To commemorate the 50th anniversary of the National Cancer Act, Dr. Lyndsay Harris describes the evolution of cancer biomarkers, including their role in cancer diagnostics, and where biomarker research is headed.

Diagnostic Biomarkers - Essential Components of Cancer Care

Diagnostics are tools and techniques that provide important information for individualized health care. Cancer biomarkers, a type of diagnostic, have utility along the spectrum of care from assessing cancer risk to monitoring a person’s disease over time. Cancer biomarker analysis relies on studying biospecimens—tumor tissue, blood, or other body fluid—to evaluate genes, proteins, or other indicators from a person with cancer.

Types of Biomarkers

- **Risk Assessment**: Identify factors to assess disease susceptibility
- **Screening/Detection**: Indicate the presence of disease; early detection
- **Diagnosis**: Definitive diagnosis and general typing
- **Prognosis**: Assess disease aggressiveness & likelihood of recurrence
- **Prediction**: Predict efficacy or response to different treatments
- **Monitoring**: Monitor disease recurrence & therapeutic response

Image from: https://www.prositalcs.com/blog/6-types-of-biomarkers-in-cancer-detection
The Evolution of Biomarkers

Beginning in the 1950s, Dr. Elwood Jensen and colleagues led decades of research to identify the estrogen receptor (ER) - the first biomarker. The ER mediates estrogen action in normal female reproductive tissue, but it was also found to be present in breast cancer biopsies, a driver of tumor growth, and a potent anticancer drug target. Early studies of the ER in cancer gave the first hint that the biological makeup of a person’s tumor could impact the trajectory of their disease. However, in the mid-20th century, the field of biomarkers for clinical use was rudimentary. The treatments available then were similarly underdeveloped - people with cancer underwent surgery and radiation therapy, but only hormonal therapy for breast or prostate cancer or chemotherapy was available.

Over the next several decades, researchers discovered more genes associated with cancer that are used as clinical biomarkers today. The discovery of \( p53 \) as a tumor suppressor gene was a crucial milestone. It turns out that \( p53 \) mutations are present in many cancer types and are usually associated with worse prognosis. Researchers also identified \( HER2 \) (\( ERBB2 \)), which is the gene that codes for the epidermal growth factor receptor-2 and determined that \( HER2 \) overexpression is associated with poorer prognosis in breast and ovarian cancers. Hard work led to the development and FDA approval of trastuzumab (Herceptin) in 1998 for the treatment of \( HER2^+ \) cancers. This treatment has saved the lives of many people; in addition to breast and ovarian cancer, \( HER2 \) is important in gastrointestinal tumors, and trastuzumab is used in this context. The \( BRCA \) gene is another important biomarker. Discovered in 1994, we now know that hereditary mutations in this gene are associated with an increase in risk for breast and other cancers. In addition, having a \( BRCA1 \) or \( BRCA2 \) gene mutation predicts benefit for a particular class of therapy, PARP inhibitors.

Genes, Cancer, and Precision Medicine

Around the time of the 1971 National Cancer Act, researchers had been studying genes for some time, but Dr. Frederick Sanger’s 1977 description of a new DNA sequencing method revolutionized the field. Sanger sequencing allowed researchers to measure a single gene at a time and many genes throughout the genome. In 2001, researchers published the sequencing of the full human genome, allowing us to understand more genes and how they affect outcomes for people with cancer. Soon after, the development of next generation sequencing (NGS) sparked the era of genomics. NGS measures all genes in a tumor faster and more extensively than previous methods.

We are now in the era of precision medicine, which is predicated on the idea that every person possesses unique molecular information that can give clues about their cancer and how to treat it. We use NGS and biomarkers in precision medicine to evaluate the molecular makeup of a person’s tumor, guide treatment decisions, and consider a person’s prognosis. For example, these diagnostics are essential elements of NCI-MATCH – the largest precision medicine clinical trial - where a person receives treatment based on the genomic sequence of their tumor.

Steps in Biomarker Development

Although research in the field of biomarker diagnostics development is prolific, few biomarkers make it through FDA approval for clinical use. This is partly because of challenges related to appropriate evaluation of biomarkers during development, but another major barrier is that the diagnostic development pathway, from gene discovery to use on the market, is difficult and complicated. It is critical, however, to maintain a high standard for assay validation both for analytic characteristics and proof of benefit to patients.
Circulating tumor (ct) DNA is a recently developed biomarker that can be used to measure genes from cancer cells circulating in the blood. ctDNA is an FDA-approved clinical biomarker for diagnosis and monitoring, so cancer can be measured over time. The term “liquid biopsy” is commonly used to refer to ctDNA, but this is only one type of circulating marker. For example, another liquid biopsy analyzes exosomes, which are small packets of genetic material that are given off by cells, particularly cancer cells, and float in the blood.

**The Cancer Diagnosis Program (CDP) and the Future of Biomarkers**

CDP’s research focus is the development of cancer diagnostic biomarkers. We focus on the methods that are used for biomarker measurements and the specific conditions that are needed to handle biospecimens prior to a biomarker test. CDP works with DCTD’s Cancer Therapy Evaluation Program (CTEP) to make sure that the biomarker assays used in CTEP-supported clinical trials are done appropriately. This involves assessing the methodology and how the tests are developed so that they can eventually be used in the clinical setting.

In the years to come, diagnostics will continue to be important for the care of people with cancer. We’re heading towards an era where genomic sequencing and other novel molecular technologies are used routinely in clinical practice. It is likely to become standard for every person with cancer to have tests on their tumor and blood to determine precisely what is the best treatment for them and to understand the basis for why someone develops a certain subtype of tumor. Continued research is essential to further scientific discoveries that can be applied to clinical practice and make a difference in people’s lives.

Lyndsay Harris, MD is the Associate Director of CDP. She arrived at NCI in 2016 after a 30-year career in translational breast cancer research, including leading programs at Yale University and Case Western Reserve University. Dr. Harris heads a diverse research program and plays a leadership role in NCI’s precision medicine clinical trials.
SPOTLIGHT – DCTD Commemorates the 50th Anniversary of the National Cancer Act

The National Cancer Act of 1971 united patients, scientists, doctors, industry, and government under one vision to accelerate research on prevention, screening, diagnosis, and treatment of cancer. Since much of this research is the foundation for DCTD’s work, we are commemorating the anniversary by highlighting some advances in cancer research over the last 50 years.

- Dating back to 1957, the Developmental Therapeutics Program (DTP) was involved in the discovery or development of more than 50 anticancer therapeutics on the market today. To commemorate the 50th anniversary of the National Cancer Act, we would like to highlight DTP’s involvement in developing the following approved cancer treatments over the last 60+ years. See the chronological list of approved agents with DTP involvement.

- Dr. Janet Eary, Associate Director of DCTD’s Cancer Imaging Program, demonstrates the power of images with a historical and visual perspective on decades of advances in imaging. Dr. Eary also congratulates the imaging community for their years of effort in this progress. Read Dr. Eary’s perspective on 50 years of imaging research.

SPOTLIGHT – NCI Spearheads Two Innovative Speaker Series on Cannabis and Psilocybin Research

The Trans NCI-NIH Integrative Medicine (IM) Course Committee* initiated two time-sensitive webinars on innovative research topics of community interest in conjunction with its IM Course. The two series, “Cannabis and Cancer” and “NIH Psilocybin Research,” brought together many of the world’s leading subject experts for in-depth and first-time scientific discussions at the NIH. The events were designed to educate the research community, assess the current state of the science, and ultimately provide input to the NIH regarding future research needs.

Cannabis and Cancer Speaker Series (March 12-May 21, 2020)

A Time-Sensitive Topic of Community Interest

- In January 2017, 28 states and the District of Columbia legalized cannabis for certain medical conditions, and some legalized it for recreational purposes.

- Because of the increased accessibility and usage of cannabis and its related products, the healthcare community and the public would benefit from receiving accurate and time-sensitive information.

Series Summary

- Speakers presented a comprehensive overview of the field as it relates to cancer - from biology, drug discovery, clinical trials, and treatment, to symptom management, assessment of population use, and patient perspectives.

*Event Contact and Trans-NCI-NIH Integrative Medicine Course Committee
Dan Xi, PhD, NCI, IM Course Director (xida@mail.nih.gov); Ann Berger, MD, NIH Clinical Center; Terry Moody, PhD, NCI; David Shurtleff, PhD, NCCIH; Farah Zia, MD NCI
Access comprehensive recordings and highlights.

Research Needs Identified

- Biological research to understand the endocannabinoid system in human physiology and cancer biology
- Preclinical research to better define cannabis
  - mechanisms of action on tumor growth, or immune and nervous systems
  - drug discovery
  - adverse effects (e.g., possible immunosuppression and progression risk for certain cancers)
  - drug-drug interactions
  - Interaction with other confounding biological variables, including the microbiome
- Well-designed, statistically powered clinical trials to evaluate safety, efficacy, and dosage in patients with cancer and other comorbidities, including those on chemo- and immunotherapies
- Public health and epidemiological studies assessing long-term health benefits or detriments of cannabis use as well as health disparities
- Standardizing the medicinal product, product source, its composition, and establishing quality control

Psilocybin Research Speaker Series (April 22-June 10, 2021)

A Time-Sensitive Topic of Community Interest

- A schedule 1 natural compound found in more than 200 species of fungi, psilocybin is converted in the body to psilocin, resulting in its hallucinogenic properties.
- FDA recently granted two breakthrough therapy designations:
  - treatment-resistant depression (2018)
  - major depressive disorder (2019)
- In 2020, Oregon legalized its clinical use.
- Clinical trials are investigating its use in a range of psychiatric disorders, including cancer-related depression or anxiety, showing some potential benefit.

Series Summary

- A five-part series with 25 speakers outside of NIH and more than 900 registrants
- Topics included preclinical mechanisms, clinical trials, drug discovery, patient perspectives, ethics, and policy
- Access details, discussions, and recordings.
Research Needs Identified in Cancer

- Public health and epidemiological studies evaluating cancer patient usage
- Preclinical research and well-designed clinical trials assessing the mechanisms and therapeutic effects in cancer-related psychiatric disorders or distress, existential distress, or quality of life
- Assessment of the potential effects of chronic use and/or microdosing on:
  - the safety and efficacy for cancer-related psychiatric disorder or distress
  - drug-drug interactions and abuse
  - the tumor and immune system relating to cancer therapeutics or cancer outcomes
- New drug discovery, imaging technology development, and health disparities research
- Standardizing the medicinal product and clinical protocol, including dosage
- Investigating the confounding factors, such as host genetics, lifestyle and environmental factors, or comorbidities

NEWS ABOUT DCTD PROGRAMS AND ACTIVITIES

Program Updates

NCI Offers Expanded Capabilities for Cell Therapy Production and Seeks Project Proposals through the NCI Experimental Therapeutics (NExT) Program

Building upon its initial efforts to support the production of CAR-T cells for clinical studies, the NCI Biopharmaceutical Development Program (BDP) at Frederick National Laboratory for Cancer Research has expanded its capabilities to also manufacture lentiviral and retroviral vectors for the genetic modification step in cell therapy production.

Investigators seeking production of clinical grade vector and/or cell therapy products can submit proposals to the NExT Program three times per year (February, June, and October). See more information on lentivirus and retrovirus production at the BDP.
Guidelines for clinical trial eligibility are important to provide safety for patients and ensure that the study population is well characterized, but excessively narrow criteria can be an impediment to progress in the development of cancer therapeutics. The Cancer Therapy Evaluation Program (CTEP) recently evaluated 122 CTEP-sponsored protocols from November 1, 2018 – April 30, 2020 to determine compliance with updated template language intended to expand eligibility criteria. The recommendations for the updated language stemmed from a 2017 joint statement from the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (Friends). CTEP described their analysis in a poster at the 2021 ASCO Annual Meeting. Compliance with the new language varied depending on characteristics of the patient population. Read more about this study and CTEP’s efforts to expand clinical trial eligibility.

The NCI Formulary Expands to Offer an Additional Agent this Fall

NCI and Eli Lilly are finalizing an agreement to offer the CD4/CDK6 inhibitor, Abemaciclib, through the NCI Formulary early this fall. The availability of agents through the NCI Formulary expedites the start of clinical trials by alleviating the lengthy agreement negotiation process—sometimes up to 18 months—that has been required for investigators to access such agents on their own. Following company approval, investigators can obtain NCI Formulary agents and test them in new preclinical or clinical studies, including combination studies of Formulary agents from different companies.

For more information, contact NCIFormulary@mail.nih.gov.
The Cancer Diagnosis Program (CDP) Participates in Two SBIR Funding Opportunities

NIH/NCI 439: Advanced Sample Processing Platforms for Downstream Single-cell Multi-omic Analysis

Linda Zane and Miguel Ossandon (CDP), Divi Rao (DCCPS), and Jian Lou (SBIR) developed this SBIR contract topic. It focuses on improving the preanalytical workflow of single cell multimodal omics (scMulti-omics) technologies to better characterize cancer cells.

Background

• Integrating multiple data sets, such as DNA, RNA, and protein expression, from a single cell can provide a more detailed understanding of the interrelationship of the involved biomolecules and their function than each dataset individually. This makes scMulti-omics powerful technologies for the in-depth characterization of cells.

• Researchers need robust sample processing technologies that are compatible with downstream sequencing analysis and can be easily integrated into the preanalytical workflow.

• Recent advances have significantly improved multi-omic analysis; however, the sample processing technologies for tumors, in particular solid tumors for multi-omic analysis, are lagging.

Project Goals

Develop several preanalytical steps to make biomolecules from tumors ready for multi-omic analysis including:

• Cell isolation and enrichment for the population of interest

• Cell lysis to release biological materials

• Processing of the materials (genomic DNA, mRNA, or expressed proteins) tailored for the downstream target analysis, since the quantity of biomolecules from single cells is usually extremely low

NIH/NCI 445: Advanced Manufacturing to Speed Availability of Emerging Autologous Cell-based Therapies

Miguel Ossandon, Linda Zane, and Brian Sorg (CDP), Anthony Welch (DTP), and Rao Divi (DCCPS) developed this FOA to improve delivery of autologous cell-based therapies to people with cancer.

Background

• Current manufacturing processes for autologous cell-based cancer therapies are complex, slow, labor intensive, and expensive.

• Current manufacturing methods are unable to support the delivery of these treatments to the large numbers of people eligible to receive them.

Project Goals

• Develop systems to process multiple patient samples simultaneously

• Improve methods or systems to become novel point of care solutions or address release time bottlenecks such as developing rapid QC assays for sterility and potency

• Systems that optimize and maintain the desired physiological and immunological status of the expanded cells, while overcoming issues of cell senescence and exhaustion
Updates from The Cancer Imaging Archive (TCIA)

TCIA has released its sixth COVID-19 emergency response dataset. This final dataset includes images and related clinical data from 1,384 people with COVID-19 at Stony Brook University with a variety of different modalities and organ sites. Radiology imaging data are extremely important in COVID-19 from both diagnostic and monitoring perspectives, given the nature of COVID-19 pulmonary disease and its rapid phenotypic changes. The clinical data consist of diagnoses, procedures, lab tests, and COVID-19 data elements, which were used in data analyses. The datasets are available for building AI systems for diagnostic and prognostic modeling.

The images show an automated identification of regions of prognostic importance on baseline chest radiographs (left). The regions of highest prognostic importance (as determined by the AI algorithm) are observed primarily in lower lung regions (right), consistent with clinical findings on the corresponding chest x-rays. View the entire collection.

The Cancer MoonshotSM Biobank’s Ethical, Legal, and Social Implications (ELSI) Sub-study

Background

The Cancer MoonshotSM Biobank (the Biobank) is a 5-year project to learn more about cancer with the help of participants who donate samples of their blood and tissue throughout their treatment. Those samples will be stored in a biobank, and researchers can access donated samples and shared information to study how cancer responds to treatment and why some become treatment resistant. The Biobank study is being conducted in partnership with medical institutions that are a part of the NCI Community Oncology Research Program (NCORP).

ELSI Sub-study

A feature of the Biobank is an embedded ELSI sub-study. An NCORP researcher or group of researchers will be selected to conduct an ELSI sub-study for the Biobank on a range of topics that could include patient and provider attitudes toward the use of eConsent, participant experiences in the Biobank program, usefulness and understanding of clinical biomarker test results, and more.

ELSI Sub-study Symposium (Event Recording)

CDP’s Biorepositories and Biospecimen Research Branch (BBRB) held a mini symposium for NCORP sites on June 16, 2021 to present:

- the ELSI sub-study application
- ELSI issues related to engaging diverse populations in biobanking
- a prior multidimensional ELSI research study embedded in the NIH Genotype-Tissue Expression project (GTEx)
The symposium speakers were:

- Dr. Claudia Baquet: Ethical Considerations for Biobank Donation and Research: Diverse, Underserved Community Concerns
- Dr. Laura Siminoff: Incorporating an ELSI Project in a Complex Biomedical National Initiative: The Genotype-Tissue Expression Project (GTEx)

Following the presentations, attendees were invited to provide input on ideas about critical ELSI issues that could be investigated within the Biobank study.

NCORP sites were notified of the opportunity to apply for the ELSI sub-study on July 16, 2021, with an application deadline of September 20, 2021. To achieve a truly embedded study, applications to the funding opportunity should include NCORP investigator(s) and may include collaborator(s) outside of NCORP.

For more information on the Biobank and the ELSI sub-study, contact Helen Moore, PhD (moorehe@mail.nih.gov).

Virtual Workshop on Next-Generation Sequencing and Radiomics

The National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA) Joint Leadership Council Next-Generation Sequencing and Radiomics Working Group is hosting: “Virtual Workshop on Next-Generation Sequencing and Radiomics – Resource Requirements for Acceleration of Clinical Applications Including AI” on September 29-30, 2021. Lyndsay Harris, MD, Cancer Diagnosis Program and Lalitha Shankar, MD, PhD, Cancer Imaging Program, are co-chairs of this workshop. Event Website/Registration

Workshop Goals

- Identify and characterize critical resource gaps in these fields, especially relating to reference standards
- Explore the landscape of existing resources that might be leveraged to accelerate growth in the NGS and radiomics spaces
- Identify opportunities to support NGS and radiomic tool development and validation, especially those using technologies such as artificial intelligence and machine learning

Related Requests for Information

- NOT-OD-21-162: Critical resource gaps and opportunities to support NGS test development, validation, and data interpretation, including through technologies such as AI/machine learning
- NOT-OD-21-163: Critical resource gaps and opportunities to support radiological tool development and clinical data interpretation using AI/machine learning
NCI Moonshot<sup>SM</sup> Workshop on Enhancing Systemic Drug Delivery to Tumors

This workshop was held April 26-27, 2021 to assess current techniques and approaches in systemic drug delivery in the context of improving cancer treatment modalities.

The three sessions were:

- How to deliver cancer therapies — different modalities, different needs
- Drug delivery technologies
- Cancer immunotherapy — delivery and treatment outcomes

For more information see the workshop summary or contact Dr. Piotr Grodzinski (grodzinp@mail.nih.gov).

Co-Clinical Imaging Research Resources Program (CIRP) 2021 Annual Virtual Meeting

The CIRP Network is a trans-NCI initiative designed to:

- Provide the broader cancer community with web-accessible research resources for quantitative imaging of co-clinical trials
- Encourage consensus on how quantitative imaging methods are optimized to improve the quality of imaging results for co-clinical therapeutic or prevention trials of adult and pediatric cancer
- Leverage existing NCI resources and programs to ensure best practices, effective outreach, and rapid dissemination

The CIRP Annual Virtual Meeting 2021 convened on June 16-17 to review the progress of the CIRP program, identify challenges in the four essential areas of CIRP (animal models, co-clinical trials, quantitative imaging, and informatics), and seek solutions to integrate data, harmonize protocols, and/or standardize methodology. See the meeting summary.

Publications, Blogs, and Press Featuring DCTD Staff

Publications


NEWS ABOUT DCTD PROGRAMS AND ACTIVITIES ... continued

NCI Cancer Currents Blog Posts

FDA approval of Rylaze will address drug shortage for childhood ALL; Malcolm Smith, MD, PhD; July 29, 2021.

Avasopasem shields normal cells from radiation, helps kill cancer cells; Michael Espey, PhD; June 23, 2021.

Nivolumab-based combinations improve survival in advanced esophageal cancer; Carmen Allegra, MD; June 17, 2021.

COVID-19 vaccines may be less effective in some people with cancer; Elad Sharon, MD, MPH; May 27, 2021.

Can an antibiotic treat cancers that become resistant to PARP inhibitors? Percy Ivy, MD; July 27, 2021.

For kids with medulloblastoma, trial suggests radiation can be tailored; Jeffrey Buchsbaum, MD, PhD; July 16, 2021.

Interviews and Press

SITC releases clinical practice guidelines to aid in the management of immune-related adverse events from ICI therapy; TargetedOnc; Marc Ernstoff, MD; July 22, 2021.

The COVID pandemic’s lingering impact on clinical trials; Nature; Meg Mooney, MD, MS; June 9, 2021.
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### NEWS ABOUT DCTD PROGRAMS AND ACTIVITIES...

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### Notices of Change

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