NATIONAL CANCER INSTITUTE

pipeline news

May 2017

DCTD Division of Cancer Treatment and Diagnosis

DCTD Staff Highlight: Tracy Lively, PhD

Tracy Lively, PhD, is Chief of the Diagnostics Evaluation Branch, Deputy Associate Director, Cancer Diagnosis Program, Division of Cancer Treatment and Diagnosis, NCI, NIH

Tracy Lively, PhD received doctoral training in Biology from the Massachusetts Institute of Technology, completed post-doctoral fellowships in cancer biology and human genetics, and was an assistant professor in the Division of Biomedical Sciences at the University of California, Riverside. During her early research career, Dr. Lively participated in two major discovery efforts: the search for the Huntington's disease gene and the characterization of both forms of the *BCR-ABL* oncogene prior to the development of Gleevec®. Dr. Lively said, "During my graduate and post-doctoral training, I worked with some of the most talented basic researchers in the world, but I always gravitated toward those aspects of the projects that promised to make a difference for the health of patients." Dr. Lively has co-authored more than 30 peer-reviewed publications on a variety of subjects, including oncogenes, cell growth in melanoma, and translating biomarker assays into oncology clinical practice, which has become a focus of her work at NCI.

Dr. Lively joined NCI's Cancer Diagnosis Program (CDP) as a program director in 1996 and is currently CDP's Deputy Associate Director and Chief of the Diagnostics Evaluation Branch. As a member of DCTD's staff for more than 20 years, she has sought to support and improve the development of clinical laboratory tests to guide therapy for cancer patients. Dr. Lively has planned and implemented targeted research initiatives for exploratory research, technology development, and patient-oriented research in cancer diagnostics.

Dr. Lively supervises the Diagnostics Evaluation Branch, which is responsible for the scientific oversight of a portfolio of investigator-initiated research grants. According to Dr. Lively, supporting the development of clinical-grade laboratory assays using the standard discovery-oriented NIH grant mechanisms can be challenging. Therefore, one

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of her most satisfying accomplishments was to assist colleagues at the Center for Scientific Review to establish the Cancer Biomarkers Study Section. This chartered study section is composed of reviewers who have the necessary expertise to review grant applications containing clinical assay development, including proficiency in laboratory and statistical methods. Over the years, Dr. Lively and colleagues in CDP have initiated a series of targeted Funding Opportunity Announcements (FOAs) using less-traditional grant mechanisms, such as the R33, to support the construction of diagnostic assay prototypes. She currently serves as the coordinator for PAR-15-095, a trans-NCI FOA that uses UH2/UH3 awards to support clinical assay development.

When Dr. Lively first arrived at NCI, microarray technology was a new research tool, and the era of comprehensive molecular characterization of human tumors was beginning. Over the ensuing two decades, CDP has supported several projects that turned gene expression profiles into successfully launched commercial diagnostic products. Since 2010, Dr. Lively has been the project scientist responsible for the Strategic Partnering to Evaluate Cancer Signatures (SPECSII) program, which developed diagnostic tests for breast cancer, lymphoma, childhood leukemia, and rhabdomyosarcoma, among others. She also serves on the steering committee for the TAILORx trial, which is refining the use of the 25-gene prognostic classifier for breast cancer offered by Genomic Health, Inc.

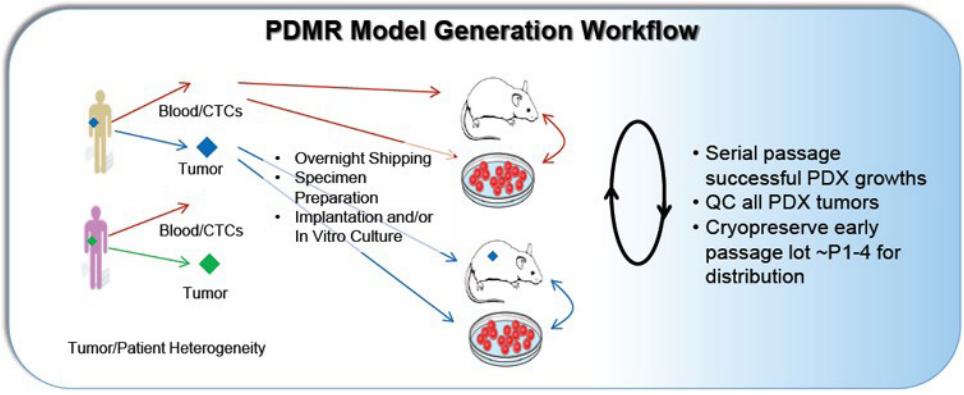
Recently, Dr. Lively has taken a more active role in the integration of diagnostic assay development into the clinical trials supported by DCTD's Cancer Therapy Evaluation Program. Since its inception in 2013, she has coordinated the Biomarker Review Committee for DCTD, which is dedicated to ensuring that integral and integrated biomarker assays in DCTD-supported trials are fit-for-purpose, whether they serve as pharmacodynamic indicators or potential future companion or complementary diagnostics.

An asset to NCI, DCTD would like to congratulate Dr. Lively on her achievements thus far during her NIH career.

Spotlight:

NCI Patient-Derived Models Repository

In 2013, NCI began developing a national Patient-Derived Models Repository (PDMR) to serve as a resource for public-private partnerships and for academic drug discovery efforts. Patient-derived models (PDMs), such as patient-derived xenografts (PDXs), are thought to reflect human tumor biology more closely than established cell lines due to their low passage number and better recapitulation of tumor heterogeneity, thereby offering the potential of more predictive models than traditional cancer cell lines.The PDMs being developed for the repository



are derived from tumor tissue or circulating tumor cells (CTCs) and are propagated both in vitro using 2D or 3D cell culture systems and in vivo via passaging in mice as PDXs.

The PDMR models are generated from tumor tissue collected from patients at NCI-designated Cancer Centers, NCI's Developmental

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Therapeutics Clinic (DTC), participating sites within NCI's Experimental Therapeutics Clinical Trials Network (ETCTN), NCI's Community Oncology Research Program (NCORP), and other participating centers. Specimens are then sent to the Biological Testing Branch (BTB) at the Frederick National Laboratory for Cancer Research (FNLCR) where they are processed and either implanted into immune-compromised mice or cultured in several in vitro modeling systems.

NCI launched the publicly accessible PDMR website in May 2017 and is now making available cryopreserved fragments of early-passage, molecularly characterized, clinically annotated PDXs and molecular fractions (including DNA, RNA, and flash-frozen tumor fragments for protein extraction) to researchers at minimal cost.

NCI initially released 100 models across the following seven histologies:

- Urothelial cancer
- Squamous cell lung cancer
- Renal cancer
- Colon adenocarcinoma
- Pancreatic adenocarcinoma
- Adult soft tissue sarcoma
- Melanoma

NCI plans to develop and make available more than 1,000 unique, quality controlled, early passage, molecularly characterized PDMs that can serve as standard resources, enabling comparison of research results across laboratories. In addition to common cancers, the repository has focused on the creation of models for less prevalent cancer types that are under-represented in the research space, such as prostate cancer, small cell lung cancer, and sarcomas, as well as developing models from racial and ethnic minority patients.

Key goals of the PDMR:

- Provide a publicly accessible PDM database that includes all associated patient and PDX data (limited medical history, PDX pathology images, and whole exome and RNASeq files) to researchers. Researchers not interested in growing PDX models in the laboratory will still be able to mine the metadata associated with the PDX models at no cost through NCI's publicly accessible PDMR web site: https://pdmr.cancer.gov/. As new models pass NCI's stringent quality control metrics, they will be added to this database along with all associated data.
- Provide a set of standard operating procedures for all aspects of PDM creation, propagation, and quality control to the scientific community. In addition, NCI is working with external groups who have (1) their own previously established early-passage PDX models or (2) viably cryopreserved patient material collected under IRB-approved protocols that, with the proper material transfer agreements, could be released to the PDMR for propagation and distribution to the scientific community.
- Perform preclinical drug studies using PDXs developed in the repository, including the preclinical modeling of the NCI-Molecular Profiling-Based Assignment of Cancer Therapy (NCI-MPACT) clinical trial. The most recent effort is to establish standard procedures for high-throughput preclinical testing, with a rolling enrollment of >50 PDX models tested against five standard agents; this study will also produce data enabling an assessment of how closely PDX model responses align with what is observed in a clinical setting with these standard-of-care agents.

A Phase 2 Trial in Patients with Desmoid Tumors Shows Clinical Promise

Desmoid tumors, also known as aggressive fibromatosis, are slow-growing, locally invasive soft tissue tumors that constitute a rare mesenchymal disease. Although desmoid tumors are non-metastatic, they may lead to impaired organ function and decreased quality of life. While surgical resection, radiation, and 'watch and wait' treatment approaches may be successful for some patients, post-surgical disease recurrence and the heterogeneity of tumors complicate effective treatment strategies. The molecular mechanisms

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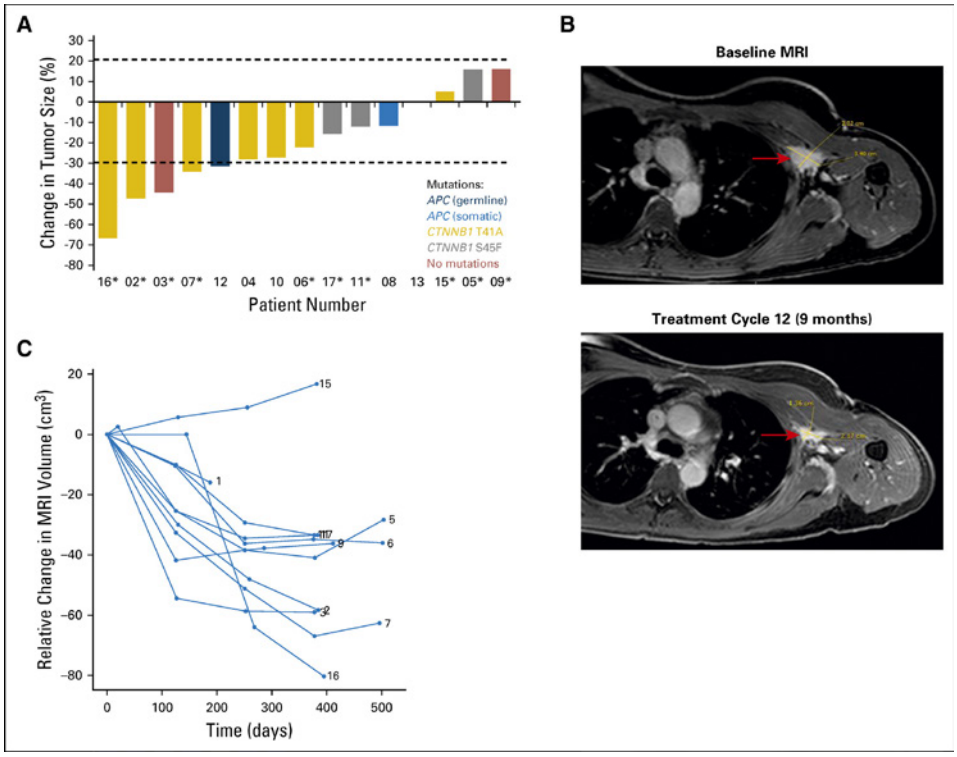
underlying the development of desmoid tumors are not well understood, but recent research has identified the Wnt/β-catenin pathway, which exhibits crosstalk with Notch signaling, as a possible clinical target. Preclinical and Phase 1 testing of agents targeting the Notch pathway in desmoid tumors, specifically with γ-secretase inhibitors, had yielded promising outcomes. These studies led to a Phase 2 trial in 17 patients with recurrent, refractory, progressive desmoid tumors who were treated with the γ-secretase inhibitor, PF-03084014, twice per day, in 21-day cycles. The trial was conducted in NCI's Developmental Therapeutics Clinic (DTC), and the results were recently published in the Journal of Clinical Oncology (Kummar, 2017).



(Kummar, 2017)

Out of 16 evaluable patients in this study, five exhibited a partial response (PR) and continue to be on study for more than two years. Another five patients remain on study with stable disease. Of the 17 accrued patients, 15 had mutations in either APC or CTNNB1, two genes of the β-catenin pathway; however, the small study size precluded analysis of associations between mutation status and clinical response. Interestingly, three of the patients experiencing a PR did not exhibit responses until approximately 2 years after starting treatment, which suggests that the mechanism of action of the γ-secretase inhibitor on this tumor may be complex and differ from routine models of cell death. The study investigators also evaluated patient-reported outcomes and determined that statistically significant improvements in symptom burden were reported in those patients exhibiting a PR. This treatment warrants further study in patients suffering from desmoid tumors and highlights the first positive results of γ-secretase inhibitor PF-03084014 in a Phase 2 trial of this rare disease.

News about DCTD Programs and Activities

Publications and Outreach

Peer-reviewed Publications

- Sharon E. Commentary on Perez et al.: How to Create a 21st Century Adverse Event Reporting System. *Clin Trials*. 2017 Jun;14(3):234-236
- Szczepanek CM, Hurley P, Good MJ, Denicoff A, Willenberg K, Dawson C, Kurbegov D. Feasibility of a Centralized Clinical Trials Coverage Analysis: A Joint Initiative of the American Society of Clinical Oncology and the National Cancer Institute. DOI: 10.1200/JOP.2016.020313 *J Oncol Pract* - published online before print May 8, 2017.

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- Cristofaro JV, Ansher SS, Zwiebel JA, Ivy P, Conley B, Abrams JS, Doroshow JH. National Cancer Institute Formulary: A Public-Private Partnership Providing Investigators Access to Investigational Anticancer Agents. *Clin Pharmacol Ther.* 2017 May;101(5):616-618. This paper is included in a special Issue of Clinical Pharmacology & Therapeutics, featuring six papers on Cancer Moonshot℠ cross-agency initiatives.

- Seymour L, Bogaerts J, Perrone A, Schwartz LH, Mandrekar S, Lin NU, Litiere S, Dancey J, Chen A, Hodi FS, Therasse P, Hoekstra OS, Shankar LK, Wolchok JD, Ballinger M, Caramella C, de Vries EG, RECIST Working Group. iRECIST: Guidelines for Response Criteria for Use in Trials Testing Immunotherapeutics. *Lancet Oncol.* 2017 May;18(3):e143-e152.

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- Tummers WS, Warram JM, Tipirneni KE, Fengler JF, Jacobs P, Shankar L, Henderson L, Ballard B, Pogue BW, Weichert JP, Bouvet M, Sorger J, Contag CH, Frangioni JV, Tweedle MF, Basilion JP, Gambhir, SS, Rosenthal EL. Regulatory Aspects of Optical Methods and Exogenous Targets for Cancer Detection. *Cancer Res.* 2017 May 1;77(9):2197-2206.

- Sharon E. Can an Immune Checkpoint Inhibitor (Sometimes) Make Things Worse? *Clin Cancer Res.* 2017 Apr 15;23(8):1879-1881.

- Balasubramanian P, Kinders RJ, Kummar S, Gupta V, Hasegawa D, Menachery A, Lawrence SM, Wang L, Ferry-Galow K, Davis D, Parchment RE, Tomaszewski JE, Doroshow JH. Antibody-independent Capture of Circulating Tumor Cells on Non-epithelial Origin with the ApoStream® System. *PLoS One.* 2017 Apr 12;12(4):e0175414.

- Enewold L, Sharon E, Harlan LC. Metastatic Melanoma: Treatment and Survival in the US after the Introduction of Ipilimumab and Vemurafenib. *Oncol Res Treat.* 2017 Apr;40(4):174-183.

- Curran C, Sharon E. Report on the FDA-AACR Immuno-oncology Drug Development Workshop. *Cancer Immunol Res.* 2017 Apr;5(4):282-285.

- Liston DR and Davis M. Clinically Relevant Concentrations of Anticancer Drugs: A Guide for Nonclinical Studies. *Clin Cancer Res.* 2017 Mar 31. pii: clincanres.3083.2016. doi: 10.1158/1078-0432.CCR-16-3083. [Epub ahead of print]

- Kummar S, O'Sullivan Coyne G, Do KT, Turkbey B, Meltzer PS, Polley E, Choyke PL, Meehan R, Vilimas R, Horneffer Y, Juwara L, Lih A, Choudhary A, Mitchell SA, Helman LJ, Doroshow, JH, Chen A. Clinical Activity of the γ-Secretase Inhibitor PF-03084014 in Adults with Desmoid Tumors (Aggressive Fibromatosis). *J Clin Oncol.* 2017 May 10;35(14):1561-1569.

- Kunos CA, Chu E, Makower D, Kaubisch A, Sznol M, Ivy SP. Phase I Trial of Triapine-Cisplatin-Paclitaxel Chemotherapy for Advanced Stage or Metastatic Solid Tumor Cancers. *Front Oncol.* 2017 Apr 4;7:62

- Lee JM, Hays JL, Chiou VL, Annunziata CM, Swisher EM, Harrell MI, Yu M, Gordon N, Sissung TM, Ji J, Figg WD, Minasian L, Likowitz S, Wood BJ, Doroshow J, Kohn EC. Phase I/Ib study of olaparib and carboplatin in women with triple negative breast cancer. *Oncotarget.* 2017 Mar 25. doi: 10.18632/oncotarget.16577. [Epub ahead of print]

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- Guo L, Hamre J, Eldridge S, Behrsing HP, Cutuli FM, Mussio J, Davis M. Editor's Highlight: Multiparametric Image Analysis of Rat Dorsal Root Ganglion Cultures to Evaluate Peripheral Neuropathy-inducing Chemotherapeutics. *Toxicol Sci.* 2017 Jan 22; 156(1):275-288.

Cancer Currents Blog Posts

- NCI ALMANAC: A New Tool for Research on Cancer Drug Combinations; **James Doroshow, MD**, Deputy Director for Clinical and Translational Research and **Jerry Collins, PhD**, Developmental Therapeutics Program; May 12, 2017.

- FDA Approves Niraparib as Maintenance Therapy for Recurrent Ovarian Cancer; **Elise Kohn, MD**, Cancer Therapy Evaluation Program; April 12, 2017.

- Advancing the Potential and Promise of Total-Body PET Imaging; **Paula Jacobs, PhD**, Cancer Imaging Program and **Antonio Sastre, PhD**, National Institute of Biomedical Imaging and Bioengineering; April 7, 2017.

- Blinatumomab Extends Survival for Patients with Advanced ALL; **Richard Little, MD**, Cancer Therapy Evaluation Program; March 30, 2017.

- Stem-Cell Based Tool May Help Measure Heart Toxicity of Cancer Drugs; **Myrtle Davis, DVM, PhD**, Developmental Therapeutics Program; March 21, 2017.

Interviews and Press

- "Million-Dollar Prize Hints at How Machine Learning May Someday Spot Cancer," **Keyvan Farahani, PhD**, Cancer Imaging Program, for Technology Review; May 9, 2017.

- "NCI Formulary Holds Promise to Speed Clinical Trials," **Sherry Ansher, PhD**, Cancer Therapy Evaluation Program and **Jason Cristofaro, PhD, JD**, Office of the Director, for IASLC Lung Cancer News (page 13); May 2017.

- "Developing New Cancer Therapies through Exceptional Responders," **Barbara Conley, MD**, Cancer Diagnosis Program, for Ideastream; March 14, 2017.

- "Old-style Chemo Is Still a Mainstay in the Age of Targeted Cancer Therapy," **Elad Sharon, MD, MPH**, Cancer Therapy Evaluation Program, for National Public Radio; March 13, 2017.

- "Latest in cancer treatment," **Elad Sharon, MD, MPH**, Cancer Therapy Evaluation Program, for Sawa Magazine (~11:00 minutes); March 9, 2017.

- "iRECIST Guideline Unveiled for Immunotherapies," **Elad Sharon, MD, MPH**, Cancer Therapy Evaluation Program, for Cancer Discovery; March 2017.

- "NCI-MATCH Assay Validation Provides Template for Others; Trial on Track to Screen 6K by May," **Barbara Conley, MD**, Cancer Diagnosis Program and **Mickey Williams, PhD**, Frederick National Laboratory for Cancer Research, for Genomeweb; February 27, 2017.

Meeting Participation

- View DCTD staff presentations at the 2017 American Society of Clinical Oncology annual meeting (June 2-6, 2017; Chicago, IL).

- Stemming from a special educational session at last year's Early Drug Development Meeting, a workshop on improving biopsy quality was held on May 22, 2017. The workshop, "NCI/DCTD Joint Pathology/Radiology Workshop," focused on practical techniques and best practices for liver and lung tumor biopsies, with a goal of developing draft procedural guidance documents.

- NCI is conducting the Exceptional Responders Initiative pilot study to evaluate the molecular alterations found in tumors from cancer patients who responded to a systemic treatment (standard or investigational) that is effective in less than 10% of patients. These patients are considered 'exceptional responders,' and NCI-supported research hopes to find reasons for the excellent outcomes in their molecular profiles. The goal is to use information gleaned from this study to design treatments that could be applied to other cancer patients.

Barbara Conley, MD, Cancer Diagnosis Program, speaks at the "Refining Precision Therapeutics using Exceptional Response and Resistance" meeting.

NCI held a workshop related to this topic on May 11-12, 2017 ("Refining Precision Therapeutics using Exceptional Response and Resistance"), which was organized by **Lyndsay Harris, MD**, Cancer Diagnosis Program. The goals of the meeting were to:

- Share insights from molecular analysis of exceptional responders to elucidate mechanistic underpinnings of extreme sensitivity to cancer therapies
- Review studies of mechanisms of resistance in patients treated with targeted agents
- Discuss preclinical models of response/resistance that facilitate translation of precision medicine to the clinic (e.g., CRISPR-Cas, PDX)
- Understand readiness to implement molecular characterization of response and resistance mechanisms into drug development

- At the Accelerating Anticancer Agent Development and Validation meeting (May 3-5, 2017; Bethesda, MD), **Jeffrey Abrams, MD**, Cancer Therapy Evaluation Program, presented the Keynote Session with Dr. Richard Pazdur, MD, FDA (White House Cancer Moonshot: Realities for Cancer Drug Development Through Implementation of NCI and FDA Moonshot Initiatives), and **Elad Sharon, MD, MPH**, Cancer Therapy Evaluation Program, was a panel member in a session ("Evolving Combination Therapies on an Immuno-Oncology Backbone; Regulatory Issues and Pathways").

- View DCTD staff presentations at the 2017 American Association for Cancer Research annual meeting (April 1-5, 2017; Washington, DC).

Program Updates

- After engaging nearly 2,000 teams and accepting more than 700 entries, the third annual Data Science Bowl (DSB) challenge competition concluded on April 12, 2017. The competition was launched in January 2017 and was presented by Booz Allen Hamilton and Kaggle in collaboration with NCI, with the goal of improving detection accuracy of low-dose computed tomography (LDCT) lung cancer screening. Using training and test data sets provided by multiple sources, including the NCI-sponsored National Lung Screening Trial (NLST), this year's competition encouraged data scientists to develop machine learning algorithms to more accurately diagnose the presence of lung cancer at lower false positive rates than are currently encountered. NCI will now work closely with the scientific community, FDA, and other stakeholders to utilize the top-ranking open source analytics-based solutions uncovered by the DSB competitors to further advance the field of LDCT lung cancer screening. Potential follow-on activities could include testing of the winning algorithms on new and more heterogenous data sets and engaging teams from the NCI Quantitative Imaging Network (QIN). Also, the FDA's interest in LDCT may lead to further validation of the winning algorithms toward utility in clinical trial settings. View the press release announcing the Data Science Bowl winners.
- A recent DCTD publication in *Cancer Research* described studies that evaluated the therapeutic activity of thousands of pairs of FDA-approved cancer drugs against the NCI-60 Human Tumor Cell Lines. The online publication of this paper in late April 2017 formally introduced the NCI ALMANAC website, which contains a publicly accessible and searchable database of the screening results described in the paper.

Honors and Awards

Richard Simon, PhD, Biometric Research Program, is the 2017 recipient of the Melvin Zelen Leadership Award in Statistical Science from the Department of Biostatistics at the Harvard T.H. Chan School of Public Health. Dr. Simon received the award in person on May 18, 2017 and presented a lecture entitled, "Translating Genomics to Personalized Oncology: Key Contributions of Statistical Scientists."

Lokesh Agrawal, PhD, Cancer Diagnosis Program, received an award for outstanding scientist from the Society of American Asian Scientists in Cancer Research in April 2017.

Carmen Allegra, MD, received an Outstanding Contributions Award for supporting NRG Oncology's research mission during the time that he was their GI Committee Co-Chair. Dr. Allegra received the award at the NRG Oncology Semiannual Meeting (February 9-11, 2017; Houston, TX).

Retirement Announcements

Barbara Conley, MD, Associate Director, Cancer Diagnosis Program and **Richard Simon, PhD**, Associate Director, Biometric Research Program have officially announced their retirements in July. DCTD would like to recognize them both for their accomplishments as Associate Directors. Look for more information on their careers and time at NIH in DCTD's August Pipeline newsletter.

Penny Svetlik, Developmental Therapeutics Program retired at the end of May. Penny joined NIH 34 years ago and worked with DTP for 30 of those years. Penny has expressed her sincere thoughts about her co-workers and her time working in DTP. DCTD would like to wish Penny the best in her retirement.