NIH NATIONAL CANCER INSTITUTE

pipeline news

February 2018

DCTD Division of Cancer Treatment and Diagnosis

DCTD Staff Highlight: Jamie Zwiebel, MD

Jamie Zwiebel, MD, former Chief, Investigational Drug Branch, Cancer Therapy Evaluation Program, DCTD, NCI, NIH

A native of Brooklyn, NY, **Jamie Zwiebel, MD** arrived at NCI in 1980 for a Public Health Service post-doctoral position in a tumor biology lab. Following further research and clinical training and devoting 21 years in DCTD's Cancer Therapy Evaluation Program (CTEP), Jamie retired from the federal government in January 2018.

How did you end up coming to NIH?

I always liked the sciences, and the limitations in our treatments for patients motivated me to go into the lab to understand cancer better. So, after medical school and completing an internal medicine residency at Mount Sinai in New York, I moved to Maryland in 1980 to join a tumor biology lab at NCI. I also decided to further my clinical training and completed a fellowship in hematology/oncology at George Washington University. I returned to NIH in 1985 to learn molecular biology techniques – specifically to develop gene therapies – at the National, Heart, Lung, and Blood Institute. I then spent a number of years at the Georgetown University Lombardi Cancer Center, where I ran my own gene therapy lab and treated hematology and oncology patients. However, having confronted the triple (actually quadruple) threat of research, teaching, patient care, and administration in academia, I found myself looking elsewhere for career satisfaction. Neither industry nor clinical practice held much appeal, so when I became aware of a position at CTEP, a program about which I knew little at the time, I decided to investigate further. I was impressed by the program's work, and, more importantly, I was drawn to the opportunity to make a wider impact in oncology while exploring scientific areas that interested me.

What was CTEP like in 1996, and how has it changed?

For one thing, just about everything was paper-based, and all documents had to be retrieved

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from banks of file cabinets in CTEP's Protocol Information Office and Regulatory Affairs Branch. Also, in 1996 there were just two sections in the Investigational Drug Branch – one for biologics and one for chemotherapy. Biologics were still at an early stage at that time, and there had been very few FDA approvals. Paclitaxel and oxaliplatin, two notable chemotherapy drugs that CTEP exclusively developed in the 1990s, are both now part of the standard of care for several cancers.

CTEP did early drug development differently then: when a new drug was brought into our program, we would issue a mass solicitation, resulting in the submission of 100 or more letters of intent (LOIs). CTEP, however, would approve only a minor fraction of the submitted LOIs, resulting in much fruitless effort by investigators. Now we've implemented drug development project teams comprised of both NCI and extramural experts in tumor biology, translational science, and clinical trials. These teams have frequent webinars over about 2 months and develop proposals for clinical trials that are enriched with biomarkers that are intended to better understand the drug's effect on tumors, as well as to select patients with tumors that are more likely to respond. The project team process has been very well-received by our academic colleagues and has strengthened CTEP's drug development efforts.

What were some major advances in cancer therapeutics during your time at CTEP?

I'd say the major scientific change is that now we can identify molecular subtypes in tumors. New drugs are directed at molecular targets, and we've begun to select patients who are more likely to benefit from a treatment, what has been called precision oncology. One well-known example is the approval of trastuzumab (Herceptin®) in breast cancer patients whose tumors overexpress the HER2 growth factor receptor. Had we not selected patients with HER2 overexpression on their tumors, the benefit of this therapy in this population would likely have been missed. Now NCI and others are trying to find out what might be the best approaches for precision oncology by conducting clinical trials like NCI-MATCH and Lung-MAP.

Based on our improved understanding of what causes cancers to survive and to grow, CTEP recognized the need for testing molecularly-targeted combination therapies and pioneered their development in the early 2000s. These efforts were enabled by the incorporation of key language in our agreements with pharmaceutical companies. Pharmaceutical companies have since followed CTEP's lead and are doing combinations studies as well now, either by working together with other companies or by adding more drugs to their own portfolios.

Another important change is the advances in immuno-oncology (IO). The impressive success of the checkpoint inhibitors in solid tumors that were previously thought to be intractable to immunologic approaches has led to an exponential increase in the numbers of trials being done. Other promising IO agents also have now entered the clinic. More recently, we've seen remarkable responses to chimeric antigen receptor (CAR) T cell therapies in certain leukemias that were refractory to all other treatments. Hopefully, these successes will translate to solid tumors as well.

What's on the horizon for CTEP?

By virtue of its collaborations with industry and its outstanding clinical trials networks, CTEP should continue to be at the forefront of cancer therapeutic development. And with the greater emphasis on biomarkers, DCTD will continue to support biomarker development and the genomic analysis of patient tumors in CTEP clinical trials. Patients will undoubtedly benefit from the scientific advances that result from these efforts.

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What are your plans after you retire?

As long as I can remember, my life has been focused on pursuing my career as a physician, and that lifetime commitment to medicine now has come to an end. Fortunately, I do have interests that should ease my transition into retirement, and I look forward to traveling both here and abroad, working on improving both my language and my photography skills, taking some courses, and spending more time with my family. And who knows, I may even occasionally pick up a stethoscope again in a primary care setting.

Spotlight:

DCTD's Cancer Imaging Program Incorporates New Nanotechnology Branch

After 12 years within NCI's Center for Strategic Initiatives, the Office of Cancer Nanotechnology Research (OCNR) transitioned to DCTD's Cancer Imaging Program (CIP) in late 2017 to form the Nanodelivery Systems and Devices Branch (NSDB). The organizational move reflects the growing technological maturity and progression of several cancer nanotechnologies developed under the NCI Alliance for Nanotechnology in Cancer program. Established in 2004, this program supports the development of nanomaterials and nanotechnology enabled devices for clinical applications in cancer diagnosis and treatment. The program includes a collection of Centers of Cancer Nanotechnology Excellence (U54 cooperative agreements), Innovative Research in Cancer Nanotechnology grants (U01/R01), Cancer Nanotechnology Training Centers (T32 grants managed through NCI's Center for Cancer

New Faces of NSDB

Piotr Grodzinski, PhD
Branch Chief

Stephanie Morris, PhD
Program Director

Christopher Hartshorn, PhD
Program Director

Christina Liu, PhD
Program Director

Julie Collier
Grants Program Analyst

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Training), and its intramural arm – the Nanotechnology Characterization Laboratory (NCL), located at the Advanced Technology Research Facility of the Frederick National Laboratory for Cancer Research. NSDB will continue to manage the Alliance program, as well as incorporate more nanotechnology into CIP's grant portfolio. Furthermore, the branch will continue to propel the translation of cancer nanotechnology into the clinic.

The Alliance program's notable accomplishments include:

- ***Establishment of several novel nanoparticle-based strategies for drug delivery and imaging.*** These delivery platforms have been thoroughly characterized from the standpoint of structure activity relationships, safety, biodistribution, and efficacy. NCL played a significant role in these studies, evaluating over 300 nanomaterial platforms and establishing important guidelines for the effective nanomedicine designs.

- ***Implementation of suitable technologies through evolving efforts.*** Early work to develop technology platforms that sought appropriate cancer applications has led to efforts that defined biological and clinical problems ahead of time and then identified suitable nanotechnologies.

- ***Evaluation of technologies in more than 20 Phase I and Phase 2 clinical trials.*** These technologies – developed by academia with Alliance program support – indicate the effectiveness of a new model of translational pipeline: innovative technology develops and matures in academic centers, then transitions to the translational stage through the formation of spin-off companies (over 100 established to-date).

- ***Training a new cadre of medical nanotechnologists.*** This occurred both through the exchange of graduate students and post-doctoral scientists among different university centers, as well as through T32 Cancer Nanotechnology Training Centers.

Spotlight:

NCI Efforts to Further Stewardship in Clinical Trials

Every year, NCI invests millions of dollars towards clinical trials in the U.S. and throughout the world. NCI is committed to supporting clinical trials that investigate a mission-relevant question that is of high priority and has the highest likelihood to advance knowledge, improve health for patients, and safeguard the Nation's investment in clinical research.

The NCI Clinical Trials Stewardship Initiative continues to build upon NCI's solid foundation of clinical trials stewardship through the implementation of a series of NIH clinical trial policies and NCI-specific procedures involving the conduct and management of funded clinical trials. Led by a committee of representatives from NCI's various Divisions, Offices, and Centers that support, or are involved in, NCI-funded clinical trials, the goal of the initiative is to ensure the following:

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- Quality of clinical trials
- Safety of research participants
- Reliability of data
- Dissemination of results
- Appropriate stewardship of funds

The NIH's Office of Extramural Research has provided information and several resources to understand the new clinical trials requirements for grants and contracts, including those shown in the list to the right. In addition, the cancer community can visit the NCI's Stewardship Initiative homepage to learn more about changes to advance the public health impact of cancer trials. This includes steps taken to achieve more consistency in the conduct and management of clinical trials funded through grants, contracts, and cooperative agreements. For instance, the following additional resources are now available to investigators:

Clinical Trial Requirements

- Clinical Trial Definition
- Why the Changes
- Good Clinical Practice
- Specific Funding Opportunities
- Clinical Trial-Specific Review Criteria
- New Form
- Single IRB Policy
- Protocol Template
- Registration and Reporting

- A new DCTD-specific clinical trial required FOA, referred to as PAR-18-560: National Cancer Institute's Investigator-Initiated Early Phase Clinical Trials for Cancer Treatment and Diagnosis (R01 Clinical Trial Required).
- A list of all NCI Funding Opportunity Announcements (FOAs) that Accept Clinical Trials is available on NCI's website, Cancer.gov.
- A referral to the new NIH Research Methods Resources website that provides key resources (FAQs, videocasts, etc.) that can help answer questions and address common methodological problems in group or cluster-randomized trials.
- Information on Clinical Trial Requirements for Grants and Contracts is available on NCI's Grant Policies website.

Visit DCTD's website to stay up-to-date on the latest information and announcements related to clinical trials and NCI's Clinical Trials Stewardship Initiative.

Spotlight:

Quantitative Imaging, Deep Learning, and Recent Advances in Imaging

Because of the complexities inherent in cancer imaging, such as the dynamic nature and heterogeneity of tumors, simple clinical images of cancer have historically not been sufficient to predict patient outcome. However, advances in quantitative image analyses now allow clinically relevant information to be extracted from cancer images for further processing and examination. For example, quantitative imaging can be used to analyze specific features in clinical PET (positron emission tomography), CT (computed tomography), or MRI (magnetic resonance imaging) to determine if a therapy is expected to change patient outcome. Quantitative imaging investigators use deep learning and artificial intelligence to identify subtle, health-related features in cancer images.

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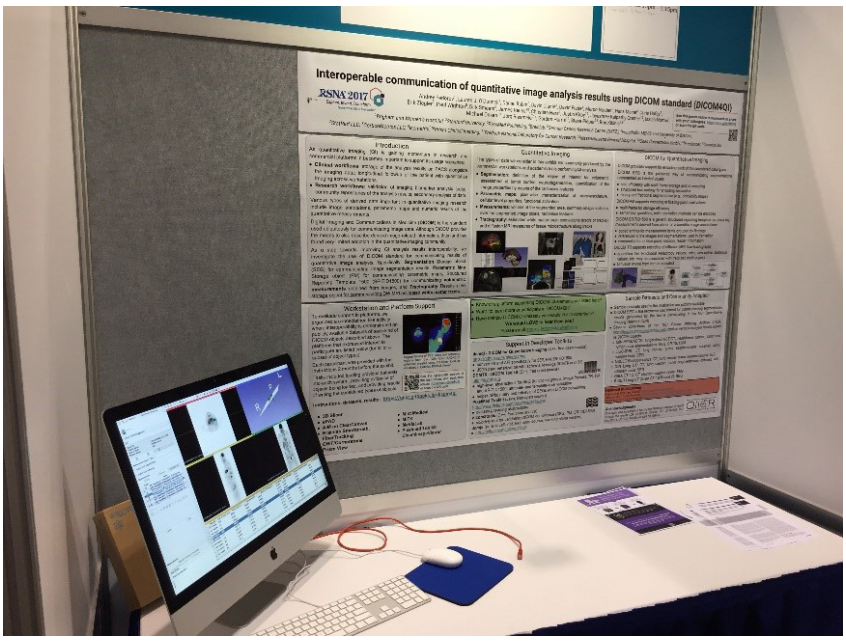
Initially, quantitative imaging analyses and techniques were designed to measure physical parameters of tumors, such as size, location, and density (e.g., a reduction in tumor size or density was considered a biomarker for therapy success). Early successes with this quantitative imaging analysis approach encouraged researchers to continue refining physical measurements of tumors, but disease recurrence after tumor reduction and other measurement failures diminished the power of these techniques as biomarkers for patient outcome in cancer.

Following these setbacks, recent research has led to improvements in the quantitative imaging process. The Quantitative Imaging Network (QIN), which is an organized network of imaging research teams supported by NCI's Cancer Imaging Program (CIP), has played an important role in this field. For example, standards are being implemented for data collection and image processing when quantitative methods are used to extract information from images. QIN investigators have developed tools (image analysis algorithms) that standardize performance characteristics of clinical imaging devices. In addition, imaging phantoms, which are objects that mimic the imaging characteristics of human body tissues, are being developed to act as "gold standards" for scanner calibration and standardization. Creation and validation of imaging phantoms are vital QIN efforts.

Advances in quantitative imaging for measuring or predicting response to oncologic therapies was a prominent topic at the recent annual meeting of the Radiological Society of North America (RSNA); November 26-December 1, 2017; Chicago, IL. Many QIN team members displayed the functionality of their newly developed tools to the imaging community during technical presentations.

Further validation studies for these tools in clinical trials have the potential to demonstrate the value of quantitative imaging methods. The Quantitative Imaging Biomarker Alliance (QIBA), created by RSNA, promotes the use of quantitative biomarkers to measure cancer therapy response in clinical trials. The QIBA recently accepted an invitation to join the QIN as an associate member to collaboratively advance quantitative methods in clinical imaging practice. Visit the new QIN website for the latest updates on the QIN.

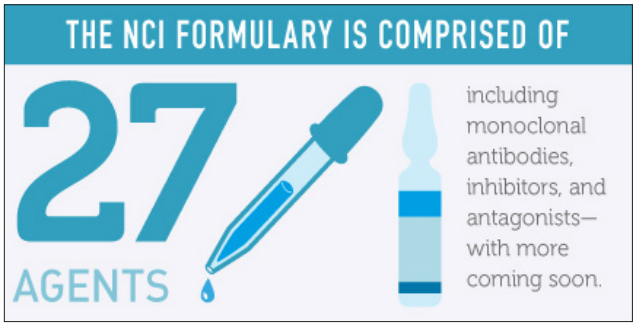


QIN developers' booth at recent 2017 RSNA annual meeting

News about DCTD Programs and Activities

Program Updates

Eligibility for Access to the NCI Formulary Has Expanded



Access to the NCI Formulary has expanded beyond the NCI Designated Cancer Centers, to now include all NCI-audited clinical research centers who are main member sites of NCTN and ETCTN. The NCI Formulary is a public-private partnership between NCI and pharmaceutical and biotechnology companies, and this eligibility expansion will provide more investigators rapid access to Formulary agents for clinical trials and preclinical research. There are now 27 agents provided by nine pharmaceutical companies - review the list of available agents. The availability of agents through the NCI Formulary will expedite the start of clinical trials by alleviating the lengthy negotiation process—sometimes up to 18 months—that has been required for investigators to access such agents on their own. Following company approval, investigators will be able to obtain agents from the available NCI Formulary list and test them in new preclinical or clinical studies, including combination studies of Formulary agents from different companies.

Data Science Bowl Update

The third annual Data Science Bowl (DSB) opened in January 2017 with the goal of improving the detection accuracy of low-dose computed tomography lung cancer screening using data curated by DCTD's Cancer Imaging Program and the Division of Cancer Prevention. The 2017 DSB, Turning Machine Intelligence Against Lung Cancer, was recently nominated for a 2018 SXSW Interactive Innovation Award, chosen in the category of Health, Med, & BioTech.

Publications and Outreach

Reports and Peer-reviewed Publications

Curran CS, Rasooly A, He M, Pickril B, Thurin M, Sharon E. Report on the NCI Microbial-Based Cancer Therapy Conference. *Cancer Immunol Res*. 2018 Feb;6(2):122-126.

Massett HA, Hampp SL, Goldberg JL, Mooney M, Parreco LK, Minasian L, Montello M, Mishkin GE, Davis C, Abrams JS. Meeting the Challenge: The National Cancer Institute's Central Institutional Review Board for Multi-Site Research. *J Clin Oncol*. 2018 Jan 31. doi: 10.1200/JCO.2017.76.9836. [Epub ahead of print]

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Predictive Biomarkers in Innovative Clinical Trial Design. *Semin Cancer Biol*. 2018 Jan 5. doi: 10.1016/j.semcancer.2018.01.003. [Epub ahead of print]

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Warner TD, Weil CJ, Andry C, Degenholtz HB, Parker L, Carithers LJ, Feige M, Wendler D, Pentz RD. Broad Consent for Research on Biospecimens: The View of Actual Donors at Four U.S. Medical Centers. *J Empir Res Hum Res Ethics*. 2018 Jan 1. doi: 10.1177/1556264617751204. [Epub ahead of print]

Rubinstein PG, Moore PC, Rudek MA, Henry DH, Ramos JC, Ratner L, Reid E, Sharon E, Noy A, AIDS Malignancy Consortium (AMC). Brentuximab Vedotin with AVD Shows Safety, in the Absence of Strong CYP3A4 Inhibitor, in Newly Diagnosed HIV-Associated Hodgkin Lymphoma. *AIDS*. 2017 Dec 26. doi: 10.1097/QAD.0000000000001729. [Epub ahead of print]

Agrawal L, Engel KB, Greytak SR, Moore HM. Understanding Preanalytical Variables and Their Effects on Clinical Biomarkers of Oncology and Immunotherapy. *Semin Cancer Biol*. 2017 Dec 16. doi: 10.1016/j.semcancer.2017.12.008. [Epub ahead of print]

Doroshow JH, Simon RM. On the Design of Combination Cancer Therapy. *Cell*. 2017 Dec 14;171(7):1476-1478.

Kohn EC, Lee J-m, Ivy SP. The HRD Decision – Which PARP Inhibitor to Use for Whom and When. *Clin Can Res*. 2017 Dec 1;23(23):7155-7157.

Roadmap for Medical Imaging Research and Development; A Report by the Interagency Working Group on Medical Imaging, Committee on Science, National Science and Technology Council. December 2017. DCTD participants: Janet Eary, MD, Lori Henderson, PhD, Paula Jacobs, PhD, Lalitha Shankar, MD, PhD, Cancer Imaging Program and Jeff Buchsbaum, MD, PhD and Bhadrasain Vikram, MD, Radiation Research Program.

Cancer Currents and Other* Blog Posts

For Rare Melanoma, Checkpoint Inhibitors May Hold Substantial Promise; **Elad Sharon, MD, MPH**, Cancer Therapy Evaluation Program; February 14, 2018.

Olaparib Approved for Treating Some Breast Cancers with BRCA Gene Mutations; **Elise Kohn, MD**, Cancer Therapy Evaluation Program; January 29, 2018.

Study Identifies Potential Cause of Hearing Loss from Cisplatin; **Percy Ivy, MD**, Cancer Therapy Evaluation Program; January 26, 2018.

Nilotinib Can Be Discontinued in Some Patients with Chronic Myelogenous Leukemia; **Richard Little, MD**, Cancer Therapy Evaluation Program; January 19, 2018.

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*Perspectives in Breast and Colorectal Cancer Research; **Carmen Allegra, MD**, Cancer Therapy Evaluation Program; NSABP Foundation Blog; January 15, 2018.

Genomic Profiling Test Cleared by FDA Can Help Guide Cancer Treatment, Clinical Trial Enrollment; **Tracy Lively, PhD**; Cancer Diagnosis Program; December 21, 2017.

Prior Cancers Common in Patients Newly Diagnosed with Cancer; **Percy Ivy, MD**, Cancer Therapy Evaluation Program; December 14, 2017.

Expanding Cancer Clinical Trial Access for Patients with HIV; **Elad Sharon, MD, MPH**, Cancer Therapy Evaluation Program; December 1, 2017.

Social Media

CTEP launched a Twitter feed in January 2018. Follow @NCICTEP_ClinRes – the official Twitter account of the NCI Cancer Therapy Evaluation Program, providing updates to the trials research community.

Meeting Participation

Several DCTD staff will present at the AACR Annual Meeting 2018 (April 14-18, 2018; Chicago, IL). A full list of DCTD staff presentations will be available on the DCTD website News & Events section in early April.

On February 13 - 14, 2018, **Naoko Takebe, MD**, Developmental Therapeutics Clinic, joined **Ted Trimble, MD, MPH**, Center for Global Health, and several other NCI staff to welcome members of a delegation from various Japanese universities. The meetings involved discussions of clinical trials, precision medicine, genomics, rare cancers, pediatric cancer, and Big Data.

Japanese delegation and NCI staff

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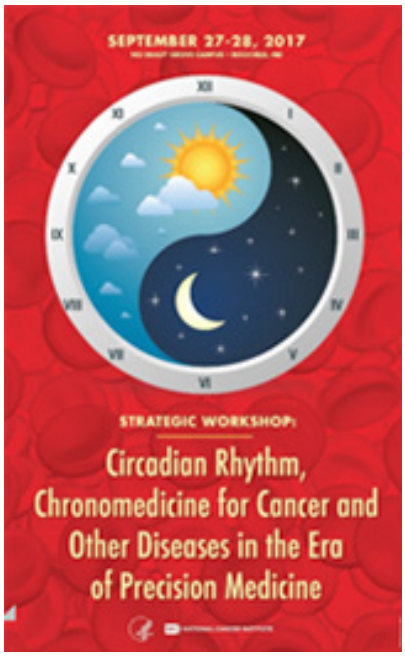
Lokesh Agrawal, PhD, Cancer Diagnosis Program, presented "Impact of Preanalytical Variables on Tissues by Studying Global Protein and Gene Expression: Implications for Use in Clinical Research" in the NGS Assays for Oncology Applications session at Molecular Med Tri-Con (February 11-16, 2018; San Francisco, CA).

Elad Sharon, MD, MPH presented, "Immunology 101: Tools and Assays Used in Clinical Trials" at the ASCO-SITC Clinical Immuno-Oncology Symposium (January 25-27, 2018; San Francisco, CA).

Members of DCTD's Cancer Therapy Evaluation Program (**Jeff Abrams, MD, Bhupinder Mann, MD,** and **Bill Timmer, PhD**) and NCI's Center for Cancer Research, Neuro-Oncology Branch (**Mark Gilbert, MD**) jointly organized a workshop on Strategies to Improve Glioblastoma (GBM) Treatment from December 14-15, 2017.

Jeff Abrams, MD and Mark Gilbert, MD



On September 27-28, 2017, the National Cancer Institute held a Strategic Workshop: Circadian Rhythm, Chronomedicine for Cancer and Other Diseases in the Area of Precision Medicine. The meeting chair, **Dan Xi, PhD**, Program Director, and Director of the Research Development and Support Program, Office of Cancer Complementary and Alternative Medicine, planned and led the workshop with input from the workshop planning committee. This comprehensive, trans-NIH workshop was co-funded by NCI's Division of Cancer Prevention, the National Institute of General Medical Sciences, the National Heart, Lung, and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute of Allergy and Infectious Diseases.

New DCTD Funding Opportunities

TITLE	ANNOUNCEMENT NUMBER	OPENING DATE	EXPIRATION DATE	ACTIVITY CODE
National Cancer Institute's Investigator-Initiated Early Phase Clinical Trials for Cancer Treatment and Diagnosis	PAR-18-560	February 15, 2018	January 8, 2021	R01