nuclear factor of κ -light polypeptide gene enhancer in B cells inhibitor- α), an inhibitor of the EGFR signaling pathway, promotes tumorigenesis in glioblasto-

mas that do not have alterations of EGFR. They analyzed 790 human glioblastomas for deletions, mutations, or expression of NFKBIA and EGFR, studying the tumor suppressor activity of NFKBIA in tumor cell culture and .comparing the molecular results with the outcome of glioblastoma in 570 affected persons. They found that deletion of NFKBIA had an effect similar to that of EGFR amplification in the pathogenesis of glioblastoma and was associated with comparatively short survival.

Phase I trial of belinostat and bortezomib in patients with relapsed or refractory acute leukemia, myelodysplastic syndrome, or chronic myelogenous leukemia in blast crisis—one-year update, Holkova B, Bose P, Tombes MB, Shrader E, Wan W, Weir-Wiggins C, Stoddert E, Sankala H, Kmiecik M, Roberts JD, Garcia-Manero G, Grant S. *American Society of Hematology Annual Meeting Abstracts*, 2012; Abstract 3588.

<https://ash.confex.com/ash/2012/webprogram/Paper48266.html>

- The primary objective of this phase 1 trial was to determine the maximum tolerated dose (MTD) for bortezomib combined with belinostat in patients with relapsed or refractory acute leukemia, MDS, or chronic myelogenous leukemia in blast crisis. The combination was well tolerated and showed evidence of activity. As of the time of this study, the MTD had not been reached.

Effects of human oral mucosal tissue, saliva, and oral microflora on intraoral metabolism and bioactivation of black raspberry anthocyanins, Mallery SR, Budendorf DE, Larsen MP, Pei P, Tong M, Holpuch AS, Larsen PE, Stoner GD, Fields HW, Chan KK, Ling Y, Liu Z. *Cancer Prevention Research (Philadelphia)*, 2011;4(8):1209–1221.

<http://www.ncbi.nlm.nih.gov/pubmed/21558412>

- The authors sought to evaluate the levels and distribution of black raspberry anthocyanin-relevant metabolic enzymes in human oral tissues. Their data support the prospect that enteric recycling of anthocyanins occurs in the mouth and that inter-patient variations in the extent of this process could directly impact the effects of locally delivered chemopreventive agents.

Integrated NY-ESO-1 antibody and CD8+ T-cell responses correlate with clinical benefit in advanced melanoma patients treated with ipilimumab, Yuan J, Adamow M, Ginsberg BA, Rasalan TS, Ritter E, Gallardo HF, Xu Y, Pogoriler E, Terzulli SL, Kuk D, Panageas KS, Ritter G, Sznol



M, Halaban R, Jungbluth AA, Allison JP, Old LJ, Wolchok JD, Gnjatic S. Proceedings of the National Academy of Sciences of the United States of America, 2011;108(40):16723–16728. <http://www.ncbi.nlm.nih.gov/pubmed/21933959>

- Data from this study showed that, in patients with advanced metastatic melanoma who were seropositive for the NY-ESO-1 antigen, those with associated CD8(+) T cells experienced greater clinical benefit, including significant survival advantage, from treatment with ipilimumab than did those with undetectable CD8(+) T cell responses. These findings suggest that integrated NY-ESO-1 immune responses may have predictive value for ipilimumab treatment.

Immunologic correlates of the abscopal effect in a patient with melanoma, Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, Mu Z, Rasalan T, Adamow M, Ritter E, Sedrak C, Jungbluth AA, Chua R, Yang AS, Roman RA, Rosner S, Benson B, Allison JP, Lesokhin AM, Gnjatic S, Wolchok JD. New England Journal of Medicine, 2012;366(10):925–931.

<http://www.ncbi.nlm.nih.gov/pubmed/22397654>

- The authors report a case of the abscopal effect—a phenomenon in which local radiotherapy is associated with the regression of metastatic cancer at a distance from the irradiated site—in a patient with melanoma treated with ipilimumab and radiotherapy. Temporal associations were noted: tumor shrinkage with antibody responses to the cancer-testis antigen NY-ESO-1, changes in peripheral-blood immune cells, and increases in antibody responses to other antigens after radiotherapy.

BLADDER CANCER

Direct cytotoxicity produced by adenoviral-mediated interferon α gene transfer in interferon-resistant cancer cells involves ER stress and caspase 4 activation, Yang Z, Zhang XQ, Dinney CN, Benedict WF. Cancer Gene Therapy, 2011;18(6):609–616.

<http://www.ncbi.nlm.nih.gov/pubmed/21681220>

- This study showed that caspase 4 activation is an early molecular event following Ad-IFN α transfection of cancer cells, an observation confirmed in exfoliated bladder cancer cells from a patient undergoing intravesical Ad-IFN α /SYN3 treatment. Data indicate that Ad-IF-

N α -mediated activation of caspase 4 signals downstream activation of caspase 3 and that this in turn is an effector of subsequent cell death in bladder cancer cells.

BRAIN TUMORS

Effective radiotherapy for malignant gliomas by using oncolytic measles virus strains encoding the sodium iodide symporter (MV-NIS), Opyrchal M, Allen C, Iankov I, Aderca I, Schroeder M, Sarkaria J, Galanis E. Human Gene Therapy, 2012;23(4):419–427.

<http://www.ncbi.nlm.nih.gov/pubmed/22185260>

- This study demonstrated that measles virus strains that have been genetically engineered to express the human sodium iodide symporter have significant antitumor activity against glioma lines and orthotopic xenografts. This compares favorably with the measles virus strain expressing the human carcinoembryonic antigen, which is currently in clinical testing.

Human adenovirus type 5 induces cell lysis through autophagy and autophagy-triggered caspase activity, Jiang H, White EJ, Ríos-Vicil CI, Xu J, Gomez-Manzano C, Fueyo J. Journal of Virology, 2011;85(10):4720–4729.

<http://www.ncbi.nlm.nih.gov/pubmed/21367888>

- This study reports for the first time that autophagy plays a role in adenovirus-induced cell lysis. The findings implicate autophagy and caspase activation as part of the mechanism for cell lysis induced by adenovirus and suggests that manipulation of the process is a potential strategy to optimize the clinical efficacy of oncolytic adenoviruses.

Magnetic resonance of 2-hydroxyglutarate in IDH1-mutated low-grade gliomas, Elkhaled A, Jalbert LE, Phillips JJ, Yoshihara HA, Parvataneni R, Srinivasan R, Bourne G, Berger MS, Chang SM, Cha S, Nelson SJ. Science Translational Medicine, 2012;4(116):116ra5.

<http://www.ncbi.nlm.nih.gov/pubmed/22238333>

- The authors provide extensive characterization of mutant isocitrate dehydrogenase-1 (IDH1) lesions, using the nuclear magnetic resonance technique of proton high-resolution magic angle spinning spectroscopy, while confirming the potential diagnostic value of the potential oncometabolite D-2-hydroxyglutarate (2HG) as a surrogate marker of patient survival.

BREAST CANCER

Dynamic reprogramming of the kinome in response to targeted MEK inhibition in triple-negative breast cancer,

Duncan JS, Whittle MC, Nakamura K, Abell AN, Midland AA, Zawistowski JS, Johnson NL, Granger DA, Jordan NV, Darr DB, Usary J, Kuan PF, Smalley DM, Major B, He X, Hoadley KA, Zhou B, Sharpless NE, Perou CM, Kim WY, Gomez SM, Chen X, Jin J, Frye SV, Earp HS, Graves LM, Johnson GL. *Cell*, 2012;149(2):307–321.

<http://www.ncbi.nlm.nih.gov/pubmed/22500798>

- In this study, kinome activity was assessed in response to MEK inhibition in triple-negative breast cancer cells and genetically engineered mice. The inhibitor-induced RTK profile suggested a kinase inhibitor combination therapy that produced tumor apoptosis and regression in the mice where single agents were ineffective. This approach defines mechanisms of drug resistance, allowing rational design of combination therapies for cancer.

Transcriptional and posttranslational up-regulation of HER3 (ErbB3) compensates for inhibition of the HER2 tyrosine kinase, Garrett JT, Olivares MG, Rinehart C, Granja-Ingram ND, Sánchez V, Chakrabarty A, Dave B, Cook RS, Pao W, McKinely E, Manning HC, Chang J, Arteaga CL. *Proceedings of the National Academy of Sciences of the United States of America*, 2011;108(12):5021–5026.

<http://www.ncbi.nlm.nih.gov/pubmed/21385943>

- This study showed that, after inhibition of the HER2 tyrosine kinase with lapatinib, there is phosphatidylinositol 3-kinase (PI3K)/Akt- and FoxO3a-dependent upregulation of HER3 mRNA and protein. The results suggest that, because of HER3-mediated compensation, current clinical inhibitors of HER2 and PI3K/Akt will not completely block the PI3K pathway. They also suggest that therapeutic inhibitors of HER3 should be used in combination with HER2 inhibitors and PI3K pathway inhibitors in patients with HER2- and PI3K-dependent cancers.

CERVICAL CANCER

Capsomer vaccines protect mice from vaginal challenge with human papillomavirus, Wu WH, Gersch E, Kwak K, Jagu S, Karanam B, Huh WK, Garcea RL, Roden RB. *PLoS One* 2011;6(11):e27141.

<http://www.ncbi.nlm.nih.gov/pubmed/22069498>

- To design the next generation of human HPV vaccines, capsomers were produced in bacteria with HPV type 16 L1 peptide alone or linked with residues 13–47 of HPV-18, HPV-31, and HPV-45 L2 in tandem. In addition to HPV-16, the latter capsomer provided complete protection against HPV challenge in an experimental mouse model.

ENDOMETRIAL CANCER

High frequency of PIK3R1 and PIK3R2 mutations in endometrial cancer elucidates a novel mechanism for regulation of PTEN protein stability, Cheung LW, Hennessy BT, Li J, Yu S, Myers AP, Djordjevic B, Lu Y, Stemke-Hale K, Dyer MD, Zhang F, Ju Z, Cantley LC, Scherer SE, Liang H, Lu KH, Broaddus RR, Mills GB. *Cancer Discovery*, 2011;1(2):170–185.

<http://www.ncbi.nlm.nih.gov/pubmed/21984976>

- This study demonstrated that PI3K pathway aberrations occur in more than 80% of endometrioid endometrial cancers, and coordinate mutations of multiple PI3K pathway members are more common than predicted by chance.

GASTROINTESTINAL CANCERS

The pan-ErbB negative regulator Lrig1 is an intestinal stem cell marker that functions as a tumor suppressor, Powell AE, Wang Y, Li Y, Poulin EJ, Means AL, Washington MK, Higginbotham JN, Juchheim A, Prasad N, Levy SE, Guo Y, Shyr Y, Aronow BJ, Haigis KM, Franklin JL, Coffey RJ. *Cell*, 2012;149(1):146–158.

<http://www.ncbi.nlm.nih.gov/pubmed/22464327>

- Using lineage mapping, the authors showed that Lrig1, a pan-ErbB inhibitor, marks predominately noncycling, long-lived stem cells that are located at the crypt base and, upon injury, proliferate and divide to replenish damaged crypts. These results shed light on the relationship between proliferative and quiescent intestinal stem cells and support a model in which intestinal stem cell quiescence is maintained by calibrated ErbB signaling with loss of a negative regulator predisposing to neoplasia.

Genomic sequencing of colorectal adenocarcinomas identifies a recurrent VTI1A-TCF7L2 fusion, Bass AJ, Lawrence MS, Brace LE, Ramos AH, Drier Y, Cibulskis K, Sougnez C, Voet D, Saksena G, Sivachenko A, Jing R, Parkin M, Pugh T, Verhaak RG, Stransky N, Boutin AT, Barretina J, Solit



DB, Vakiani E, Shao W, Mishina Y, Warmuth M, Jimenez J, Chiang DY, Signoretti S, Kaelin WG, Spardy N, Hahn WC, Hoshida Y, Ogino S, Depinho RA, Chin L, Garraway LA, Fuchs CS, Baselga J, Taberero J, Gabriel S, Lander ES, Getz G, Meyerson M. *Nature Genetics*, 2011;43(10):964–968.

<http://www.ncbi.nlm.nih.gov/pubmed/21892161>

- This study reports the results of whole-genome sequencing from nine individuals with colorectal cancer, showing previously unidentified levels of genomic rearrangements in colorectal carcinoma that can lead to essential gene fusions and other oncogenic events. In particular, the discovery of recurrent VTI1A-TCF7L2 fusion in colorectal cancers highlights the functional importance of genomic rearrangements and other oncogenic events.

The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers, Diaz LA Jr, Williams RT, Wu J, Kinde I, Hecht JR, Berlin J, Allen B, Bozic I, Reiter JG, Nowak MA, Kinzler KW, Oliner KS, Vogelstein B. *Nature*, 2012;486(7404):537–540.

<http://www.ncbi.nlm.nih.gov/pubmed/22722843>

- The authors studied the development of acquired resistance in patients receiving monotherapy with panitumumab (anti-EGFR antibody). The results suggest that the emergence of KRAS mutations is a mediator of acquired resistance to EGFR blockade and that these mutations can be detected in a noninvasive manner, helping to explain why solid tumors develop resistance to targeted therapies.

HEAD AND NECK CANCER

The mutational landscape of head and neck squamous cell carcinoma, Stransky N, Egloff AM, Tward AD, Kostic AD, Cibulskis K, Sivachenko A, Kryukov GV, Lawrence MS, Sougnez C, McKenna A, Shefler E, Ramos AH, Stojanov P, Carter SL, Voet D, Cortés ML, Auclair D, Berger MF, Saksena G, Guiducci C, Onofrio RC, Parkin M, Romkes M, Weissfeld JL, Seethala RR, Wang L, Rangel-Escareño C, Fernandez-Lopez JC, Hidalgo-Miranda A, Melendez-Zajgla J, Winckler W, Ardlie K, Gabriel SB, Meyerson M, Lander ES, Getz G, Golub TR, Garraway LA, Grandis JR. *Science*, 2011;333(6046):1157–1160.

<http://www.ncbi.nlm.nih.gov/pubmed/21798893>

- To uncover the mutational spectrum of squamous cell head and neck cancer, the authors analyzed whole-exome sequencing data from 74 tumor-normal pairs. In addition to identifying previously known HNSCC genes, their analysis revealed many genes not previously implicated in this malignancy.

Phase II trial of pemetrexed and bevacizumab in patients with recurrent or metastatic head and neck cancer, Argiris A, Karamouzis MV, Gooding WE, Branstetter BF, Zhong S, Raez LE, Savvides P, Romkes M. *Journal of Clinical Oncology*, 2011;29(9):1140–1145.

<http://www.ncbi.nlm.nih.gov/pubmed/21343546>

- This phase 2 study demonstrated promising efficacy outcomes with the addition of bevacizumab to pemetrexed in patients with previously untreated, recurrent, or metastatic squamous cell head and neck cancer.

LEUKEMIA

Validation of ITD mutations in FLT3 as a therapeutic target in human acute myeloid leukaemia, Smith CC, Wang Q, Chin CS, Salerno S, Damon LE, Levis MJ, Perl AE, Travers KJ, Wang S, Hunt JP, Zarrinkar PP, Schadt EE, Kasarskis A, Kuriyan J, Shah NP. *Nature*, 2012;485(7397):260–263.

<http://www.ncbi.nlm.nih.gov/pubmed/22504184>

- The authors report point mutations at three residues within the kinase domain of internal tandem duplication mutations in FLT3-ITD that confer substantial in vitro resistance to AC220 (quizartinib), an active investigational inhibitor of FLT3, KIT, PDGFRA, PDGFRB, and RET.

Quantitative DNA methylation analysis identifies a single CpG dinucleotide important for ZAP-70 expression and predictive of prognosis in chronic lymphocytic leukemia, Claus R, Lucas DM, Stilgenbauer S, Ruppert AS, Yu L, Zucknick M, Mertens D, Bühler A, Oakes CC, Larson RA, Kay NE, Jelinek DF, Kipps TJ, Rassenti LZ, Gribben JG, Döhner H, Heerema NA, Marcucci G, Plass C, Byrd JC. *Journal of Clinical Oncology*, 2012;30(20):2483–2491.

<http://www.ncbi.nlm.nih.gov/pubmed/22564988>

- This study demonstrates that loss of methylation of a single dinucleotide in the ZAP-70 promoter is highly predictive of poor prognosis in patients with chronic lymphocytic leukemia.

LUNG CANCERS

Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing, Imielinski M, Berger AH, Hammerman PS, Hernandez B, Pugh TJ, Hodis E, Cho J, Suh J, Capelletti M, Sivachenko A, Sougnez C, Auclair D, Lawrence MS, Stojanov P, Cibulskis K, Choi K, de Waal L, Sharifnia T, Brooks A, Greulich H, Banerji S, Zander T, Seidel D, Leenders F, Ansén S, Ludwig C, Engel-Riedel W, Stoelben E, Wolf J, Goparju C, Thompson K, Winckler W, Kwiatkowski D, Johnson BE, Jänne PA, Miller VA, Pao W, Travis WD, Pass HI, Gabriel SB, Lander ES, Thomas RK, Garraway LA, Getz G, Meyerson M. *Cell*, 2012;150(6):1107–1120.

<http://www.ncbi.nlm.nih.gov/pubmed/22980975>

- In this study, exome and genome sequencing of lung adenocarcinoma tumor–normal DNA pairs revealed a mean exonic somatic mutation rate of 12.0 events per megabase and identified the majority of genes previously reported as significantly mutated in lung adenocarcinoma. The candidate genes identified are attractive targets for biological characterization and therapeutic targeting of lung adenocarcinoma.

Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer, Rudin CM, Durinck S, Stawiski EW, Poirier JT, Modrusan Z, Shames DS, Bergbower EA, Guan Y, Shin J, Guillory J, Rivers CS, Foo CK, Bhatt D, Stinson J, Gnad F, Haverty PM, Gentleman R, Chaudhuri S, Janakiraman V, Jaiswal BS, Parikh C, Yuan W, Zhang Z, Koeppen H, Wu TD, Stern HM, Yauch RL, Huffman KE, Paskulin DD, Illei PB, Varella-Garcia M, Gazdar AF, de Sauvage FJ, Bourgon R, Minna JD, Brock MV, Seshagiri S. *Nature Genetics*, 2012;44(10):1111–1116.

<http://www.ncbi.nlm.nih.gov/pubmed/22941189>

- Examining exome, transcriptome, and copy-number alteration data from primary human small-cell lung cancer (SCLC) and normal tissue pairs, the authors identified 22 significantly mutated genes in SCLC and found that several members of the SOX family of genes were mutated. SOX2 amplification was also found in more than one-quarter of the samples. These data provide an in-depth view of the spectrum of genomic alterations in SCLC and identify several potential targets for therapeutic intervention.

Identifying and targeting ROS1 gene fusions in non-small cell lung cancer, Davies KD, Le AT, Theodoro MF, Skokan MC, Aisner DL, Berge EM, Terracciano LM, Cappuzzo F, Incarbone M, Roncalli M, Alloisio M, Santoro A, Camidge DR, Varella-Garcia M, Doebele RC. *Clinical Cancer Research*, 2012;18(17):4570–4579.

<http://www.ncbi.nlm.nih.gov/pubmed/22919003>

- The authors showed that ROS1 inhibition may be an effective treatment strategy for the subset of patients with NSCLC whose tumors express ROS1 fusion genes.

Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers, Katayama R, Shaw AT, Khan TM, Mino-Kenudson M, Solomon BJ, Halmos B, Jessop NA, Wain JC, Yeo AT, Benes C, Drew L, Saeh JC, Crosby K, Sequist LV, Iafrate AJ, Engelman JA. *Science Translational Medicine*, 2012;4(120):120ra17.

<http://www.ncbi.nlm.nih.gov/pubmed/22277784>

- This study of lung cancer patients with acquired resistance to the ALK TKI crizotinib found a diverse array of secondary mutations distributed throughout the ALK tyrosine kinase domain, in addition to ALK gene amplification, aberrant activation of other kinases, and evidence of multiple resistance mechanisms developing simultaneously. These results highlight the unique features of TKI resistance in ALK-positive NSCLCs and provide the rationale for pursuing combinatorial therapeutics that are tailored to the precise resistance mechanisms identified in patients who relapse on crizotinib treatment.

Combined EGFR/MET or EGFR/HSP90 inhibition is effective in the treatment of lung cancers codriven by mutant EGFR containing T790M and MET, Xu L, Kikuchi E, Xu C, Ebi H, Ercan D, Cheng KA, Padera R, Engelman JA, Jänne PA, Shapiro GI, Shimamura T, Wong KK. *Cancer Research*, 2012;72(13):3302–3311.

<http://www.ncbi.nlm.nih.gov/pubmed/22552292>

- The authors developed a preclinical platform to evaluate potential therapies for NSCLC by generating transgenic mouse lung cancer models expressing EGFR-mutant Del19-T790M or L858R-T790M, each with concurrent MET overexpression. Finding that monotherapy targeting EGFR or MET alone did not produce significant tumor regression, they showed that combination therapies targeting EGFR and MET simultaneously were highly efficacious against EGFR TKI-resistant tumors codriv-



en by Del19-T790M or L858R-T790M and MET. These findings provide an in vivo model of intrinsic resistance to reversible TKIs and offer preclinical proof of principle that combination targeting of EGFR and MET may benefit patients with NSCLC.

LYMPHOMA

Elevated serum free light chains are associated with event-free and overall survival in two independent cohorts of patients with diffuse large B-cell lymphoma, Maurer MJ, Micallef IN, Cerhan JR, Katzmann JA, Link BK, Colgan JP, Habermann TM, Inwards DJ, Markovic SN, Ansell SM, Porrata LF, Johnston PB, Nowakowski GS, Thompson CA, Gupta M, Syrbu SI, Kurtin PJ, Macon WR, Nikcevich DA, Witzig TE. *Journal of Clinical Oncology*, 2011;29(12):1620–1626. <http://www.ncbi.nlm.nih.gov/pubmed/21383282>

- This study explored the association of pretreatment free light chains (FLC) with event-free and overall survival in patients with diffuse large B-cell lymphoma. The results indicated that increased serum FLC is an independent, adverse prognostic factor for event-free and overall survival and warrants further evaluation as a biomarker in this cancer.

Cytotoxic T lymphocytes simultaneously targeting multiple tumor-associated antigens to treat EBV negative lymphoma, Gerdemann U, Katari U, Christin AS, Cruz CR, Tripic T, Rousseau A, Gottschalk SM, Savoldo B, Vera JE, Heslop HE, Brenner MK, Bollard CM, Rooney CM, Leen AM. *Molecular Therapy*, 2011;19(12):2258–2268. <http://www.ncbi.nlm.nih.gov/pubmed/21915103>

- The authors developed an approach to obtain a lymphoma patient's cytotoxic T cells and train these T cells to recognize an array of nonvirus tumor-specific antigens. Using multiple tumor-specific antigens and including pro-survival and pro-proliferative cytokines, investigators generated autologous T cells that targeted self antigens. These studies support the future use of such autologous cytotoxic T cells for the treatment of patients with EBV-negative lymphoma.

MYELOMA

Targeting the insulin-like growth factor-1 receptor to overcome bortezomib resistance in preclinical models of multiple myeloma, Kuhn DJ, Berkova Z, Jones RJ, Woessner R,

Bjorklund CC, Ma W, Davis RE, Lin P, Wang H, Madden TL, Wei C, Baladandayuthapani V, Wang M, Thomas SK, Shah JJ, Weber DM, Orlowski RZ. *Blood*, 2012;120(16):3260–3270. <http://www.ncbi.nlm.nih.gov/pubmed/22932796>

- This study showed that signaling through the IGF-1/IGF-1R axis contributes to acquired bortezomib resistance in multiple myeloma. The findings provide a rationale for combining bortezomib with IGF-1R inhibitors like OSI-906 to overcome or possibly prevent the emergence of bortezomib-refractory disease in the clinic.

A small molecule inhibitor of ubiquitin-specific protease-7 induces apoptosis in multiple myeloma cells and overcomes bortezomib resistance, Chauhan D, Tian Z, Nicholson B, Kumar KG, Zhou B, Carrasco R, McDermott JL, Leach CA, Fulciniti M, Kodrasov MP, Weinstock J, Kingsbury WD, Hideshima T, Shah PK, Minvielle S, Altun M, Kessler BM, Orlowski R, Richardson P, Munshi N, Anderson KC. *Cancer Cell*, 2011;22(3):345–358. <http://www.ncbi.nlm.nih.gov/pubmed/22975377>

- The authors show that P5091 is an inhibitor of deubiquitylating enzyme USP7, which induces apoptosis in multiple myeloma cells resistant to conventional and bortezomib therapies. This preclinical study supports the clinical evaluation of USP7 inhibitor, alone or in combination, as a potential therapy for multiple myeloma.

Lenalidomide after stem-cell transplantation for multiple myeloma, McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, Giral S, Stadtmauer EA, Weisdorf DJ, Vij R, Moreb JS, Callander NS, Van Besien K, Gentile T, Isola L, Maziarz RT, Gabriel DA, Bashey A, Landau H, Martin T, Qazilbash MH, Levitan D, McClune B, Schlossman R, Hars V, Postiglione J, Jiang C, Bennett E, Barry S, Bressler L, Kelly M, Seiler M, Rosenbaum C, Hari P, Pasquini MC, Horowitz MM, Shea TC, Devine SM, Anderson KC, Linker C. *New England Journal of Medicine*, 2012;366(19):1770–1781. <http://www.ncbi.nlm.nih.gov/pubmed/22571201>

- This randomized clinical trial was carried out to investigate whether lenalidomide maintenance therapy prolongs the time to disease progression after stem cell transplantation in patients with multiple myeloma. Compared with placebo, lenalidomide was associated with more toxicity and second cancers but a significantly longer time to disease progression and significantly improved overall survival.

OVARIAN CANCER

Biological roles of the Delta family Notch ligand Dll4 in tumor and endothelial cells in ovarian cancer, Hu W, Lu C, Dong HH, Huang J, Shen DY, Stone RL, Nick AM, Shahzad MM, Mora E, Jennings NB, Lee SJ, Roh JW, Matsuo K, Nishimura M, Goodman BW, Jaffe RB, Langley RR, Deavers MT, Lopez-Berestein G, Coleman RL, Sood AK. *Cancer Research*, 2011;71(18):6030–6039.
<http://www.ncbi.nlm.nih.gov/pubmed/21795478>

- The authors investigated the clinical and biological significance of Dll4 in ovarian cancer. Their findings establish that Dll4 plays a functionally important role in both the tumor and endothelial compartments of ovarian cancer and that targeting Dll4 in combination with anti-VEGF treatment might improve outcomes of ovarian cancer treatment.

Programmable bio-nano-chip systems for serum CA125 quantification: toward ovarian cancer diagnostics at the point-of-care, Raamanathan A, Simmons GW, Christodoulides N, Floriano PN, Furmaga WB, Redding SW, Lu KH, Bast RC Jr, McDevitt JT. *Cancer Prevention Research (Philadelphia)*, 2012;5(5):706–716.
<http://www.ncbi.nlm.nih.gov/pubmed/22490510>

- This paper describes the adaptation of the programmable bionanochip (p-BNC), an integrated, microfluidic, and modular (programmable) platform, for CA125 serum quantitation. Screening patients for ovarian cancer can be achieved in 30 minutes with blood from a finger stick and this nanotechnology.

PANCREATIC CANCER

Oncogenic Kras is required for both the initiation and maintenance of pancreatic cancer in mice, Collins MA, Bednar F, Zhang Y, Brisset JC, Galbán S, Galbán CJ, Rakshit S, Flannagan KS, Adsay NV, Pasca di Magliano M. *Journal of Clinical Investigation*, 2012;122(2):639–653.
<http://www.ncbi.nlm.nih.gov/pubmed/22232209>

- The authors generated two transgenic mouse models of pancreatic tumorigenesis, showing that oncogenic KRAS played a key role in the early stages of tumor development, during tumor maintenance, and in metastasis of pancreatic cancer. The data suggest that KRAS is required at all stages of pancreatic carcinogenesis and that targeting

KRAS or its downstream signaling pathway could have a therapeutic effect, but prolonged use could result in acquired resistance in pancreatic cancer.

Metastatic pancreatic cancer is dependent on oncogenic Kras in mice, Collins MA, Brisset JC, Zhang Y, Bednar F, Pierre J, Heist KA, Galbán CJ, Galbán S, di Magliano MP. *PLoS One*, 2012;7(12):e49707.
<http://www.ncbi.nlm.nih.gov/pubmed/23226501>

- These investigators describe a new model of metastatic pancreatic adenocarcinoma based on pancreas-specific, inducible and reversible expression of an oncogenic form of Kras, together with pancreas-specific expression of a mutant form of the tumor suppressor p53. The data identify Kras* as a key oncogene in pancreatic cancer maintenance but raises the possibility of acquired resistance should Kras inhibitors become available for use in pancreatic cancer.

Computational modeling of pancreatic cancer reveals kinetics of metastasis suggesting optimum treatment strategies, Haeno H, Gonen M, Davis MB, Herman JM, Iacobuzio-Donahue CA, Michor F. *Cell*, 2012;148(1-2):362–375.
<http://www.ncbi.nlm.nih.gov/pubmed/22265421>

- Investigators used a stochastic mathematical model to study the progression and metastasis of pancreatic cancer. With the help of the model, they predicted mutation rate, metastasis rate, epigenetic alteration, and risk of harboring metastasis. This interdisciplinary model provides insight into the dynamics of pancreatic cancer and its metastasis.

The deubiquitinase USP9X suppresses pancreatic ductal adenocarcinoma, Pérez-Mancera PA, Rust AG, van der Weyden L, Kristiansen G, Li A, Sarver AL, Silverstein KA, Grützmann R, Aust D, Rümmele P, Knösel T, Herd C, Stemple DL, Kettleborough R, Brosnan JA, Li A, Morgan R, Knight S, Yu J, Stegeman S, Collier LS, ten Hoeve JJ, de Ridder J, Klein AP, Goggins M, Hruban RH, Chang DK, Biankin AV, Grimmond SM; Australian Pancreatic Cancer Genome Initiative, Wessels LF, Wood SA, Iacobuzio-Donahue CA, Pilarsky C, Largaespada DA, Adams DJ, Tuveson DA. *Nature*, 2012;486(7402):266–270.
<http://www.ncbi.nlm.nih.gov/pubmed/22699621>

- The authors used Sleeping Beauty transposon-mediated insertional mutagenesis in a mouse model of pancreatic



ductal preneoplasia to identify genes that cooperate with oncogenic Kras(G12D) to accelerate tumorigenesis and promote progression. Their screen revealed new candidate genes for pancreatic ductal adenocarcinoma and confirmed the importance of many previously implicated genes and pathways.

A lethally irradiated allogeneic granulocyte-macrophage colony stimulating factor-secreting tumor vaccine for pancreatic adenocarcinoma: a phase II trial of safety, efficacy, and immune activation, Lutz E, Yeo CJ, Lillemoe

KD, Biedrzycki B, Kobrin B, Herman J, Sugar E, Piantadosi S, Cameron JL, Solt S, Onners B, Tartakovsky I, Choi M, Sharma R, Illei PB, Hruban RH, Abrams RA, Le D, Jaffee E, Laheru D. *Annals of Surgery*, 2011;253(2):328–335.

<http://www.ncbi.nlm.nih.gov/pubmed/21217520>

- This study was carried out to test the safety and efficacy of a GM-CSF–based immunotherapy administered in patients with resected pancreatic adenocarcinoma. Results show that an immunotherapy approach integrated with chemoradiation is safe and demonstrates an overall survival that compares favorably with published data for resected pancreas cancer.

PROSTATE CANCER

Therapeutic targeting of SPINK1-positive prostate cancer, Ateeq B, Tomlins SA, Laxman B, Asangani IA, Cao Q, Cao X, Li Y, Wang X, Feng FY, Pienta KJ, Varambally S, Chinnaiyan AM. *Science Translational Medicine*, 2011;3(72):72ra17.

<http://www.ncbi.nlm.nih.gov/pubmed/21368222>

- This study identified SPINK1 as an extracellular therapeutic target for an aggressive subtype of prostate cancer. Using preclinical models, the authors demonstrated the therapeutic potential of monoclonal antibody to SPINK1. They also showed that SPINK1 mediates its oncogenic effects in part through EGFR and that a monoclonal antibody to EGFR shows activity in SPINK1+ prostate cancer.

Distinct transcriptional programs mediated by the ligand-dependent full-length androgen receptor and its splice variants in castration-resistant prostate cancer, Hu R, Lu C, Mostaghel EA, Yegnasubramanian S, Gurel M, Tannahill C, Edwards J, Isaacs WB, Nelson PS, Blum E, Plymate SR, Luo J. *Cancer Research*, 2012;72(14):3457–3462.

<http://www.ncbi.nlm.nih.gov/pubmed/22710436>

- In this study, suppression of ligand-mediated AR-FL signaling by targeting the AR ligand-binding domain led to increased AR-V expression in two cell line models of castration-resistant prostate cancer. The findings support an adaptive shift toward AR-V–mediated signaling in a subset of castration-resistant prostate cancer tumors as the AR ligand-binding domain is rendered inactive, suggesting an important mechanism contributing to drug resistance.

EZH2 oncogenic activity in castration-resistant prostate cancer cells is Polycomb independent, Xu K, Wu ZJ, Groner

AC, He HH, Cai C, Lis RT, Wu X, Stack EC, Loda M, Liu T, Xu H, Cato L, Thornton JE, Gregory RI, Morrissey C, Vessella RL, Montironi R, Magi-Galluzzi C, Kantoff PW, Balk SP, Liu XS, Brown M. *Science*, 2012;338(6113):1465–1469.

<http://www.ncbi.nlm.nih.gov/pubmed/23239736>

- The authors found that EZH2 expresses its oncogenic function through co-activation of critical transcription factors, including AR. This functional switch is dependent on phosphorylation of EZH2 and requires an intact methyltransferase domain. Hence, targeting the non-PRC2 function of EZH2 may have therapeutic efficacy for treating metastatic, hormone-refractory prostate cancer.

Treatment-induced damage to the tumor microenvironment promotes prostate cancer therapy resistance through WNT16B, Sun Y, Campisi J, Higano C, Beer TM, Porter P, Coleman I, True L, Nelson PS. *Nature Medicine*, 2012;18(9):1359–1368.

<http://www.ncbi.nlm.nih.gov/pubmed/22863786>

- Using a genome-wide analysis of transcriptional responses to genotoxic cancer therapeutics, investigators identified a spectrum of secreted proteins derived from the tumor microenvironment that included WNT16B, whose expression in the prostate tumor microenvironment attenuated the effects of cytotoxic chemotherapy, promoting tumor cell survival and disease progression.

Clusterin inhibition using OGX-011 synergistically enhances Hsp90 inhibitor activity by suppressing the heat shock response in castrate-resistant prostate cancer, Lamoureux F, Thomas C, Yin MJ, Kuruma H, Beraldi E, Fazli L, Zoubeidi A, Gleave ME. (*Cancer Research*, 2011;71(17):5838–5849.

<http://www.ncbi.nlm.nih.gov/pubmed/21737488>

- OGX-011, an antisense drug that targets clusterin, potentiated the efficiency of Hsp90 inhibitors by suppressing the heat shock response in castration-resistant prostate cancer, leading to an 80% inhibition of tumor growth with prolonged survival. These preclinical findings demonstrate that Hsp90 inhibitor-induced activation of the heat shock response and clusterin can be attenuated by antisense treatment, leading to delayed progression of castration-resistant prostate cancer.

The mutational landscape of lethal castration-resistant prostate cancer, Grasso CS, Wu YM, Robinson DR, Cao X, Dhanasekaran SM, Khan AP, Quist MJ, Jing X, Lonigro RJ, Brenner JC, Asangani IA, Ateeq B, Chun SY, Siddiqui J, Sam L, Anstett M, Mehra R, Prensner JR, Palanisamy N, Ryslik GA, Vandin F, Raphael BJ, Kunju LP, Rhodes DR, Pienta KJ, Chinnaiyan AM, Tomlins SA. *Nature*, 2012;487(7406):239–243. <http://www.ncbi.nlm.nih.gov/pubmed/22722839>

- Integrated exome-based profiling of the mutational landscape of metastatic tumors from patients with castration-resistant prostate cancer identified a diverse series of potential driver mutations and copy number alterations in both known and novel genes. This study also confirmed the clonal nature of metastatic disease.

Personalized oncology through integrative high-throughput sequencing: a pilot study, Roychowdhury S, Iyer MK, Robinson DR, Lonigro RJ, Wu YM, Cao X, Kalyana-Sundaram S, Sam L, Balbin OA, Quist MJ, Barrette T, Everett J, Siddiqui J, Kunju LP, Navone N, Araujo JC, Troncoso P, Logothetis CJ, Innis JW, Smith DC, Lao CD, Kim SY, Roberts JS, Gruber SB, Pienta KJ, Talpaz M, Chinnaiyan AM. *Science Translational Medicine*, 2011;3(111):111ra21. <http://www.ncbi.nlm.nih.gov/pubmed/22133722>

- This paper reports on a pilot effort to implement biomarker-based personalized oncology through integrative high-throughput sequencing. Tumors of individual patients with advanced refractory cancer were extensively evaluated with whole-genome sequencing and transcriptome sequencing (RNA-Seq) to identify potentially informative and actionable mutations. Several mutations, including structural rearrangements, copy number alterations, point mutations, and gene expression alterations, were found.

RENAL CANCER

Genetic and functional studies implicate HIF1 α as a 14q kidney cancer suppressor gene, Shen C, Beroukhi R, Schumacher SE, Zhou J, Chang M, Signoretti S, Kaelin WG Jr. *Cancer Discovery*, 2011;1(3):222–235. <http://www.ncbi.nlm.nih.gov/pubmed/22037472>

- This study identified focal homozygous deletions of the HIF-1 α locus on 14q in clear-cell carcinoma and found that all somatic HIF-1 α mutations that were identified in kidney cancers resulted in a loss of function. The results of this study show that HIF-1 α has the credentials of a kidney cancer suppressor gene and that its loss of function portends a poor prognosis.

SARCOMA

A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites, Errani C, Zhang L, Sung YS, Hajdu M, Singer S, Maki RG, Healey JH, Antonescu CR. *Genes Chromosomes Cancer*, 2011;50(8):644–653. <http://www.ncbi.nlm.nih.gov/pubmed/21584898>

- The authors report a new gene fusion product (WWTR1-CAMTA1) that is present in rare tumors called epithelioid hemangioendothelioma. The lesion occurs in specimens from bones, soft tissue, and visceral locations such as lung and liver. This finding has the potential to improve the diagnostics in histologically uncertain cases.

SKIN CANCER

Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion, Straussman R, Morikawa T, Shee K, Barzily-Rokni M, Qian ZR, Du J, Davis A, Mongare MM, Gould J, Frederick DT, Cooper ZA, Chapman PB, Solit DB, Ribas A, Lo RS, Flaherty KT, Ogino S, Wargo JA, Golub TR. *Nature*, 2012;487(7408):500–504. <http://www.ncbi.nlm.nih.gov/pubmed/22763439>

- Proposing that the tumor microenvironment confers innate resistance to therapy, these investigators developed a co-culture system to systematically assay the ability of 23 stromal cell types to influence the innate resistance of 45 cancer cell lines to 35 anticancer drugs. They found a significant correlation between innate resistance and the secretion of hepatocyte growth factor by stromal cells.



The results suggest RAF plus HGF or MET inhibitory combination therapy is a potential therapeutic strategy for BRAF-mutant melanoma.

Proinvasion metastasis drivers in early-stage melanoma are oncogenes, Scott KL, Nogueira C, Heffernan TP, van Doorn R, Dhakal S, Hanna JA, Min C, Jaskelioff M, Xiao Y, Wu CJ, Cameron LA, Perry SR, Zeid R, Feinberg T, Kim M, Vande Woude G, Granter SR, Bosenberg M, Chu GC, DePinho RA, Rimm DL, Chin L. *Cancer Cell*, 2011;20(1):92–103. <http://www.ncbi.nlm.nih.gov/pubmed/21741599>

- These investigators integrated genetically engineered mouse models, comparative oncogenomics, and functional genomics and identified six genes that were capable of driving invasion and transformation in early-stage melanomas. They also showed that one proinvasion oncogene, ACP5, confers spontaneous metastasis *in vivo*, engages a key pathway governing metastasis, and is prognostic in human primary melanomas.

Exome sequencing identifies recurrent somatic RAC1 mutations in melanoma, Krauthammer M, Kong Y, Ha BH, Evans P, Bacchicchi A, McCusker JP, Cheng E, Davis MJ, Goh G, Choi M, Ariyan S, Narayan D, Dutton-Regester K, Capatana A, Holman EC, Bosenberg M, Sznol M, Kluger HM, Brash DE, Stern DF, Materin MA, Lo RS, Mane S, Ma S, Kidd KK, Hayward NK, Lifton RP, Schlessinger J, Boggon TJ, Halaban R. *Nature Genetics*, 2012;44(9):1006–1014. <http://www.ncbi.nlm.nih.gov/pubmed/22842228>

- The authors characterized the mutational landscape by exome sequencing of 147 melanomas and identified a recurrent ultraviolet-signature, somatic RAC1 mutation (RAC1P29S) in 9.1% of sun-exposed melanomas. Their data suggest that pharmacological inhibition of RAC1 might be of therapeutic benefit in the treatment of melanomas.

THE CANCER GENOME ATLAS

Comprehensive molecular portraits of human breast tumours, Cancer Genome Atlas Network. *Nature*, 2012;490(7418):61–70. <http://www.ncbi.nlm.nih.gov/pubmed/23000897>

- TCGA collaborators analyzed primary breast cancers by genomic DNA copy number arrays, DNA methylation, exome sequencing, messenger RNA arrays, microRNA sequencing, and reverse-phase protein arrays. The inves-

tigators' ability to integrate information across platforms provided key insights into previously defined gene expression subtypes and demonstrated the existence of four main breast cancer classes when combining data from five platforms, each of which shows significant molecular heterogeneity. This finding raises the hypothesis that much of the clinically observable plasticity and heterogeneity occurs within, and not across, these major biological subtypes of breast cancer.

Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma, Noushmehr H, Weisenberger DJ, Diefes K, Phillips HS, Pujara K, Berman BP, Pan F, Pelloski CE, Sulman EP, Bhat KP, Verhaak RG, Hoadley KA, Hayes DN, Perou CM, Schmidt HK, Ding L, Wilson RK, Van Den Berg D, Shen H, Bengtsson H, Neuvial P, Cope LM, Buckley J, Herman JG, Baylin SB, Laird PW, Aldape K; Cancer Genome Atlas Research Network. *Cancer Cell*, 2010;17(5):510–522.

<http://www.ncbi.nlm.nih.gov/pubmed/20399149>

- These investigators profiled alterations in promoter DNA methylation in 272 glioblastoma tumors in the context of The Cancer Genome Atlas (TCGA). Their findings indicate the existence of a glioma-CpG island methylator phenotype as a distinct subset of human gliomas on molecular and clinical grounds.

EARLY DETECTION RESEARCH NETWORK

Unlocking biomarker discovery: large-scale application of aptamer proteomic technology for early detection of lung cancer, Ostroff RM, Bigbee WL, Franklin W, Gold L, Mehan M, Miller YE, Pass HI, Rom WN, Siegfried JM, Stewart A, Walker JJ, Weissfeld JL, Williams S, Zichi D, Brody EN. *PLoS One*, 2010;5(12):e15003.

<http://www.ncbi.nlm.nih.gov/pubmed/21170350>

- This comprehensive clinical biomarker study of lung cancer is the first large-scale clinical application of a new aptamer-based proteomic technology to discover blood protein biomarkers. The investigators measured 813 proteins in archived serum samples from four independent studies of NSCLC in long-term tobacco-exposed populations. They identified 44 candidate biomarkers and developed a 12-protein panel that discriminates NSCLC from controls with high sensitivity and specificity. The study provides a solid foundation to develop tests to identify early stage lung cancer.

COLLABORATIONS WITH THE NCI INTRAMURAL PROGRAM

Exome sequencing identifies *GRIN2A* as frequently mutated in melanoma, Wei X, Walia V, Lin JC, Teer JK, Prickett TD, Gartner J, Davis S; NISC Comparative Sequencing Program, Stemke-Hale K, Davies MA, Gershenwald JE, Robinson W, Robinson S, Rosenberg SA, Samuels Y. *Nature Genetics*, 2011;43(5):442–446.

<http://www.ncbi.nlm.nih.gov/pubmed/21499247>

- To systematically analyze genetic alterations in melanoma, these investigators performed exome sequencing of 14 matched normal and metastatic tumor DNAs and identified somatic mutations in 68 genes. The study identified recurring genetic alterations in the *TRRAP* gene and revealed that *GRIN2A* (glutamine signaling pathway) was mutated in 33% of melanoma samples.

OTHER COLLABORATIVE STUDIES

Discovery and prioritization of somatic mutations in diffuse large B-cell lymphoma (DLBCL) by whole-exome sequencing, Lohr JG, Stojanov P, Lawrence MS, Auclair D, Chapuy B, Sougnez C, Cruz-Gordillo P, Knoechel B, Asmann YW, Slager SL, Novak AJ, Dogan A, Ansell SM, Link BK, Zou L, Gould J, Saksena G, Stransky N, Rangel-Escareño C, Fernandez-Lopez JC, Hidalgo-Miranda A, Melendez-Zajgla J, Hernández-Lemus E, Schwarz-Cruz y Celis A, Imaz-Rosshandler I, Ojesina AI, Jung J, Pedamallu CS, Lander ES, Habermann TM, Cerhan JR, Shipp MA, Getz G, Golub TR. *Proceedings of the National Academy of Sciences of the United States of America*, 2012;109(10):3879–3884.

<http://www.ncbi.nlm.nih.gov/pubmed/22343534>

- To gain insight into the genomic basis of diffuse large B-cell lymphoma, these investigators performed massively parallel whole-exome sequencing of 55 primary tumor samples and matched normal tissue. They identified recurrent mutations in genes that are well known to be functionally relevant in this cancer. Their data provide an unbiased view of the landscape of mutations in diffuse large B-cell lymphoma, and this in turn may point toward new therapeutic strategies for the disease.

Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes, Biankin AV, Waddell N, Kassahn KS, Gingras MC, Muthuswamy LB, Johns AL, Miller DK, Wilson PJ, Patch AM, Wu J, Chang DK, Cowley MJ, Gardiner

BB, Song S, Harliwong I, Idrisoglu S, Nourse C, Nourbakhsh E, Manning S, Wani S, Gongora M, Pajic M, Scarlett CJ, Gill AJ, Pinho AV, Rooman I, Anderson M, Holmes O, Leonard C, Taylor D, Wood S, Xu Q, Nones K, Fink JL, Christ A, Bruxner T, Cloonan N, Kolle G, Newell F, Pinese M, Mead RS, Humphris JL, Kaplan W, Jones MD, Colvin EK, Nagrial AM, Humphrey ES, Chou A, Chin VT, Chantrill LA, Mawson A, Samra JS, Kench JG, Lovell JA, Daly RJ, Merrett ND, Toon C, Epari K, Nguyen NQ, Barbour A, Zeps N; Australian Pancreatic Cancer Genome Initiative, Kakkar N, Zhao F, Wu YQ, Wang M, Muzny DM, Fisher WE, Brunnicardi FC, Hodges SE, Reid JG, Drummond J, Chang K, Han Y, Lewis LR, Dinh H, Buhay CJ, Beck T, Timms L, Sam M, Begley K, Brown A, Pai D, Panchal A, Buchner N, De Borja R, Denroche RE, Yung CK, Serra S, Onetto N, Mukhopadhyay D, Tsao MS, Shaw PA, Petersen GM, Gallinger S, Hruban RH, Maitra A, Iacobuzio-Donahue CA, Schlick RD, Wolfgang CL, Morgan RA, Lawlor RT, Capelli P, Corbo V, Scardoni M, Tortora G, Tempero MA, Mann KM, Jenkins NA, Perez-Mancera PA, Adams DJ, Largaespada DA, Wessels LF, Rust AG, Stein LD, Tuveson DA, Copeland NG, Musgrove EA, Scarpa A, Eshleman JR, Hudson TJ, Sutherland RL, Wheeler DA, Pearson JV, McPherson JD, Gibbs RA, Grimmond SM. *Nature*, 2012;491(7424):399–405.

<http://www.ncbi.nlm.nih.gov/pubmed/23103869>

- These investigators performed exome sequencing and copy number analysis to define genomic aberrations in patients with early-stage sporadic pancreatic ductal adenocarcinoma. Their analysis revealed novel mutated genes and provides further supportive evidence for the potential involvement of axon guidance genes in pancreatic carcinogenesis.

EGF receptor is required for *KRAS*-induced pancreatic tumorigenesis, Ardito CM, Grüner BM, Takeuchi KK, Lubeseder-Martellato C, Teichmann N, Mazur PK, Delgiorno KE, Carpenter ES, Halbros CJ, Hall JC, Pal D, Briel T, Herner A, Trajkovic-Arsic M, Sipos B, Liou GY, Storz P, Murray NR, Threadgill DW, Sibilina M, Washington MK, Wilson CL, Schmid RM, Raines EW, Crawford HC, Siveke JT. *Cancer Cell*, 2012;22(3):304–317.

<http://www.ncbi.nlm.nih.gov/pubmed/22975374>

- In mouse models, using genetic and pharmacological approaches, the investigators showed that oncogenic *KRAS* upregulated *EGFR* expression and activation. Pharmacological inhibition or genetic ablation of *EGFR* or its ligand (*ADAM17*) eliminated *KRAS*-driven tumori-



genesis. These results indicate that without EGFR activity, active RAS levels are not sufficient to induce robust MEK/ERK activity, a requirement for epithelial transformation.

Imatinib potentiates antitumor T cell responses in gastrointestinal stromal tumor through the inhibition of

Ido, Balachandran VP, Cavnar MJ, Zeng S, Bamboat ZM, Ocuin LM, Obaid H, Sorenson EC, Popow R, Ariyan C, Rossi F, Besmer P, Guo T, Antonescu CR, Taguchi T, Yuan J, Wolchok JD, Allison JP, DeMatteo RP. *Nature Medicine*, 2011;17(9):1094–1100.

<http://www.ncbi.nlm.nih.gov/pubmed/21873989>

- Using a mouse model of spontaneous gastrointestinal stromal tumor, the authors found that T cells are crucial to the antitumor effects of imatinib in this cancer, suggesting that concomitant immunotherapy may further improve outcomes in human cancers treated with targeted agents.

Control of cervicovaginal HPV-16 E7-expressing tumors by the combination of therapeutic HPV vaccination and vascular disrupting agents, Zeng Q, Peng S, Monie A, Yang M, Pang X, Hung CF, Wu TC. *Human Gene Therapy*, 2011;22(7):809–819.

<http://www.ncbi.nlm.nih.gov/pubmed/21128743>

- The authors tested the combination of 5,6-dimethylx-anthenone-4-acetic acid (DMXAA) treatment with therapeutic HPV-16 E7 peptide-based vaccination for their ability to generate E7-specific CD8+ T-cell immune responses, as well as to control E7-expressing tumors in a subcutaneous and a cervicovaginal tumor model. The resulting data demonstrated that administration of DMXAA enhances therapeutic HPV vaccine-induced cytotoxic T-lymphocyte responses and antitumor effects against E7-expressing tumors in two different locations.

Ovarian cancer biomarker performance in prostate, lung, colorectal, and ovarian cancer screening trial specimens,

Cramer DW, Bast RC Jr, Berg CD, Diamandis EP, Godwin AK, Hartge P, Lokshin AE, Lu KH, McIntosh MW, Mor G, Patriotic C, Pinsky PF, Thornquist MD, Scholler N, Skates SJ, Sluss PM, Srivastava S, Ward DC, Zhang Z, Zhu CS, Urban N. *Cancer Prevention Research (Philadelphia)*, 2011;4(3):365–374.

<http://www.ncbi.nlm.nih.gov/pubmed/21372036>

- The ovarian cancer segment of the Prostate, Lung, Colon, and Ovarian Cancer (PLCO) screening trial investigated whether screening for CA-125 plus ultrasound could identify ovarian cancer at earlier stages or decrease mortality. Although additional panels of biomarkers were evaluated, none could improve upon the performance of CA-125 in either the phase 2 or the phase 3 setting.

Potential role of HE4 in multimodal screening for epithelial ovarian cancer,

Urban N, Thorpe JD, Bergan LA, Forrest RM, Kampani AV, Scholler N, O'Briant KC, Anderson GL, Cramer DW, Berg CD, McIntosh MW, Hartge P, Drescher CW. *Journal of the National Cancer Institute*, 2011;103(21):1630–1634.

<http://www.ncbi.nlm.nih.gov/pubmed/21917606>

- Evaluating a number of serum markers specific for malignancy, the authors found that HE4 performed better than transvaginal ultrasound as a second-line screen in subjects from the PLCO screening trial. A longitudinal algorithm might further improve the performance of HE4.

A low-frequency variant at 8q24.21 is strongly associated with risk of oligodendroglial tumors and astrocytomas with IDH1 or IDH2 mutation,

Jenkins RB, Xiao Y, Sicotte H, Decker PA, Kollmeyer TM, Hansen HM, Kosel ML, Zheng S, Walsh KM, Rice T, Bracci P, McCoy LS, Smirnov I, Patoka JS, Hsuang G, Wiemels JL, Tihan T, Pico AR, Prados MD, Chang SM, Berger MS, Caron AA, Fink SR, Halder C, Rynearson AL, Fridley BL, Buckner JC, O'Neill BP, Giannini C, Lachance DH, Wiencke JK, Eckel-Passow JE, Wrensch MR. *Nature Genetics*, 2012;44(10):1122–1125.

<http://www.ncbi.nlm.nih.gov/pubmed/22922872>

- The authors used tag SNP genotyping and imputation, pooled next-generation sequencing with long-range polymerase chain reaction, and subsequent validation to identify seven low-frequency SNPs at 8q24.21 that were strongly associated with glioma risk.

Germline mutations in HOXB13 and prostate-cancer risk,

Ewing CM, Ray AM, Lange EM, Zuhlke KA, Robbins CM, Tembe WD, Wiley KE, Isaacs SD, Johng D, Wang Y, Bizon C, Yan G, Gielzak M, Partin AW, Shanmugam V, Izatt T, Sinari S, Craig DW, Zheng SL, Walsh PC, Montie JE, Xu J, Carpten JD, Isaacs WB, Cooney KA. *New England Journal of Medicine*, 2012;366(2):141–149.

<http://www.ncbi.nlm.nih.gov/pubmed/22236224>

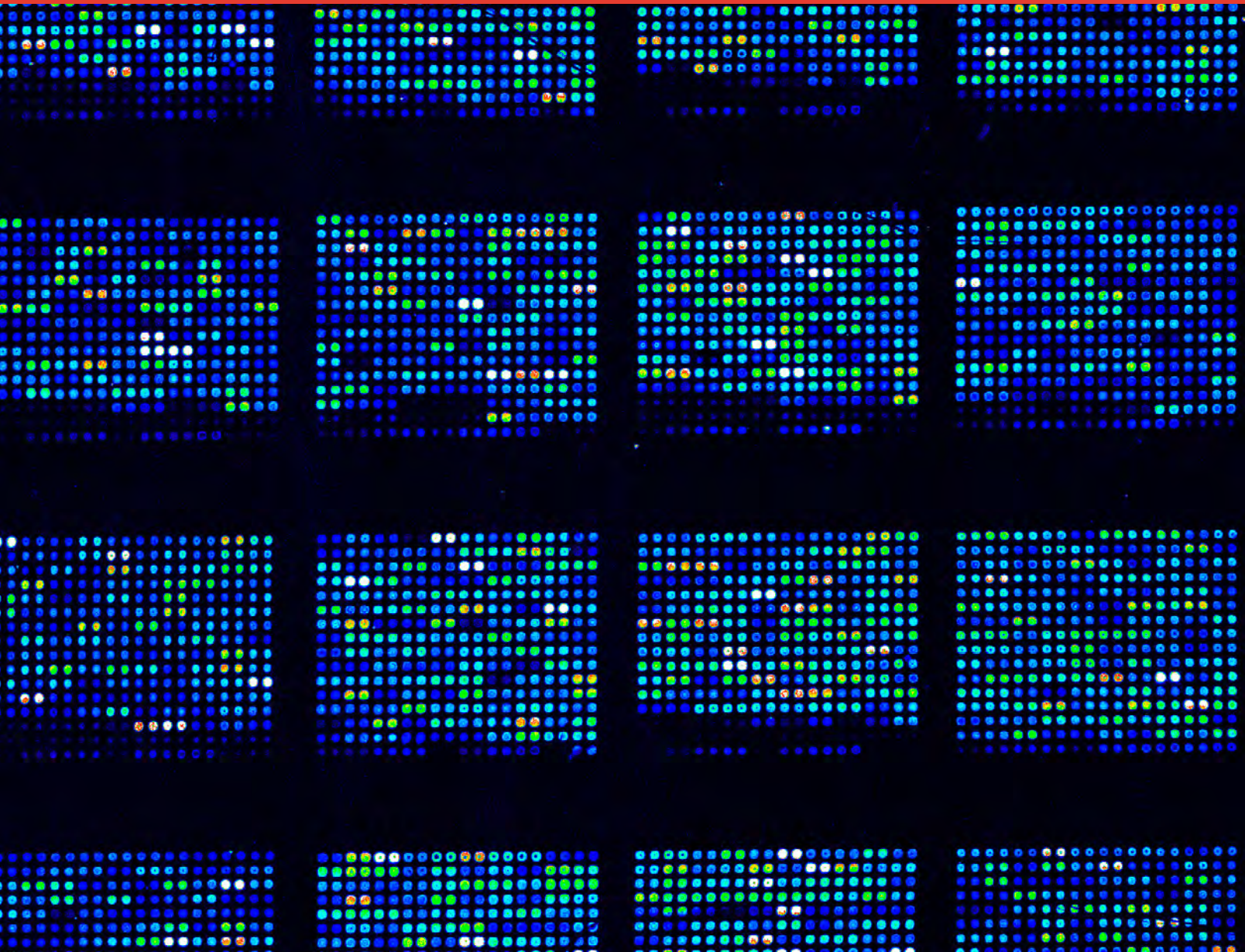
-
- To explore the molecular basis for the association of family history with prostate cancer risk, these investigators screened more than 200 genes in the 17q21-22 region by sequencing germline DNA from 94 unrelated patients with prostate cancer from families selected for linkage to the candidate region. Family members, additional case subjects, and control subjects were tested to characterize the frequency of the identified mutations. The novel HOXB13 G84E variant was found to be associated with a significantly increased risk of hereditary prostate cancer. Although the variant accounts for a small fraction of all prostate cancers, this finding has implications for prostate-cancer risk assessment and may provide new mechanistic insights into this common cancer.



TRANSLATIONAL
RESEARCH PROGRAM **TRP**

2012 PROGRAM ACCOMPLISHMENTS

BIOMETRIC RESEARCH BRANCH





OVERVIEW

The **Biometric Research Branch (BRB)** is the statistical and computational biology component of the National Cancer Institute's (NCI's) Division of Cancer Treatment and Diagnosis (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, BRB investigators conduct self-initiated research. This has enabled BRB to recruit and retain a world-class research staff, provide high-quality collaboration and consultation to DCTD and NCI scientists, and make major research contributions motivated by important problems of cancer research. BRB does not have a grant, cooperative agreement, or contract portfolio and does not sponsor or fund extramural research.

The major areas of BRB research encompass:

- Efficient clinical trial designs
- Integrating genomics in clinical trials
- Biomarkers in clinical trials
- Computational and systems biology of cancer
- Bioinformatics resources for the research community

BACKGROUND

EXTRAMURAL CLINICAL STUDIES

Specific BRB staff members are designated to collaborate with the DCTD programs covering clinical trials, drug discovery, molecular diagnostics, and biomedical imaging. It is the philosophy of BRB that a statistician must be deeply involved in a research area to make important contributions in that area. For extramural clinical trials, statisticians are assigned responsibilities by cancer type so that they develop in-depth knowledge about their areas of responsibility. BRB statisticians:

- Review protocols for all DCTD-sponsored clinical trials
- Participate with NCI and extramural scientists in strategy development, concept review, and protocol review meetings
- Serve on all Cooperative Group data monitoring committees and were instrumental in the establishment of the data monitoring committee system

- Serve on Intergroup Clinical and Correlative Science Review Committees
- Serve as liaison to Cooperative Group statistical centers
- BRB statisticians work closely with the staffs of the Cancer Diagnosis Program and the Cancer Imaging Program on a wide variety of projects
- Review correlative science and cancer imaging protocols submitted by the Cooperative Groups
- Participate in the development of treatment-related molecular and imaging biomarkers
- Collaborate on the planning and conduct of extramural programs for the development and application of molecular and imaging diagnostics technology

From these collaborations, BRB staff conducts research on new biostatistical methodology for clinical trials, preclinical drug development, and evaluation of molecular diagnostics and cancer imaging.

GENOMIC ANALYSIS

The objective of the **Computational and Systems Biology Group (CSB)** is to develop and apply mathematical, statistical, and computational methods for the utilization of genomic, gene expression, and other molecular biology data to cancer research and to train scientists in using computational biology, statistical genomics, and bioinformatics in cancer research. The CSB has established itself as an international center of expertise for the analysis of DNA microarray gene expression profile data, particularly in the development and validation of gene expression-based prognostic or predictive signatures. BRB staff members have published the book *Design and Analysis of DNA Microarray Investigations* as well as influential review articles in major medical journals that identify major problems in the use of array technology. In addition, BRB has developed an integrated software platform for microarray gene expression and copy number analysis. The software, **BRB-ArrayTools**, is targeted to biologists and has been distributed on request to more than 15,000 users in over 65 countries. The software is used in all major cancer centers and pharmaceutical and biotechnology companies. BRB-ArrayTools incorporates the best statistical analysis methods and serves as a vehicle for education in the proper analysis of DNA microarray data. Staff of the CSB teach classes on the analysis of DNA microarray data for users of the NCI microarray facility. The training program includes

RICHARD M. SIMON

CHIEF



Richard Simon, PhD, holds a doctoral degree in applied mathematics and computer science from Washington University in St. Louis, Missouri. He has been at the National Institutes of Health since 1969 and has developed many of the statistical methods used today in cancer clinical trials. He has published more than 450 papers on the application of biostatistical methodology to cancer research and biomedicine. His publications have had a major impact on the conduct of cancer clinical trials and statistical genomics. Dr. Simon became involved with DNA microarrays in 1997 based on his interactions with Dr. Jeff Trent of the National Human Genome Research Institute. After completing numerous courses in biotechnology, genomics, and computational biology, he established the Molecular Statistics and Bioinformatics Section, a multidisciplinary group of statistical, computational, and biological scientists to develop and apply methods for the application of genomic, gene expression, and other molecular data to cancer research. His group has pioneered methods for the development and validation of predictive biomarkers using high-throughput genomic assays and has developed integrated software (BRB-ArrayTools) for the analysis of microarray data that has more than 15,000 registered users in 65 countries. In recent years, Dr. Simon has established himself as an international leader in statistical genomics and innovative clinical trial designs for the development of new drugs with genomic companion diagnostics. He has established a team of computational and systems biologists to provide the DCTD with the expertise to utilize the wealth of genomic data available for human tumors to improve the development of effective therapeutics and diagnostics for cancer patients.

training of postdoctoral research fellows in statistical genomics. BRB has hosted visitors from several countries on extended visits for training and research in the use of genomics in cancer research.

Areas in which CSB research has recently focused include the following:

- Development of analytically validated computational pipelines for clinical-grade, high-throughput DNA sequencing
- Development of a bioinformatics system for therapeutic clinical studies in which drugs are selected based on the genomic variants in individual tumors
- Utilization of whole-exome sequencing of tumor cell line panels for understanding the genomic basis of therapeutic activity, resistance, and synergism
- Development of methods for analysis of tumor DNA sequencing studies for elucidating the evolutionary history of the tumor and development of methods for analysis of whole-exome, single-cell DNA sequencing of multiple cells from the same tumor for understanding intratumor heterogeneity

INTRAMURAL COLLABORATION

BRB collaborates with numerous intramural laboratories on the analysis of gene expression, copy number variation, and genomic sequencing data, providing CCR researchers in neuro-oncology, urologic oncology, metabolism, pediatric oncology, molecular imaging, and pathology with access to statistical expertise in the analysis of their studies. In 2011–2012, these collaborations resulted in 16 publications (four in neuro-oncology, two in molecular imaging, three in urology, one in metabolism, three in pediatric oncology, one in radiation oncology, and two in pathology). BRB also provides extensive collaboration and consultation to CCR by providing analysis of high-dimensional genomic data for CCR laboratories.



PROGRAM ACCOMPLISHMENTS

CLINICAL TRIAL DESIGN

Early Trials

DCTD and CCR have pioneered small, first-in-human, proof-of-principle, phase 0 studies. These studies, permitted by a 2006 guidance from the U.S. Food and Drug Administration (FDA), will be extremely helpful in expediting early drug development and in determining, at a very early point in development, whether an agent is effectively addressing its intended molecular target. BRB provided statistical leadership to the NCI phase 0 Clinical Trials Working Group, which comprises DCTD and CCR staff, and developed an innovative statistical design to assess pharmacodynamic endpoints for the NCI phase 0 poly(ADP ribose) polymerase inhibitor trial and in the development of methodology for the analysis of molecular assay endpoints.

BRB assisted in the creation of guidelines for the design of early-phase clinical trials for the development of combinations of new targeted drugs with radiation therapy. BRB investigators have demonstrated that a modification to a new phase 1 design, the time-to-event continual reassessment method (TITE-CRM), affords greater patient safety and have evaluated predictors of survival for newly diagnosed glioblastoma patients in phase 2 protocols. They also helped to develop innovative dual-endpoint designs to enable evaluation in phase 2 trials of new agents for which both tumor response rate and progression-free survival are important. In

addition, they have collaborated with extramural investigators to analyze the relationship between dose and response in a large collection of phase 1 datasets.

BRB has been extensively involved in the design and conduct of a new type of early-phase clinical trial in which patients are treated with drugs that are selected based on real-time molecular characterization of the genomic variants in their tumors. A randomized clinical trial of this type, the Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT), will be conducted in the NIH Clinical Center and then extended to other cancer centers. Other BRB collaborations have been conducted with the DNA sequencing center to develop an analytically validated computational pipeline for clinical-grade sequencing and making variant calls, as well as the development of prespecified rules for identifying actionable variants based on biological annotation of the functional effects of mutations and short insertions and deletions and on the molecular targets of the available drugs. A bioinformatic system developed by BRB will serve as the communication hub and database for this complex multisite study. The system obtains genomic variant files from the tumor characterization center and clinical data from the clinical sites and provides annotations for the detected variants and treatment assignments for the patients, using a rules-based, biology-driven system overseen by senior investigators.

BRB is also involved in the design of a second study of the type just described, in which drugs are matched to the genomic characterization of individual tumors. The purpose of this study is to identify new treatments for BRAF wild-type metastatic melanoma (Stand Up to Cancer Consortium

Genomics-Enabled Medicine for Melanoma: Using Molecularly Guided Therapy for Patients with BRAF Wild-Type Metastatic Melanoma). The study, led by Dr. Jeffrey Trent at the Translational Genomics Institute and Dr. Patricia Lorusso of Wayne State University, will assign patients to novel targeted therapies on the basis of their molecule profiles.

Randomized Phase 3 Trials

It has been suggested in the literature that a useful modification of the standard randomized clinical trial would be to change the randomization ratio as the trial progresses, so that trial arms in which patients are doing better are (randomly) assigned a higher proportion of patients (outcome-adaptive randomization). A rigorous evaluation of outcome-adaptive randomization by BRB has shown that there is little to no gain in using it and that it adds complexity and potential bias to the trial results.

In some situations, there is not enough preliminary efficacy information about an experimental treatment to proceed to a phase 3 trial. In particular, there may have been no phase 2 trial of the treatment. In some of these situations, a phase 2/3 trial design, in which a phase 2 bar must be passed in order to continue on to a full phase 3 accrual, can be quite efficient. BRB has investigated the benefits and parameters of this type of design.

It has been suggested in the literature that a high proportion of NCI Cooperative Group phase 3 trials end early because of inadequate accrual. A rigorous look at the data by BRB investigators suggested that the proportion was less than previously reported (approximately 20% of the trials), but additionally this represented only about 2% of the patients on trials.

Are randomized trials always needed, or can one use other statistical methods to attempt to ascertain a causal relationship between treatments and outcomes without randomization? These statistical methods, which are sometimes used in comparative effectiveness research, can be quite complex, with assumptions that are not transparent. In a series of papers, BRB investigators have described these methods and have delineated their assumptions and limitations.

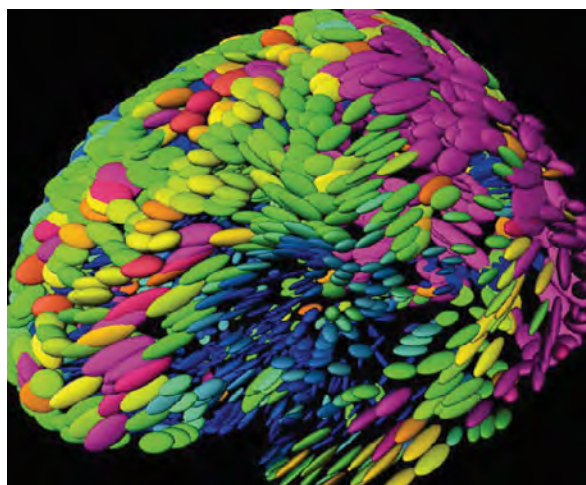
Interim Monitoring

An interim monitoring plan specifies when the accruing outcome data should be analyzed and what positive results would be needed to stop the trial early for futility and/or inefficacy. BRB investigators have noted the importance of inefficacy monitoring and have suggested a general inefficacy monitoring rule that is easy to understand and implement, has good statistical properties in terms of stopping early when the null hypothesis is true, and loses very little power as compared with a trial design without futility monitoring. Recent concerns have been raised in the literature that interim monitoring will lead to too many false-positive results and that results released early because of interim monitoring will be biased in a positive direction. BRB addressed these concerns in two ways. Investigators conducted a comprehensive review of all NCI Cooperative Group randomized trials that stopped early for positive results and showed that, with further follow-up, the results of these trials remained strongly positive for nearly all of the trials. They also examined, from a statistical perspective, the positive bias expected because of early stopping, showing that when this bias is examined properly, it is relatively small except for trials that are stopped very early.

Choice of Endpoint

Progression-free survival—the time from randomization to tumor progression or death—has been increasingly used as an endpoint in randomized trials in oncology. This endpoint is observed sooner than overall survival, has direct clinical relevance in some settings, and most important, is not confounded by effective salvage treatments that are given after progression. However, in an unblinded trial, there can be multiple sources of bias in using progression-free survival as an endpoint. In addition, BRB investigators have argued that if the salvage therapies are standardly used, then even though differences in overall survival may be diminished because of their use, overall survival is the appropriate endpoint when progression-free survival does not represent clinical benefit.

When progression-free survival does represent clinical benefit, it may be the appropriate endpoint. Using computer simulations, BRB investigated the effects of measurement error in progression-free survival on trial conclusions and showed that it was small. BRB has also developed an audit strategy for use when there is the potential for treatment arm-specific bias in measuring progression-free survival in an unblinded



trial. Using central blinded review, the strategy assesses any bias at a lesser cost than doing a full central blinded review of the progression-free survival data.

Genomics in Clinical Trial Design

Standard approaches to clinical trials have in some cases led to overtreatment of many patients with drugs from which only a minority benefit. The hallmark of cancer is heterogeneity, and molecularly targeted drugs are likely to benefit only a subset of treated patients. Hence, the effectiveness of targeted agents may be missed when the traditional broad approach to eligibility is used in randomized clinical trials. Early papers from BRB on the enrichment design demonstrated that the number of patients needed for randomized clinical trials can be greatly reduced if a genomic biomarker is used to select those patients who are most likely to benefit or to exclude those who are least likely to benefit. BRB has subsequently introduced adaptive designs for use with candidate predictive biomarkers in randomized trials where the credentials of the biomarkers are not sufficiently well established for use as eligibility exclusion criteria. Multiple publications introduced increasingly flexible adaptive designs that preserved the study-wise type I error. They permit the prospective use of multiple candidate biomarkers and unspecified thresholds of positivity. The adaptive signature design was featured at a meeting of the Friends of Cancer Research and the Brookings Institution and earned the support of FDA representatives. It has since been accepted by the FDA for use in pivotal phase 3 oncology clinical trials. BRB investigators have published a cross-validated extension of the adaptive signature design that considerably improves the ability both to identify a predictive biomarker and to

establish its validity for identifying patients who do and do not benefit from the new treatment. These new designs have been of major interest to the pharmaceutical and biotechnology industries as well as FDA.

BRB has often hosted scientists interested in cancer genomics and clinical trial methodology from academic institutions in the United States and overseas. A collaboration with a recent visitor, Dr. Fangxin Hong from the Dana Farber Cancer Institute, aimed to develop a design for utilizing a biomarker measured after treatment administration as a predictive biomarker for identifying patients who benefit from a new drug. The run-in-based design that emerged from that collaboration is highly efficient and may enhance the ability to use predictive biomarkers for improving the efficiency of clinical trials and for providing patients with drugs that are more likely to benefit them.

Recognizing that it is not always feasible to conduct prospective clinical trials for evaluating the value of predictive biomarkers, BRB investigators published an influential paper concerning the use of archived tissues from randomized clinical trials for the focused evaluation of a candidate marker. Their “prospective-retrospective design” approach was used to establish that patients with K-RAS-mutated advanced colorectal cancer do not benefit from anti-epidermal growth factor receptor (EGFR) antibodies and led to the restriction of the labeling indication for cetuximab and panitumumab. The publication revised a previously published “Levels of Evidence Scale for Biomarkers” and has been used by the American Society of Clinical Oncology (ASCO) in its standards-of-care recommendations.

Definitive evaluation of the clinical utility of predictive biomarkers requires conducting large randomized controlled trials. Efficient design of such trials is therefore crucial for the timely introduction of these medical advances into clinical practice. A variety of designs have been proposed for this purpose, including the enrichment design (i.e., randomize only those patients who are biomarker positive), the biomarker strategy design (i.e., randomize between a control arm and a strategy arm where the treatment is determined by the biomarker), and the biomarker-stratified design (i.e., randomize all patients between the two treatment arms and record the biomarker status on all to allow for separate evaluations of the treatment effect in the different biomarker status subgroups). To guide the design and interpretation of these types of randomized trials evaluating predictive biomarkers, BRB presented an in-depth comparison of the advantages and disadvantages of commonly used biomarker-based phase 3 trial designs. BRB also provided an overview of phase 2 and 3 designs incorporating biomarkers, including discussion of more recently proposed adaptive designs.

BRB researchers actively pursue development of novel biomarker-based trial designs and keep abreast of new designs proposed by others. A critical decision in the development of a targeted therapy is whether and when the efficacy of that therapy should be evaluated in a patient population enriched for a putative target marker or in an unselected patient population. BRB colleagues developed a biomarker-based phase 2 trial design that aims to answer this question. Their proposed trial design provides an approach to decide whether a targeted drug should proceed to phase 3 testing at all, and if it does proceed, whether the design of the phase 3 trial should be a biomarker enrichment design or a biomarker-stratified design or whether the biomarker should be abandoned in the further development of the drug. Because many tumor markers of therapeutic relevance occur in fairly small subpopulations of patients, many strategies for conducting trials in rare-disease populations apply in this setting. BRB investigators have described statistical challenges in the evaluation of treatments in rare diseases and small targeted patient subgroups. Other colleagues at BRB critically evaluated a trial design proposed by other researchers based on estimation of individual patient risk, demonstrating that the approach was seriously flawed. An in-depth BRB review of biomarker-adaptive clinical trial designs offered important insights into the strengths and limitations of a wide variety of designs.

BIOMARKERS

For a biomarker to be used clinically, it must be demonstrated that the biomarker assay meets acceptable standards of analytical performance. In addition, if the biomarker assay will be performed in more than one laboratory, the results must be comparable across laboratories. An international working group that included BRB staff noted that a lack of harmonization of assay methods for the measurement of the proliferation marker Ki67 in breast cancer was a major barrier to its translation into clinical practice. In response to the working group's report, an international subcommittee was formed to assess the current state of reproducibility of Ki67 assessments across different laboratories. BRB researchers were responsible for the statistical design and data analysis for that study. Results from the first phase of the study showed a concerning lack of concordance of Ki67 assessments on a common set of specimens among eight laboratories regarded as experts in the assessment of Ki67 by immunohistochemistry. These results were presented at the 2012 San Antonio Breast Cancer Symposium, and a manuscript has been drafted for submission for publication. These findings prompted efforts to develop a Web-based training tool to standardize and harmonize Ki67 scoring. BRB staff have been involved in developing the training system and analyzing the data. They helped to design a second international reproducibility study, currently ongoing, that will assess whether harmonization efforts were successful.

BRB staff co-chaired an NCI-sponsored workshop in 2011 on the development and evaluation of omics-based tests for use in clinical trials. The workshop was attended by nearly 200 participants, including laboratory scientists, pathologists, clinicians, statisticians, bioinformaticians, regulatory officials, and patient advocates. The goal was to promote cross-disciplinary education and to enhance dialogue among various stakeholders. As an outgrowth of that workshop, staff from BRB and the Cancer Diagnosis Program, along with experts outside of NCI, have drafted a manuscript proposing items to consider in assessing the readiness of an omics-based test for use in a clinical trial.

A statistical methodologic problem that arises in marker reproducibility studies is how to calculate a confidence interval for an estimate of intraclass correlation coefficient, which is a commonly used measure of reproducibility. Although various approaches have been proposed in the statistical literature, rigorous comparisons of some more recent methods



had not been published. BRB investigators collaborated on a paper comparing several commonly suggested approaches and found that confidence intervals for an intraclass correlation coefficient that is derived from Bayesian methods tended to have unreliable performance compared with frequentist competitors.

Lack of standardization regarding specimen handling and biomarker assay methods can be problematic even after biomarker tests have been accepted into clinical practice. BRB staff participated in a 2007 ASCO–College of American Pathologists (CAP) panel that developed testing guidelines for HER2, as well as a new panel convened to update the HER2 testing guidelines based on additional data emerging since the issuance of the original guidelines. BRB staff were also active on an ASCO-CAP committee charged with developing testing guidelines for estrogen and progesterone receptors in breast cancer. Another ASCO committee in which BRB was involved is the committee that developed a provisional clinical opinion on the utility of EGFR mutation testing for patients with advanced non–small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy.

Poor reporting of tumor marker studies has been suggested as major factor contributing to the disappointing rate of translation of tumor marker research into clinically useful tests. In 2005, BRB colleagues published a landmark paper issuing guidance on the reporting of tumor marker studies. Many journals have incorporated these guidelines, the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK), as part of their instructions to authors. To further enhance the understanding and usage of the REMARK guidelines, BRB colleagues published a comprehensive explanation and elaboration of the REMARK guidelines. In collaboration with members of the former NCI Office of Biorepositories and Biospecimen Research and other international colleagues, BRB was involved in the development of the Biospecimen Reporting for Improved Study Quality (BRISQ) guidelines, which are aimed specifically at the reporting of information about biospecimens used in research studies. The creation of these guidelines was motivated by increasing evidence that pre-analytical factors affecting biospecimens could alter biomarker profiles and distort the research findings generated from them. BRB was also involved in an international collaboration to develop a tumor marker study registry as another means of promoting the dissemination of tumor marker research. A prototype database that hosts this registry has been launched.

BRB has collaborated in a variety of biomarker and genomic studies conducted in CCR and other intramural divisions of NCI. These collaborative studies include a study examining gene expression pathways to predict response to neoadjuvant docetaxel and capecitabine for breast cancer, studies of microRNA expression profiling in lung cancer, and a study of the prognostic implications of circulating levels of immune and inflammatory markers in lung cancer. A statistical methodologic problem motivated by the microRNA expression profiling studies is the choice of normalization method for data produced by microRNA expression arrays. BRB collaborators published a paper that compared a wide range of normalization approaches and recommended a method that was both feasible and performed well in the data sets they examined.

BRB researchers reviewed studies in which prognostic gene expression signatures were developed for early-stage non–small-cell lung cancer. They found that none of the signatures had demonstrated patient utility and uncovered serious methodological problems in the studies. Their review was published in the *Journal of the National Cancer Institute*. A follow-up article on the evaluation of prognostic signature studies was published in *Nature Reviews: Clinical Oncology*.

It has been recognized that many imaging-derived measurements can be viewed as biomarkers. When imaging-derived measurements are used, issues of measurement reproducibility and clinical study design arise that are similar to those in laboratory-based biomarker assays. BRB has been involved in the Quantitative Imaging Biomarkers Alliance Metrology Working group to define best practices for assessing and reporting technical performance of imaging devices. BRB investigators collaborated in a study evaluating diffusion parameters as early biomarkers of disease progression in glioblastoma multiforme.

IMAGING

Imaging can serve in a variety of roles in phase 2 and phase 3 clinical trials, due to its ability to measure a variety of tumor characteristics, such as size, morphology, metabolic activity, cell proliferation, and receptor expression, with minimal invasiveness. Imaging can be used in staging and stratification, in assessment of progression, and as a surrogate in place of a definitive endpoint. Before an imaging assay is ready for use in these types of roles, however, it must undergo extensive studies to evaluate characteristics such as the following:

- Analytic performance
- Clinical validity
- Validity as a trial-level or individual-level surrogate endpoint

Analytic performance is the variability of repeated measurements on the same patient under identical conditions or the agreement between the imaging assay's measurements and a "gold standard." Clinical validity is the association between the imaging assay's measurements and a clinical endpoint such as overall survival.

The work of BRB statisticians in imaging has focused on designs and statistical techniques for these types of studies. They are currently participating in an initiative by the Quantitative Imaging Biomarkers Alliance (QIBA) to compile a series of papers reviewing statistical techniques in the literature for assessing and comparing the analytic performances of imaging assays. They are also involved in work establishing the validity of imaging as surrogate endpoints, in collaboration with QIBA and the FDA.

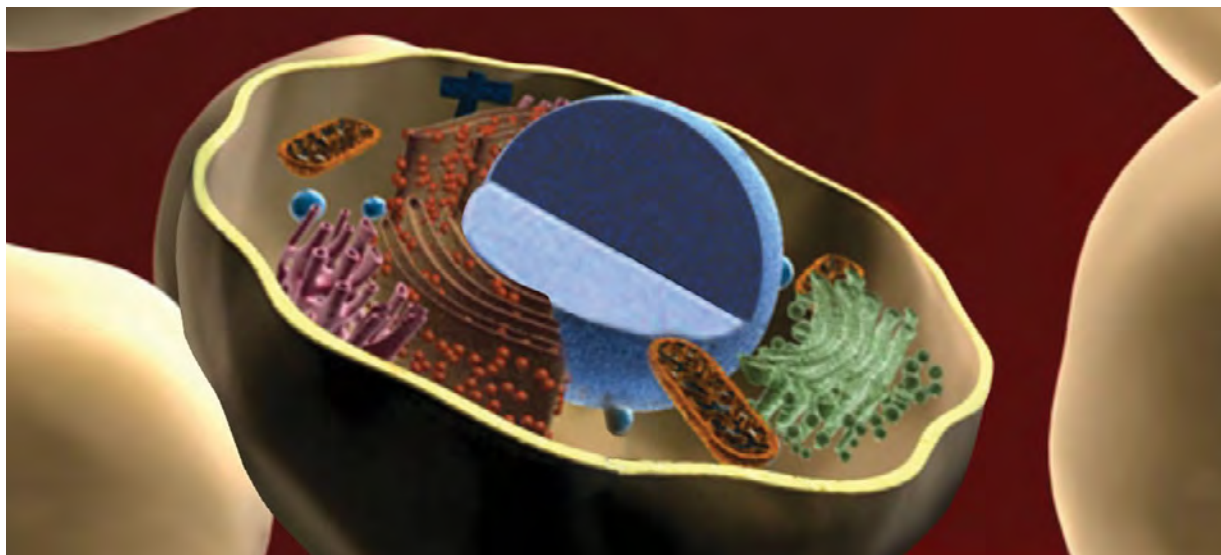
BIOINFORMATICS AND COMPUTATIONAL AND SYSTEMS BIOLOGY

BRB-ArrayTools is a comprehensive software program that is widely recognized as the most statistically sound software package available for the analysis of DNA microarray data. The package supports the use of data from all current expression platforms and has been extended to incorporate genomic copy number and methylation data. The computations are performed by sophisticated and powerful analytics, using state-of-the-art statistical and computational methods. The existing suite of tools is continually updated as new methods of analysis and elucidation of pathway annotation are developed. BRB-ArrayTools software may be downloaded from BRB's website. The software has over 15,000 registered users in 66 countries and has been cited in more than 2,200 publications. It is a successful experiment in using software to empower biomedical scientists to take advantage of DNA microarray software. BRB actively adds features to the power of BRB-ArrayTools, including new analysis and visualization tools, new types of genomic data that can be analyzed, and new ways of integrating pathway information and other biological data into the genomic analyses.

The BRB website contains other software, such as that for the generation of optimal and minimax two-stage phase 2 clinical trial designs, managing dose administration for patients on accelerated-titration phase 1 designs, and designing clinical trials for the co-development of targeted therapies and companion diagnostics. The website also contains technical reports and slide presentations of talks given by BRB staff. The BRB website averages approximately 50,000 page hits per month by external users. The interactive sample size tools themselves are accessed several thousand times each month.

BRB has developed a bioinformatics system called GeneMed to support personalized oncology clinical trials (sometimes called "N of 1" clinical trials), in which patients receive drugs matched to the genomic alterations in their tumors. This system is being used for the MPACT clinical trial being conducted at the NIH Clinical Center, and tumor characterization is being performed at a sequencing center at the Fredrick National Laboratory for Cancer Research. This system collects data on DNA variants detected in the patient's tumor, annotates those variants for treatment actionability, facilitates drug assignment, and collects clinical data on response of the patient to treatment. This study will be extended to selected extramural cancer centers.

BRB staff and postdoctoral fellows have developed statistical and computational methods for identifying driver mutations and for reconstructing some aspects of the early evolutionary history of individual tumors. The method for identifying driver mutations is based on DNA sequence data for multiple tumors of the same histologic type and has improved sensitivity and specificity compared with previously published methods. The method also better utilizes the genetic code and allows for improved assessment of the functional effects of individual mutations. The methods for reconstructing some aspects of the evolutionary history of individual tumors can be used to determine which mutations are the key "founder" mutations of the tumor and are contained in all subclones of the tumor. The methods can also be used to determine which mutations increase the background mutation rate and thereby serve to destabilize the genome. Methods have also been developed for the analysis of deep sequencing studies in which whole-exome, single-cell sequences from multiple samples of a tumor are obtained.



INTERNATIONAL LEUKEMIA/LYMPHOMA MOLECULAR PROFILING PROJECT

BRB statisticians have been focused on the analysis of high-dimensional genetic data, particularly with respect to the molecular characterization of lymphoma. In this enterprise, BRB has been involved in an extensive collaboration with CCR and with the Lymphoma/Leukemia Molecular Profiling Project (LLMPP). LLMPP is an international consortium of institutes that have pooled resources, expertise, and patient samples in an effort to understand the molecular underpinnings of lymphoid malignancies, redefining their classification in molecular terms. In addition, LLMPP hopes to define molecular correlates of clinical parameters that can be used in prognosis and in the selection of appropriate therapy. For this project, BRB has been providing statistical expertise, analyzing the vast array of data that this group has compiled and generating models that are statistically rigorous and accurate as well as biologically meaningful. The LLMPP has begun a collaboration with commercial entities in the hopes of bringing insights learned in the laboratory into the clinic. The goal of this project is to develop a gene expression-based test that would distinguish subtypes of aggressive lymphoma from paraffin-embedded tissue. Ongoing trials are indicating that these distinctions, which are indistinguishable via morphology alone, are likely to inform future treatment. Although microarray remains the current mainstay for expression analysis, direct sequencing methods are becoming increasingly popular. CCR has used this technology in various applications such as digital gene expression, identification of protein binding sites, mutation detection, and multiplex short hairpin RNA screening. Each of these

investigations produces different styles of data that require different analysis techniques; BRB staff have developed statistical methodology as necessary.

FUTURE INITIATIVES

In upcoming years, BRB plans to focus on the following activities:

- Development and application of statistical and computational methods to facilitate and accelerate the development and clinical evaluation of effective molecularly targeted therapeutics for individual patients and companion diagnostics
- Development and application of statistical and computational methods for enhancing the understanding of oncogenesis with massively parallel sequencing, whole-genome characterization technology, and systems biology approaches
- Development and application of statistical and computational methods for using genomic data to elucidate tumor pathogenesis and to identify key molecular targets for cancer prevention, early detection, and therapy
- Development of statistical methods for enhancing the effectiveness of cancer clinical trials and for expediting the development of technology of potential importance for biomedical investigation
- Further development of BRB-ArrayTools software and development of bioinformatics systems to utilize tumor genomics for identifying important molecular targets in human tumors

SELECTED PUBLICATIONS

CLINICAL TRIAL METHODOLOGY

An audit strategy for progression-free survival, Dodd LE, Korn EL, Freidlin B, Gray R, Bhattacharya S. *Biometrics* 2011;67(3):1092–1099.

<http://www.ncbi.nlm.nih.gov/pubmed/21210772>

- The authors propose a blinded independent central review (BICR) audit strategy as an alternative to a complete-case BICR to provide assurance of the presence of a treatment effect. The method is applied retrospectively to a large oncology trial that had a complete-case BICR, showing the potential for efficiency improvements.

Causal inference for definitive clinical endpoints in a randomized clinical trial with intervening nonrandomized treatments, Korn EL, Freidlin B. *Journal of Clinical Oncology* 2010;28(24):3800–3802.

<http://www.ncbi.nlm.nih.gov/pubmed/20660828>

- In the context of an article appearing in this issue of the *Journal of Clinical Oncology* (London et al. 2010;28:3808–3815), this editorial comments on the evaluation of cancer treatments using causal inference methods, recommending caution with regard to their often limited precision.

Outcome-adaptive randomization: is it useful? Korn EL, Freidlin B. *Journal of Clinical Oncology* 2011;29(6):771–776.

<http://www.ncbi.nlm.nih.gov/pubmed/21172882>

- This study compares outcome-adaptive randomization with designs that use 1:1 and 2:1 fixed-ratio randomizations. With no differential patient accrual rates because of the trial design, no benefits were found for outcome-adaptive randomization over 1:1 randomization, and the latter is recommended.

Overall survival as the outcome for randomized clinical trials with effective subsequent therapies, Korn EL, Freidlin B, Abrams JS. *Journal of Clinical Oncology*, 2011;29(17):2439–2442.

<http://www.ncbi.nlm.nih.gov/pubmed/21555691>

- This report examines how overall survival (OS) comparisons should be interpreted with the increasing availability of effective therapies that can be given subsequently to the treatment assigned in a randomized clinical trial.

It is concluded that, in disease settings in which there is no intermediate end point that directly measures clinical benefit, OS should be the primary end point of a randomized controlled trial. The observed difference in OS should be considered the measure of clinical benefit to the patients, regardless of subsequent therapies, provided that the subsequent therapies used in both treatment arms follow the current standard of care.

Inefficacy monitoring procedures in randomized clinical trials: the need to report, Korn EL, Freidlin B. *American Journal of Bioethics*, 2011;11(3):2–10.

<http://www.ncbi.nlm.nih.gov/pubmed/21400374>

- The authors discuss the importance of reporting, along with the results of a trial, the formal interim inefficacy monitoring guidelines that were utilized, and, if none were used, the reasons for their absence.

Design issues in randomized phase II/III trials, Korn EL, Freidlin B, Abrams JS, Halabi S. *Journal of Clinical Oncology*, 2012;30(6):667–671.

<http://www.ncbi.nlm.nih.gov/pubmed/22271475>

- The authors discuss phase 2/3 design parameters, give examples of phase 2/3 trials, and provide recommendations concerning efficient phase 2/3 trial designs.

Methodology for comparative effectiveness research: potential and limitations, Korn EL, Freidlin B. *Journal of Clinical Oncology*, 2012;30(34):4185–4187.

<http://www.ncbi.nlm.nih.gov/pubmed/23071226>

- This editorial accompanies a special series on comparative effectiveness research in this issue of the *Journal of Clinical Oncology*.

A method for utilizing co-primary efficacy outcome measures to screen regimens for activity in two-stage Phase II clinical trials, Sill MW, Rubinstein L, Litwin S, Yothers G. *Clinical Trials*, 2012;9(4):385–395.

<http://www.ncbi.nlm.nih.gov/pubmed/22811448>

This paper describes a method for designing a single-arm, two-stage clinical trial with dichotomous co-primary endpoints of efficacy. The design is illustrated with a clinical trial that examined bevacizumab in patients with recurrent endometrial cancer and was found to be competitive when compared with modified procedures in the literature.

Meta-analysis of the relationship between dose and benefit in phase I targeted agent trials, Gupta S, Hunsberger S, Boerner SA, Rubinstein L, Royds R, Ivy SP, Lorusso P. *Journal of the National Cancer Institute*, 2012;104(24):1860–1866. <http://www.ncbi.nlm.nih.gov/pubmed/23169991>

- In this retrospective meta-analysis, outcomes of patients in CTEP-sponsored, multiple-institution, phase 1 trials of molecularly targeted agents were analyzed to determine whether trials with such agents require a maximum tolerated dose (MTD) for efficacy. Contrary to data from single institutions, the results suggested clinical benefit from the use of MTD in terms of increasing response and overall survival with increasing dose.

Weighted logrank test for interval censored data when assessment times depend on treatment, Fay M, Shih JH. *Statistics in Medicine*, 2012;31(28):3760–3772. <http://www.ncbi.nlm.nih.gov/pubmed/22786795>

- This paper describes a modification of the multiple imputation logrank tests of Huang et al. (*Statistics in Medicine*, 2008;27:3217–3226), showing that the distribution of the rank-like scores asymptotically does not depend on assessment times. As shown through simulations, the modifications retain the type I error rate in all cases studied, even with assessment-treatment dependence and a small number of individuals in each treatment group.

METHODOLOGY FOR GENOMIC CLINICAL TRIALS

Adaptive clinical trial designs for simultaneous testing of matched diagnostics and therapeutics, Scher HI, Nasso SF, Rubin EH, Simon R. *Clinical Cancer Research*, 2011;17(21):6634–6640. <http://www.ncbi.nlm.nih.gov/pubmed/22046024>

- The authors develop for castrate-resistant prostate cancer an adaptive phase 3 trial design that can be used to identify a suitable target population during the early course of the trial, enabling the efficacy of an experimental therapeutic to be evaluated within the target population as a later part of the same trial. The design was previously developed by BRB investigators and has now been approved by the FDA for use in several pivotal phase 3 clinical trials.

Moving from correlative science to predictive oncology, Simon R. *The EPMA Journal* 1(3):377–387, 2010. <http://www.ncbi.nlm.nih.gov/pubmed/23199082>

- The authors address some of the issues that accompany the development of drugs with companion diagnostics and the resulting need to adapt the design and analysis of clinical trials, commenting specifically on the design of clinical studies for evaluating the clinical utility and robustness of prognostic and predictive biomarkers.

Translational research in oncology: key bottlenecks and new paradigms, Simon R. *Expert Reviews in Molecular Medicine*, 2010;12:e32. <http://www.ncbi.nlm.nih.gov/pubmed/20929594>

- This paper discusses some of the key obstacles to effective translational research in oncology, reviewing some prospective phase 3 designs that have been developed to facilitate the transition from the era of correlative science to one of reliable predictive and personalized oncology.

Randomized phase II designs with biomarkers, Freidlin B, McShane LM, Polley MY, Korn EL. *Journal of Clinical Oncology*, 2012;30(26):3304–3309. <http://www.ncbi.nlm.nih.gov/pubmed/22869885>

- The authors propose a randomized phase 2 biomarker trial design that, after completion, recommends the type of phase 3 trial to be used for the definitive testing of the therapy and the biomarker.

A two-stage Bayesian design for co-development of new drugs and companion diagnostics, Karuri SW, Simon R. *Statistics in Medicine*, 2012;31(10):901–914. <http://www.ncbi.nlm.nih.gov/pubmed/22238151>

- This paper describes a two-stage Bayesian design that includes both marker-positive and marker-negative patients in a clinical trial. It is demonstrated that the design controls type I errors, gives adequate power, and enables the early futility analysis of test-negative patients to be based on prior specification of the strength of evidence in the biomarker.

Clinical trials for predictive medicine, Simon R. *Statistics in Medicine*, 2012;31(25):3031–3040. <http://www.ncbi.nlm.nih.gov/pubmed/22714719>

- This paper reviews prospective designs for the development of new therapeutics and predictive biomarkers to inform their use, outlining a prediction-based approach to the analysis of randomized clinical trials that both preserves the type I error and provides a reliable, internally validated basis for predicting which patients are most likely or unlikely to benefit from the new regimen.

CANCER BIOMARKERS

Reporting recommendations for tumor marker prognostic studies (REMARK): explanation and elaboration, Altman DG, McShane LM, Sauerbrei W, Taube SE. *BMC Medicine*, 2012;10:51.

<http://www.ncbi.nlm.nih.gov/pubmed/22642691>

- In this paper, the authors expand on the REMARK recommendations, which consist of 20 items to report for published tumor marker prognostic studies.

Genomic biomarkers in predictive medicine: an interim analysis, Simon R. *EMBO Molecular Medicine*, 2011;3(8):429–435.

<http://www.ncbi.nlm.nih.gov/pubmed/21744497>

- The author discusses the potential of advances in genomics and biotechnology to facilitate the development of biomarkers to predict individual disease risk, enable early detection of disease, and improve diagnostic classification to better inform individualized treatment, commenting on progress to date and obstacles to future success.

Biomarker studies: a call for a comprehensive biomarker study registry, Andre F, McShane LM, Michiels S, Ransohoff DF, Altman DG, Reis-Filho JS, Hayes DF, Puztai L. *Nature Reviews Clinical Oncology*, 2011;8(3):171–176.

<http://www.ncbi.nlm.nih.gov/pubmed/21364690>

- The authors propose the creation of a comprehensive biomarker study registry, outlining how it could be initially established and eventually developed and enumerating its potential benefits for biomarker research.

Publication of tumor marker research results: the necessity for complete and transparent reporting, McShane LM, Hayes DF. *Journal of Clinical Oncology*, 2012;30(34):4223–4232.

<http://www.ncbi.nlm.nih.gov/pubmed/23071235>

- The authors discuss several measures to address problems in the literature on tumor markers, including development of a tumor marker study registry, greater attention to assay analytic performance and specimen quality, use of more rigorous study designs and analysis plans to establish clinical utility, and adherence to higher standards for reporting tumor marker studies.

Statistical challenges in the development and evaluation of marker-based clinical tests, McShane LM. *BMC Medicine*, 2012;10:52.

<http://www.ncbi.nlm.nih.gov/pubmed/22642713>

- This commentary focuses on the statistical challenges in translational marker research, specifically in the development and validation of marker-based tests that have clinical utility for therapeutic decision-making.

Identification of unique expression signatures and therapeutic targets in esophageal squamous cell carcinoma, Yan W, Shih JH, Rodriguez-Canales J, Tangrea MA, Ylaya K, Hipp J, Player A, Hu N, Goldstein AM, Taylor PR, Emmert-Buck MR, Erickson HS. *BMC Research Notes*, 2012;5:73.

<http://www.ncbi.nlm.nih.gov/pubmed/22280838>

- The authors describe a unique tissue microdissection strategy and microarrays that they used to measure gene expression profiles associated with cell differentiation versus tumorigenesis in normal basal squamous epithelial cells, normal differentiated squamous epithelium, and squamous cell cancer. Three genes (ODC1, POSTN, ASPA) were dysregulated in the same pattern at both the mRNA and protein levels. The findings provide information that may be potentially useful in designing novel therapeutic interventions.

STATISTICAL GENOMICS

An evaluation of resampling methods for assessment of survival risk prediction in high-dimensional settings, Subramanian J, Simon R. *Statistics in Medicine*, 2011;30(6):642–653.

<http://www.ncbi.nlm.nih.gov/pubmed/21337359>

- Using real and simulated datasets, the authors compared several resampling techniques for their ability to estimate the accuracy of risk prediction models, recommending more widespread adoption of methods that provide a good balance between bias and variability for a wide range of data settings.

Probabilistic classifiers with high-dimensional data, Kim KI, Simon R. *Biostatistics*, 2010;12(3):399–412.

<http://www.ncbi.nlm.nih.gov/pubmed/21087946>

- The authors introduce two criteria for the assessment of probabilistic classifiers—well-calibratedness and refinement—and develop corresponding evaluation mea-

tures. Several published high-dimensional probabilistic classifiers are evaluated, and extensions of the Bayesian compound covariate classifier are developed. The authors provide this evaluation for several probabilistic classifiers and evaluate their refinement as a function of sample size under weak and strong signal conditions. Also presented is a cross-validation method for evaluating the calibration and refinement of any probabilistic classifier on any data set.

Using cross-validation to evaluate predictive accuracy of survival risk classifiers based on high-dimensional data, Simon RM, Subramanian J, Li MC, Menezes S. *Briefings in Bioinformatics*, 2011;12(3):203–214.

<http://www.ncbi.nlm.nih.gov/pubmed/21324971>

- The authors review methodology for classifying patients into survival risk groups and for using cross-validation to evaluate such classifications.

Optimally splitting cases for training and testing high-dimensional classifiers, Dobbin KK, Simon RM. *BMC Medical Genomics*, 2011;4:31.

<http://www.ncbi.nlm.nih.gov/pubmed/21477282>

- This paper reports on the development of a nonparametric algorithm for determining an optimal splitting proportion that can be applied with a specific dataset and classifier algorithm. The algorithm can be applied to any dataset, using any predictor development method, to determine the best split.

Microarray-based cancer prediction using single genes, Wang X, Simon R. *BMC Bioinformatics*, 2011;12:391.

<http://www.ncbi.nlm.nih.gov/pubmed/21982331>

- Exploring the use of single-gene classification methods to construct classification models, the authors found that single-gene methods appeared to work as well as more standard methods for many datasets, suggesting that simple models be considered in microarray-based cancer prediction.

BIOINFORMATICS AND COMPUTATIONAL AND SYSTEMS BIOLOGY

Identifying cancer driver genes in tumor genome sequencing studies, Youn A, Simon R. *Bioinformatics*, 2011;27(2):175–181.

<http://www.ncbi.nlm.nih.gov/pubmed/21169372>

- The authors propose a new and more accurate method for identifying cancer driver genes that accounts for the functional impact of mutations on proteins, variation in background mutation rate among tumors, and the redundancy of the genetic code.

Estimating the order of mutations during tumorigenesis from genome sequencing data, Youn A, Simon R. *Bioinformatics*, 2012;28(12):1555–1561.

<http://www.ncbi.nlm.nih.gov/pubmed/22492649>

- This article describes a method for inferring some aspects of the order of mutational events during tumorigenesis based on genome sequencing data for a set of tumors. The model may be a useful tool for better understanding the process of tumorigenesis.

2012 PROGRAM ACCOMPLISHMENTS

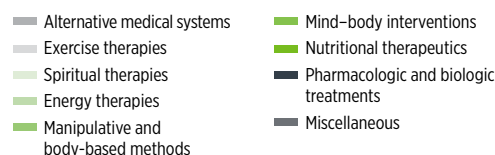
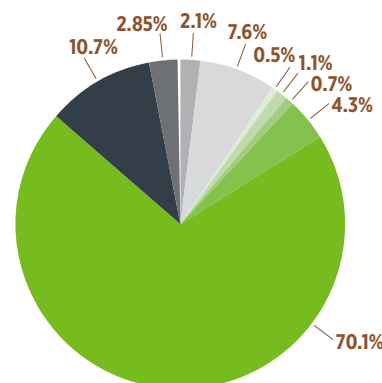
OFFICE OF CANCER COMPLEMENTARY AND ALTERNATIVE MEDICINE



OVERVIEW

The Office of Cancer Complementary and Alternative Medicine (OCCAM) was established within the Office of the Director of the National Cancer Institute (NCI) in 1998 to:

- Collaborate with the National Center for Complementary and Alternative Medicine (NCCAM) on phase 3 clinical trials on shark cartilage and other complementary and alternative medicine (CAM) therapies
- Improve NIH's information resources on CAM
- Foster interactions with health care practitioners utilizing CAM approaches in managing cancer patients and stimulate high-quality research on such approaches
- Coordinate and expand, but not necessarily manage, the CAM-relevant research grant activities in the areas of prevention, diagnosis, treatment, and symptom and side effect management
- Track NCI's CAM research expenditures



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

NCI CAM RESEARCH BY CATEGORY, FISCAL YEAR 2011

In 2007, the NCI director moved OCCAM into the Division of Cancer Treatment and Diagnosis (DCTD) to augment the activities of the different divisions at NCI that were already supporting CAM research. OCCAM continues to promote and support 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.

BACKGROUND

MISSION

The mission of OCCAM is to improve the quality of care for cancer patients, those at risk for cancer, and those recovering from cancer treatment by contributing to the advancement of 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 general 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. In the Metabolism Branch, he performed laboratory research in immunology and molecular biology and 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. In October 1998, he was chosen to serve as director of the newly created NCI OCCAM.

HISTORY

OCCAM was initially established within the NCI Office of the Director (1998–2007) to increase the number and quality of CAM research projects within the NCI portfolio. The office was created not to serve as a central CAM grant management program for all NCI CAM grants, but rather to provide expertise in CAM. After a congressional inquiry about the amount of funding for CAM research at NCI, a reliable system of reporting these figures was created. A competitive, peer-reviewed supplement program was established and implemented to support pilot projects, with the ultimate goal of increasing the number of R01 research projects on CAM and building CAM research expertise within the NCI-designated Cancer Centers. The following six centers were funded:

1. Johns Hopkins University
2. University of Medicine and Dentistry of New Jersey
3. Wake Forest University
4. University of California at San Francisco
5. University of Chicago
6. University of Colorado

OCCAM also assisted with the development of Physician Data Query (PDQ®) CAM summaries for patients and health professionals.

OCCAM was moved to DCTD in 2007. Within DCTD, OCCAM identified three research areas with potential for therapeutic advances. Designed to mesh with DCTD goals, these areas focus on:

1. Identifying novel therapeutics in the pharmacopeia of traditional medical systems as defined by the World Health Organization
2. Using complementary approaches to improve the therapeutic ratio of standard and investigational anticancer therapies
3. Research on lifestyle modifications (e.g., diet, exercise, mind–body approaches) for their impact on cancer outcomes (e.g., response to conventional cancer therapy, survival)



PROGRAM ACCOMPLISHMENTS

OCCAM GRANTS

The Program Announcement “Developmental Projects in Complementary Approaches to Cancer Care and Treatment (R21)” has increased the amount of high-quality CAM research supported by NCI while keeping projects integrated in the relevant program portfolios. This Program Announcement has been issued three times, the last version being PA-09-167, and once for R03 grants, PA-09-168. The announcement was a source of funded grants for each of the four extramural granting divisions. Of all the NCI active CAM R21 grants in fiscal year 2007, 51% were received in response to this series of announcements. More than 120 publications have resulted from funded projects. This program announcement expired in May 2012.

HERBAL MIXTURE PROGRAM PROJECT GRANT

NCI’s first program project grant (P01) of an herbal mixture (1P01CA154295-01A1), “Chinese Herbal Medicine as a Novel Paradigm for Cancer Chemotherapy,” is being led by Principal Investigator Yung-chi (Tommy) Cheng, PhD, of Yale University. In fiscal year 2011, NCI, along with NCCAM and the NIH Office of the Director, funded a grant to investigate the effectiveness of PHY906 as a modulator of the chemotherapy drug irinotecan in the treatment of patients with metastatic colorectal cancer. PHY906 is an extract of four herbs based on a formula of traditional Chinese medicine (TCM) known as huang qin tang (HQT). HQT is used as a

treatment for gastrointestinal ailments, including diarrhea, nausea, and vomiting. Animal research demonstrated that PHY906 improved the gastrointestinal side effects of irinotecan while simultaneously increasing the drug’s anticancer activity.

NCI BEST CASE SERIES PROGRAM

The NCI Best Case Series Program is the only program in the world advertised as willing and interested to review the case records of patients treated with unconventional cancer therapies. The program was converted to an NCI protocol in January 2011 and received approvals from the NCI Special Studies Institutional Review Board and the NIH Clinical Center. The primary objective of the program is to identify unconventional approaches to the treatment of cancer that may warrant NCI-initiated research. Since inception of the protocol, 135 cases have been submitted for review, of which 41 cases have met the eligibility criteria.

PATIENT EDUCATION RESOURCE

In early 2013, OCCAM published a patient education resource, “Talking about Complementary and Alternative Medicine with Health Care Providers: A Workbook and Tips.” This workbook was created to help patients and their health care providers have meaningful discussions about the use of CAM during and after cancer care.

NCI CAM INVENTORY

In 2011, OCCAM completed an inventory to learn about the CAM-related work being performed in NCI's Cancer Centers Program and Integrative Medicine Programs, including the Consortium of Academic Health Centers for Integrative Medicine. The inventory brought to light information about the cancer CAM research, practice, and educational services conducted at these centers. OCCAM's communication goals for this project included identifying the main contacts within the patient education departments of these institutions to learn about patient education activities surrounding CAM. This helps aid ongoing projects in advocacy and patient education.

CONFERENCES

The 2011 China–U.S. Symposium on Traditional Chinese Medicine and Cancer was held July 8–10 in Beijing. The conference was jointly organized with the China Academy for Chinese Medical Sciences and financially supported by the U.S. Department of Health and Human Services. Its purpose was to strengthen communication and promote China–U.S. international collaborations related to research on the use of TCM for the treatment of cancer patients and the integration of TCM with conventional Western cancer management.

OCCAM worked with the Cancer Therapy Evaluation Program to host a roundtable discussion, “The State of the Science of Alpha-Lipoic Acid Plus Low-Dose Naltrexone for the Treatment of Cancer,” on March 19, 2012. The meeting's purpose was to provide an opportunity for NCI staff and outside experts to review case reports and preclinical research on alpha-lipoic acid plus low-dose naltrexone as a possible anticancer therapy and to assess the justification and potential for further research in this area.

TRAINING

OCCAM has continued to train Cancer Research Training Award fellows and Health Communications Interns and has accepted interns from the Introduction to Cancer Research Careers Program of NCI.

RESEARCH RESOURCES

Nonfederal funding is often needed to back preliminary research that aids in providing proof of concept required to acquire larger-scale grants from NIH. Nonfederal funding can be difficult to locate or identify and thus can be a barrier to obtaining federal funding for foundational or exploratory research. To assist cancer CAM researchers in identifying potential funding sources for their proposed projects, OCCAM developed a directory of nonfederal funding sources that was then converted into a database called the Cancer CAM Research Funding Database. The database contains contact information, organizational characteristics, an overview of the organization's funding programs and processes, and the particular CAM funding interests of a growing number of foundations, advocacy groups, nonfederal government organizations, and private-sector organizations.

COLLABORATIONS

INTERDIVISIONAL COLLABORATIONS

Annual Report on CAM

OCCAM produces NCI's *Annual Report on Complementary and Alternative Medicine* with support from all NCI divisions and the Office of the Director to highlight CAM research, training, and communication activities at NCI.

Office of Communications and Education

With the Office of Market Research and Evaluation, part of NCI's Office of Communications and Education, OCCAM participated in Open Call testing of its patient education workbook. This testing consisted of soliciting feedback from members of the public—in this case, cancer patients and survivors—on their opinions of the design, functionality, and content of two versions of the patient education workbook. Soliciting feedback from the public is a cornerstone of creating patient-centered, highly relevant patient education that will enhance cancer care and knowledge. OCCAM also provides content expertise on CAM for patient education materials and other NCI publications, including the *NCI Cancer Bulletin*.

Office of Cancer Centers

In 2012, OCCAM participated in a webinar, “Complementary and Alternative Medicine Cancer Research and the National Cancer Institute,” as part of the Office of Cancer Centers Learning Series. This webinar, viewed by nearly 150 participants, covered topics ranging from specific funding announcements to guidance on the NIH grants process and provided answers to frequently asked questions. The Office of Cancer Centers webinar series is composed of monthly webinars with NCI offices and extramural grantees and is promoted to the 67 NCI-designated Cancer Centers and other interested viewers. Viewing is free, and presentation slides are archived. OCCAM’s webinar slides and speaker contact information are available online at <http://cancercenters.cancer.gov/Webinar/OCCAM/OCCAMWebinar.html>.

Center for Cancer Research

OCCAM collaborates on a number of projects with NCI’s Center for Cancer Research (CCR):

- CCR’s Laboratory of Molecular Immunoregulation is studying Kushing injection, an herbal mixture containing extracts from *Sophora flavescens* and *Rhizoma smilacis glabrae*, for its anticancer effects and ability to decrease cancer-related pain.
- In CCR’s Cancer Stem Cell Section, the Laboratory of Cancer Prevention is researching compounds derived from TCM (e.g., cryptotanshinone) for their toxic effects on prostate cancer stem cells.
- The Laboratory of Cancer Prevention in CCR’s Gene Regulation Section has undertaken a comparative analysis of TCM used to prevent or treat cancer with mouse models of similar types of cancer.
- In NCI’s Division of Cancer Prevention, OCCAM staff members serve as reviewers on concept and protocol review committees for the Community Clinical Oncology Program when a proposed trial addresses a CAM topic. Expertise is provided on medical oncology research and CAM content.

INTRADIVISIONAL AND INTERNATIONAL COLLABORATIONS

Together with the Natural Products Branch (NPB) within DCTD’s Developmental Therapeutics Program (DTP), OCCAM collaborated with the Kunming Institute of Botany (KIB) in China on novel natural products derived from plant specimens. For this research, KIB supplied the natural products and DTP screened them in the NCI-60 cell line panel.

Under a Memorandum of Understanding between the State Key Laboratory of Chemistry for Natural Products in Guizhou Province, China, and NCI in March 2010, OCCAM and NPB conducted collaborative research on 57 novel natural products derived from plant specimens that were supplied by the Chinese laboratory. More than 500 botanical extracts have been produced and will be screened by DTP in the NCI-60 cell line panel.

FELLOWSHIPS AND GUEST RESEARCHERS

Two international visiting fellows from Guang An Men Hospital in Beijing, China, have consecutively joined investigators from the Laboratory of Molecular Immunoregulation at NCI’s Frederick National Laboratory of Cancer Research to explore the anticancer activity and immune-stimulating effects of the Sheng Qi formula. The formula is a mixture of herbs that is often used at Guang An Men Hospital to decrease the side effects of chemotherapy. A novel aspect of the project is the use of a murine model of inflammatory breast cancer to assess the impact of the herbal formula on the function of myeloid immunosuppressive cells.

FUTURE INITIATIVES

Because industry and academia are not likely to invest in the 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. The amount and availability of patient information materials on CAM and cancer have increased, but a need remains for tailored patient education. OCCAM will develop

evidence-based patient education resources. A clinical research program is planned:

- Translational research with medicinal botanicals and bioactive food components that have a strong preclinical research base and meet one of OCCAM's research priorities of special interest will be further explored in both the laboratory and the clinic.
- Phase 1 and 2 studies will be designed and implemented through the DTP clinic for those compounds possessing the most convincing preclinical evidence for anticancer activity.
- Investigation and development of novel complementary approaches to the treatment of cancer will be an objective.

SELECTED PUBLICATIONS

GRANTEE PUBLICATIONS

Prospective randomised evaluation of traditional Chinese medicine combined with chemotherapy: a randomised phase II study of wild toad extract plus gemcitabine in patients with advanced pancreatic adenocarcinomas, Meng Z, Garrett CR, Shen Y, Liu L, Huo Y, Zhao Q, Spelman AR, Ng CS, Chang DZ, Cohen L. *British Journal of Cancer*, 2012;107(3):411–416.

<http://www.ncbi.nlm.nih.gov/pubmed/22782343>

- Huachansu is an intravenous formulated extract derived from the venom of the wild toad *Bufo bufo gargarizans* Cantor or *Bufo melanostictus* Schneider. It is currently used in China for the treatment of lung, liver, pancreatic, and colorectal cancers. This randomized, single-blinded, phase 2 clinical study of huachansu plus gemcitabine versus placebo plus gemcitabine was carried out in patients with locally advanced and/or metastatic pancreatic adenocarcinomas. It was found that huachansu combined with gemcitabine did not improve outcomes.

Sham-controlled, randomised, feasibility trial of acupuncture for prevention of radiation-induced xerostomia among patients with nasopharyngeal carcinoma. Meng Z, Kay Garcia M, Hu C, Chiang J, Chambers M, Rosenthal DI, Peng H, Wu C, Zhao Q, Zhao G, Liu L, Spelman A, Lynn Palmer J, Wei Q, Cohen L. *European Journal of Cancer*, 2012;48(11):1692–1699.

<http://www.ncbi.nlm.nih.gov/pubmed/22285177>

- The goal of this small pilot study was to determine the feasibility of conducting a sham-controlled trial of acupuncture and whether acupuncture could prevent xerostomia among patients with head and/or neck cancer who were undergoing radiotherapy. It was demonstrated that true acupuncture, given concurrently with radiotherapy, significantly reduced xerostomia symptoms and improved quality of life when compared with sham acupuncture.

Utilization of and attitudes towards traditional Chinese medicine therapies in a Chinese cancer hospital: a survey of patients and physicians,

McQuade JL, Meng Z, Chen Z, Wei Q, Zhang Y, Bei W, Palmer JL, Cohen L. *Evidence-Based Complementary and Alternative Medicine*, 2012;2012:504507.

<http://www.ncbi.nlm.nih.gov/pubmed/23093982>

- This article reports the results of parallel surveys on the utilization of TCM conducted among 245 patients and 72 allopathic physicians at the Fudan University Shanghai Cancer Center in China. Among the responses it was found that the use of TCM by Chinese cancer patients is exceptionally high, and physicians are generally well informed and supportive of patients' use. Botanical agents are much more commonly used than acupuncture or movement-based therapies.

Pancreatic cancer: understanding and overcoming chemoresistance, Wang Z, Li Y, Ahmad A, Banerjee S, Azmi AS, Kong D, Sarkar FH. *Nature Reviews: Gastroenterology & Hepatology*, 2011;8(1):27–33.

<http://www.ncbi.nlm.nih.gov/pubmed/21102532>

- In this review, the authors summarize current knowledge of the biological significance of the epithelial–mesenchymal transition, cancer stem cells, and microRNAs in the context of drug resistance in patients with pancreatic cancer, as well as how this knowledge could be applied to overcoming chemoresistance.

STAFF PUBLICATIONS

Cancer complementary and alternative medicine research at the US National Cancer Institute, Jia L. Chinese Journal of Integrative Medicine, 2012;18(5):325–332.

<http://www.ncbi.nlm.nih.gov/pubmed/22241505>

- The author describes and discusses examples of various NCI-supported intramural and extramural research projects on cancer CAM. Also discussed are international research projects supported by OCCAM.

Systematic review: generating evidence-based guidelines on the concurrent use of dietary antioxidants and chemotherapy or radiotherapy, Nakayama A, Alladin KP, Igbokwe O, White JD. Cancer Investigation, 2011;29(10):655–667.

<http://www.ncbi.nlm.nih.gov/pubmed/22085269>

- In this review, the authors assess the medical literature on the concurrent use of antioxidants with chemotherapy or radiotherapy and suggest further steps for generating evidence-based guidelines.

Herbal therapy use by cancer patients: a literature review on case reports, Olaku O, White JD. European Journal of Cancer, 2011;47(4):508–514.

<http://www.ncbi.nlm.nih.gov/pubmed/21185719>

- The authors report on the results of a literature review to assess which herbal approaches have had associated cancer case reports and to determine which have been studied in prospective research. Mechanisms to support prospective research with such approaches are discussed.

2012 PROGRAM ACCOMPLISHMENTS

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