



STAFF HIGHLIGHT: Bhadrasain Vikram, MD



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Bhadrasain Vikram, MD, has served as Chief of the Clinical Radiation Oncology Branch, Radiation Research Program (RRP) since 2006. He oversees a portfolio of clinical and translational grants within RRP and assists the Cancer Therapy Evaluation Program (CTEP) with Clinical Trials Networks. Dr. Vikram describes crucial research opportunities in radiation oncology that may help improve the lives of cancer patients.

What do you consider to be critical focus areas for radiation oncology research?

Radiation therapy (RT) has been used for more than 100 years, and it is an essential component of therapy for many patients. For some diseases, like early breast cancer and vocal cord cancer, patients do very well, but it does not cure many patients with larger tumors or metastatic disease. Improving treatment for patients with locally advanced or metastatic disease is the area with the greatest need. RRP has been working closely with CTEP to support clinical trials that include combination studies

with RT. Adding immunotherapy to radiation for locally advanced lung cancer has been one success story; however, we need to study RT earlier in the drug development process if we are to help more patients.

While research has been done in cell lines and in animals, we also need to understand better the biological basis for a tumor's resistance to RT in humans. Knowing what caused treatment failure to occur after RT could lead to the identification of new therapeutic targets. The culture of the radiation oncology community has been that research biopsies are difficult, but I hope that will change soon, assisted in part by progress in liquid biopsies. By performing tumor biopsies before and after treatment, supplemented by blood analysis and imaging during treatment, we can assess tumor biology as it evolves in response to RT. Developing biomarkers for RT is a part of this strategy. Once we have a better understanding of why radiation fails or succeeds, we can better determine what therapy a patient should receive and when.

In this issue

Spotlight - Results of a Phase II Trial of the MEK Inhibitor, Selumetinib, in Patients with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN) 3
Spotlight - Updates from the NCI Experimental Therapeutics (NExT) Program 3
News about DCTD Programs and Activities 4

What are some promising areas of radiation oncology research?

In the last ten years, the progress in stereotactic radiation, which precisely delivers high-dose radiation to the visible tumor, gives me hope. Any living cell can be killed if we give it enough radiation, but the challenge is to give enough without damaging normal tissue. Some newer technologies allow us to give radiation with precision down to a millimeter, but it's often hard to determine where the cancer ends and normal cells begin. While we have reduced the extent of radiation 'spilling' into the normal tissue, we still need to maintain a margin around the visible tumor, which creates radiation side effects. Therefore, harnessing advanced imaging techniques is crucial.

Another important area is using radiation to stimulate the immune system. Some of the earliest research was done in my lab at Albert Einstein in the 1990s, when we showed that focal radiation to a tumor caused it to reveal its immune markers, making metastases more vulnerable to immunotherapy. This field is now thriving with many preclinical and clinical studies aiming to prolong survival of patients with metastatic cancers.

Gains from targeted therapies have been limited by acquired drug resistance and tumor heterogeneity, but we've been impressed with the potential of adding a radioactive "payload" to antibodies that allows radiation to access microscopic metastases. Some radioactive particles have a range of a few microns, so if the antibody attaches to one cell, the radiation is likely to kill nearby cancer cells as well - even those not expressing the target. It is gratifying that there are now more than two dozen companies active in this area of research.

NCI has also supported research on protons and heavier charged particles like carbon ions since the 1970s. When I arrived at NCI, these approaches were being used in a few clinics,

but there was no Level 1 evidence to support their use. With support from Dr. Harold Varmus and by working with CTEP and grantees, there are now several prospective randomized trials for a variety of cancers. Results should become available during the next few years.

What unique opportunities have been available to you at NCI?

When I arrived at NCI, the National Institute of Allergy and Infectious Diseases (NIAID) was developing a countermeasures program using drugs and devices to mitigate the effects of possible radiation injury on soldiers and civilians. We thought that cancer patients may benefit from this approach by reducing their radiation side effects. RRP had an opportunity to collaborate with NIAID and NCI's Small Business Innovation Research (SBIR) program to test agents for this purpose. This has been a productive relationship, and we recently published a paper ([Zakeri K, 2019](#)) on the companies' progress. This work could not have been done anywhere but at NCI, and we could not have made this level of progress without support from NIAID, Walter Reed, and the Biomedical Advanced Research and Development Authority. We hope some of these drugs will soon enter the clinic.

In 2002, I went to Vienna, Austria on a 6-month sabbatical to work with the International Atomic Energy Agency of the United Nations. My focus was on assisting low-resource countries with improving oncology care, and this project was extended to almost five years. This work changed my perspective on cancer care, prompting me to focus personal efforts in low-resource countries. I've had opportunities at NCI to further this goal by collaborating with NCI's Center for Global Health. We funded a few grants for low-cost devices that may facilitate sophisticated treatments that we take for granted in this country. I hope to make RT more accessible in low-resource countries, increase the cancer cure rate, and decrease toxicity.

SPOTLIGHT - Results of a Phase II Trial of the MEK Inhibitor, Selumetinib, in Patients with Neurofibromatosis Type 1 (NFI) and Inoperable Plexiform Neurofibromas (PN)

In April 2019, the US Food and Drug Administration announced breakthrough designation for selumetinib, an oral MEK inhibitor, based on two early-phase studies for children with NFI and inoperable PN. Patients in these studies had an unprecedented 71% and 74% response rate, respectively. Results of an ongoing [phase II clinical trial](#) of selumetinib treating adult patients with NFI and PN were recently presented at the [AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics](#) in Boston, MA. This study is being conducted collaboratively with Dr. Brigitte Widemann in the Pediatric Oncology Branch of NCI's Center for Cancer Research (CCR), [NCI's](#)



Geraldine O'Sullivan Coyne speaks about selumetinib at the Molecular Targets meeting.

[Developmental Therapeutics Clinic](#) (DTC), and the Pharmacodynamic Assay Development and Implementation Section, Frederick National

Laboratory for Cancer Research. Of the first 21 patients enrolled and treated with selumetinib, 15 (71%) experienced a partial response, and most patients reported decreased pain associated with their tumors. Pharmacodynamic studies using the patients' biopsies are ongoing to determine the levels of signaling proteins that may be involved

in the mechanism of this targeted therapy. Geraldine O'Sullivan Coyne, MD, PhD, DTC, presented the trial's results in a proffered paper session at the meeting ([AACR Press Release](#)).

SPOTLIGHT - Updates from the NCI Experimental Therapeutics (NEXt) Program

The [NCI's Experimental Therapeutics \(NEXt\) Program](#) provides resources to domestic and international researchers in academia, non-profit, government, and industry for projects focused on developing therapies for unmet needs that are not adequately addressed by the private sector.

- One NEXt project is supporting the development of two [inhibitors of p97 ATPase](#). This novel therapeutic target ensures that misfolded proteins are cleared from the cytoplasm; therefore, its inhibition can lead to an accumulation of toxic cytoplasmic proteins and ultimately, cancer cell death.

The p97 inhibitor drug development project is a collaborative effort among the NEXt Program's Chemical Biology Consortium (CBC), Cleve Biosciences, and NCI's Comparative Oncology Program, Center for Cancer Research.

- On May 4, 2019 the Space X CRS 17/Falcon 9 rocket launched containing several NIH-supported research projects, including a NEXt CBC project. The goal of this project is to crystallize Taspase 1 - a protein involved in cancer - in microgravity to better understand its complex, three-dimensional structure to help guide the design of potent drugs. On



September 23, 2019, The Children's Inn at NIH partnered with NIH's National Center for Advancing Translational Sciences, the International Space Station, and the Amateur Radio on the International Space Station and held a livestream, "Ask an Astronaut (in Space)!" This event helped Inn children learn about life in space and the translational

science research being done there. During contact, astronaut Nick Hague mentioned the X-ray crystallography component of the NExT project.

- The NExT Program's CBC is planning its third annual symposium for early in 2020 at the Salk Institute in San Diego, CA. The goal of the CBC Symposia is to bring together chemical biologists and molecular oncologists from government, industry, and academia to address unmet therapeutic needs in oncology. For information on the CBC Symposium, contact Barbara Mroczkowski, PhD (mroczkowskib@mail.nih.gov). In addition, Dr. Mroczkowski recently presented at the [AMRI Symposium](#): "NCI Chemical Biology Consortium: Advancing Small Molecular Therapeutics to the Clinic."

NEWS ABOUT DCTD PROGRAMS AND ACTIVITIES

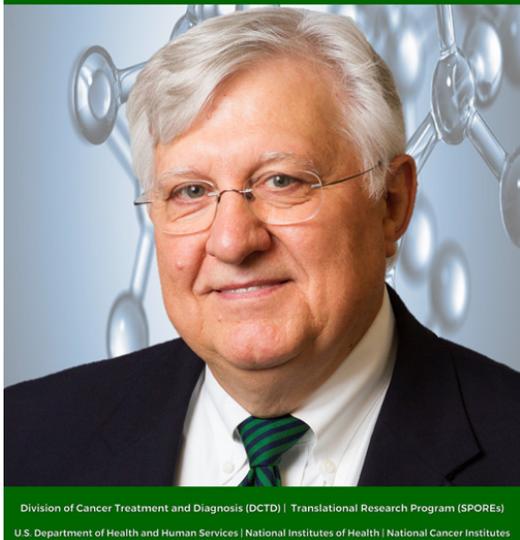
Program Updates

Updates from the Translational Research Program (TRP)

NIH NATIONAL CANCER INSTITUTE

Genitourinary Perspectives 2019 Workshop: In Honor of Dr. Andrew Hruszkewycz

Friday, August 23, 2019
NCI-Shady Grove, Conference Room TE406



Division of Cancer Treatment and Diagnosis (DCTD) | Translational Research Program (SPOREs)
U.S. Department of Health and Human Services | National Institutes of Health | National Cancer Institutes

Genitourinary Perspectives 2019 Workshop: In Honor of Andrew Hruszkewycz, MD, PhD

In late August, friends and devoted colleagues celebrated the life of the late Andrew Hruszkewycz, MD, PhD, Translational Research Program, with a workshop on genitourinary (GU) cancers. NCI colleagues provided welcoming remarks, followed by presentations by GU investigators and grantees who knew Andrew well.

Fiscal Year 2019 Specialized Programs of Research Excellence (SPORE) Grantees

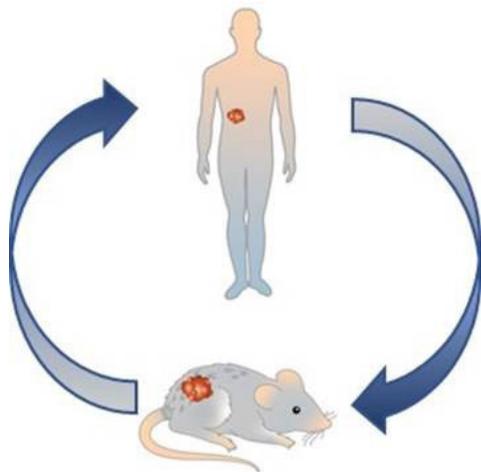
TRP recently announced its successfully competed [FY2019 SPORE grantees](#). The SPORE Program uses the P50 and U54 grant funding mechanisms to promote collaborative, interdisciplinary, translational cancer multi-project research. SPOREs are primarily focused on organ site disease and themes that cut across organ sites. There are now 54 funded SPOREs located at academic centers in 20 states. The FY2019 SPORE grantees include seven new grants and ten grant renewals, which is the largest number of SPOREs selected for funding in ten years.

SPORE Grantee Receives Nobel Prize

On October 7, 2019, Dr. William Kaelin, Jr, Dana-Farber Cancer Institute, jointly received the [Nobel Prize in Physiology or Medicine](#) with Drs. Gregg L. Semenza and Peter J. Ratcliffe. Dr. Kaelin is a longtime NCI grantee, serving as

a co-Investigator of the [Beth Israel Deaconess Medical Center Kidney SPORE](#) since it was initially funded in 2003 and as a Multiple Principal Investigator of the SPORE since 2014.

NCI-funded PDX Network Coordinates Pre-Clinical Testing of Therapeutic Targets in Patient-derived Models



A network of patient-derived xenograft (PDX) laboratory research units and a PDX coordinating center comprise the [PDX Development and Trial Centers Research Network - PDXNet](#). This network, which is part of the NCI's Cancer Moonshot-funded grants, was established to coordinate collaborative, large-scale development and pre-clinical testing of targeted therapeutic agents in patient-derived models to advance the vision of cancer precision medicine.

NCI Supports Research in Cell-based Immunotherapies of Human Cancer

A long-term goal of the NCI is to promote greater efficacy and broad-based adoption of cell-based immunotherapies for both hematological and solid tumors. To achieve this goal, NCI provided [supplemental funding](#) to P30 Cancer Center Support Grants and P50 Specialized Programs of Research Excellence Grants to perform developmental and preclinical research that addresses specific

challenges in cell-based immunotherapies. This support addresses several challenges in the field, including, identifying new targets for cell-based immunotherapy for solid tumors, increasing efficacy and/or safety of cell-based immunotherapies using known targets, improving vectors and their production and yield, etc.

A New Educational Video on Brachytherapy for Spanish-speaking Women

A new [patient video](#) is now available to Spanish-speaking women as an educational tool to describe the key components and critical importance of brachytherapy for the treatment of uterine and cervical cancer. The

video emphasizes the importance for women to finish all their radiotherapy treatments – both external radiation therapy and internal brachytherapy – in order to have the best chance of recovery.

Publications and Outreach

Publications

Cesano, A, Marincola FM, and Thurin M. [Status of Immune Oncology: Challenges and Opportunities](#). *Methods Mol Biol*. 2020;2055:3-21.

Cohen JW, Widemann BC, Derdak J, et al. [Cediranib Phase-II Study in Children with Metastatic Alveolar Soft-part Sarcoma \(ASPS\)](#). *Pediatr Blood Cancer*. 2019 Dec;66(12):e27987.

Rokita JL, Rathi KS, Cardenas MF, et al. [Genomic Profiling of Childhood Tumor Patient-derived Xenograft Models to Enable Rational Clinical Trial Design](#). *Cell Rep*. 2019 Nov 5;29(6):1675-1689.

Mena E, Lindenberg ML, Turkbey IB, et al. [¹⁸F-DCFPyL PET/CT Imaging in Patients with Biochemical Recurrence Prostate Cancer after Primary Local Therapy](#). *J Nucl Med*. 2019 Nov 1. Epub ahead of print.

Hartshorn CM, Russel LM, and Grodzinski P. [National Cancer Institute Alliance for Nanotechnology in Cancer-catalyzing Research and Translation toward Novel Cancer Diagnostics and Therapeutics](#). *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2019 Nov;11(6) e1570.

Kopp LM, Malemati S, Krailo M, et al. [Phase II Trial of the Glycoprotein Non-metastatic B-targeted Antibody-drug Conjugate, Glembatumumab Vedotin \(CDX-011\), in Recurrent Osteosarcoma AOST1521: A Report from the Children's Oncology Group](#). *Eur J Cancer*. 2019 Nov;121:177-183.

Kunos CA, Andrews SJ, Moore KN, et al. [Randomized Phase II Trial of Triapine-Cisplatin-Radiotherapy for Locally Advanced Stage Uterine Cervix or Vaginal Cancers](#). *Front Oncol*. 2019 Oct 15;9:1067.

Makhlouf H, Watson MA, Lankes HA, et al. [Toward Improving Practices for Submission of Diagnostic Tissue Blocks for National Cancer Institute Clinical Trials](#). *Am J Clin Pathol*. 2019 Oct 15. Epub ahead of print.

Kunos CA, Capala J, Dicker AP, et al. [Clinical Outcome Assessments Toolbox for Radiopharmaceuticals](#). *Front Oncol*. 2019 Oct 10;9:1028.

Bhattacharya T, Brettin T, Doroshow JH, et al. [AI Meets Exascale Computing: Advancing Cancer Research with Large-scale High Performance Computing](#). *Front Oncol*. 2019 Oct 2;9:984.

Xu H, Zhao X, Bhojwani D, et al. [ARID5B Influences Anti-metabolite Drug Sensitivity and Prognosis of Acute Lymphoblastic Leukemia](#). *Clin Cancer Res*. 2019 Oct 1. Epub ahead of print.

Min DJ, Zhao Y, Monks A, et al. [Identification of Pharmacodynamic Biomarkers and Common Molecular Mechanisms of Response to Genotoxic Agents in Cancer Cell Lines](#). *Cancer Chemother Pharmacol*. 2019 Oct;84(4):771-780.

Sparano JA, Gray RJ, Makower DF, et al. [Clinical Outcomes in Early Breast Cancer with a High 21-Gene Recurrence Score of 26 to 100 Assigned to Adjuvant Chemotherapy Plus Endocrine Therapy: A Secondary Analysis of the TAILORx Randomized Clinical Trial](#). *JAMA Oncol*. 2019 Sep 30. Epub ahead of print.

Foster JC, Freidlin B, Kunos CA, et al. [Single-arm Phase II Trials of Combination Therapies: A Review of the CTEP Experience 2008-2017](#). *J Natl Cancer Inst*. 2019 Sep 23. Epub ahead of print.

Khodadoust MS, Rook AH, Porcu P, et al. [Pembrolizumab in Relapsed and Refractory Mycosis Fungoides and Sezary Syndrome: A Multicenter Phase II Study](#). *J Clin Oncol*. 2019 Sep 18. Epub ahead of print.

Grodzinski P. [NCI Centers of Cancer Nanotechnology Excellence \(CCNEs\) – A Full Story to Set the Record Straight.](#) *J Control Release.* 2019 Sept 10;309:341-342.

Holmes EM, Bradbury I, Williams LS, et al. [Are We Assuming Too Much with Our Statistical Assumptions? Lessons Learned from the ALTO Trial.](#) *Ann Oncol.* 2019 Sep 1;30(9):1507-1513.

He M, Grkovic T, Evans JR, et al. [The NCI library of traditional Chinese medicinal plant extracts - Preliminary assessment of the NCI-60 activity and chemical profiling of selected species.](#) *Fitoterapia.* 2019 Sep;137. Epub ahead of print.

Ivy SP, Kunos CA, Arnaldez, et al. [Defining and Targeting Wild-type BRCA High-grade Serous Ovarian Cancer: DNA Repair and Cell Cycle Checkpoints.](#) *Expert Opin Investig Drugs.* 2019 Sep;28(9):771-785.

Jhaveri KL, Wang XV, Makker V, et al. [Ado-trastuzumab Emtansine \(T-DM1\) in Patients with HER2 Amplified Tumors Excluding Breast and Gastric/Gastro-esophageal Junction \(GEJ\) Adenocarcinomas: Results from the NCI-MATCH Trial \(EAY131\) Sub-protocol Q.](#) *Ann Oncol.* 2019 Aug 27. Epub ahead of print.

Masset HA, Mishkin G, Moscow JA, et al. [Transforming the Early Drug Development Paradigm at the National Cancer Institute: The Formation of NCI's Experimental Therapeutics Clinical Trials Network \(ETCTN\).](#) *Clin Cancer Res.* 2019 Aug 22. Epub ahead of print.

Yung RL and Korde LA. [Hereditary Cancer Evaluation in 2019 – A Rapidly Evolving Landscape.](#) *JAMA Oncol.* 2019 Aug 20. Epub ahead of print.

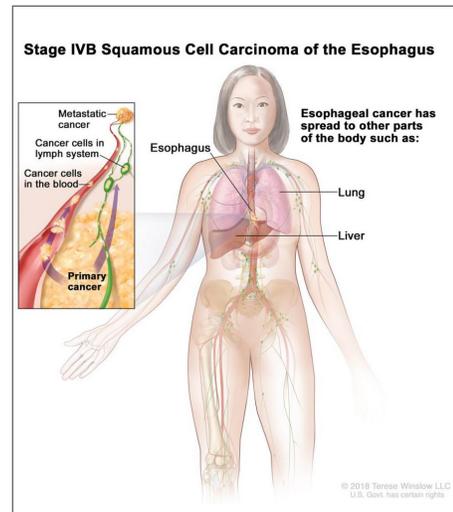
NCI Cancer Currents Blog Posts

[Analysis Shows Women with High Breast Cancer Recurrence Scores Benefit from Chemo;](#) Larissa Korde, MD, Cancer Therapy Evaluation Program; October 24, 2019.

[For Children with Neuroblastoma, Trial Results Highlight Continued Evolution of Treatment;](#) Nita Seibel, MD, Cancer Therapy Evaluation Program; September 23, 2019.

TRK GENE FUSIONS
— ARE FOUND IN UP TO —
90%
OF RARE CANCERS
Source: Cocco E, et al. Nature Reviews Clinical Oncology 2018;15(12):731-747.

[FDA Approves Entrectinib Based on Tumor Genetics Rather Than Cancer Type;](#) Nita Seibel, MD, Cancer Therapy Evaluation Program; September 17, 2019.



[Pembrolizumab Approved for Some Patients with Advanced Esophageal Cancer;](#) Carmen Allegra, MD, Cancer Therapy Evaluation Program; August 28, 2019.

[Study Tests Immunotherapy in People with Cancer and Autoimmune Diseases;](#) Elad Sharon, MD, MPH, Cancer Therapy Evaluation Program; August 26, 2019.

Interviews and Press

Radio Device Shows Promise as Liver Cancer Treatment, NC Study Finds; Bhadrasain Vikram, MD, Radiation Research Program; North Carolina Health News; October 15, 2019.

Rethinking a Common Surgery Technique for Early Cervical Cancer; Elise Kohn, MD, Cancer Therapy Evaluation Program; Cancer; September 26, 2019.

Why a Promising, Potent Cancer Therapy Isn't Used in the US; Norman Coleman, MD, Radiation Research Program; Wired; August 21, 2019.

Expert Panel Updates Advice on BRCA Cancer Gene Screening; Larissa Korde, MD, Cancer Therapy Evaluation Program; Reuters; August 20, 2019.



Study Quantifies Impact of NCI-sponsored Trials on Clinical Cancer Care; NCI Press Release; September 18, 2019.

Related interview: **NCI-sponsored Clinical Trials Cost-effective,**

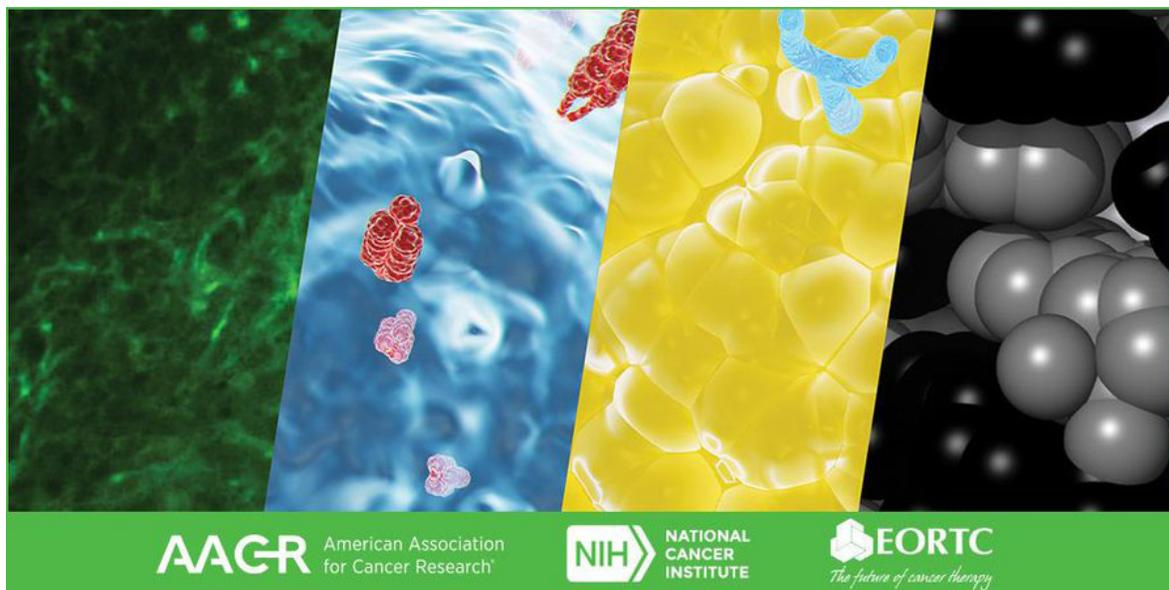
'Practice Influential'; James Doroshov, MD; HemOnc Today; October 22, 2019.

TMB Faces Validation Hurdles; Lisa McShane, PhD, Biometric Research Program; Cancer Discovery; September 5, 2019.

The New Ovarian Cancer Landscape: Many Questions, Much Hope; Elise Kohn, MD, Cancer Therapy Evaluation Program; OncLive; September 3, 2019.

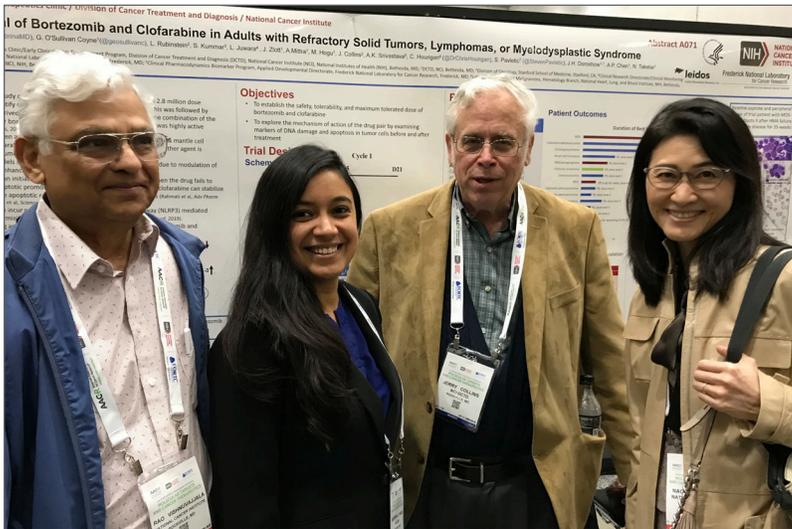
Conferences and Meetings

EORTC-NCI-AACR International Conference on Molecular Targets and Cancer Therapeutics

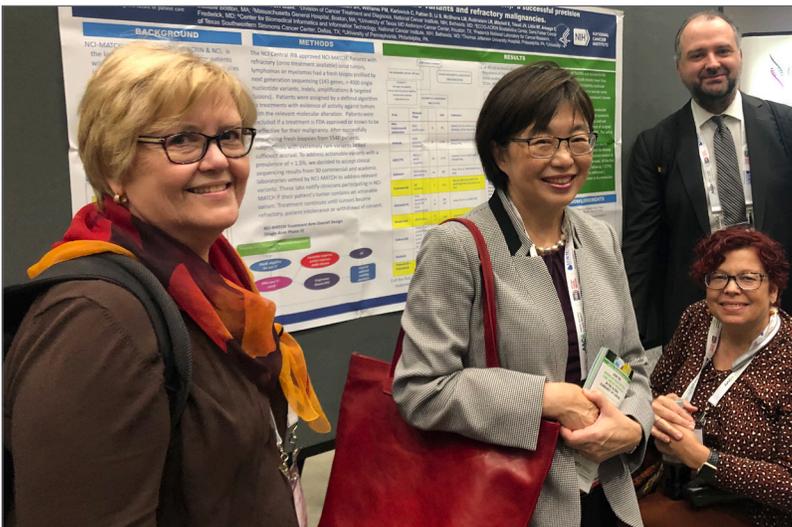


DCTD staff presented [research results](#) at the 2019 Molecular Targets meeting in Boston, MA in late October. Poster and presentation topics included NCI-MATCH, trials being supported through the Developmental Therapeutics Clinic, and pharmacodynamic studies being done at the Frederick National Laboratory for Cancer Research. See photographs from the meeting below.

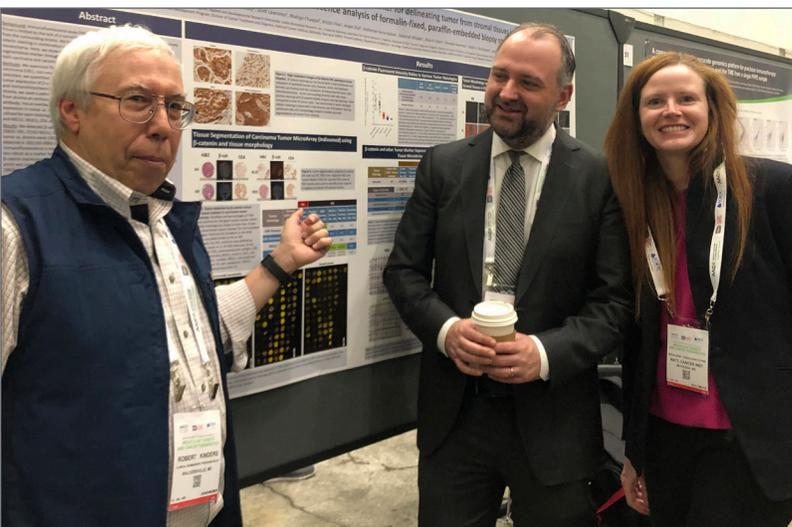
NEWS ABOUT DCTD PROGRAMS AND ACTIVITIES ... continued



L to R: Rao Vishnuvajjala, Sabrina Khan, Jerry Collins, and Naoko Takebe at the bortezomib/clofarabine poster

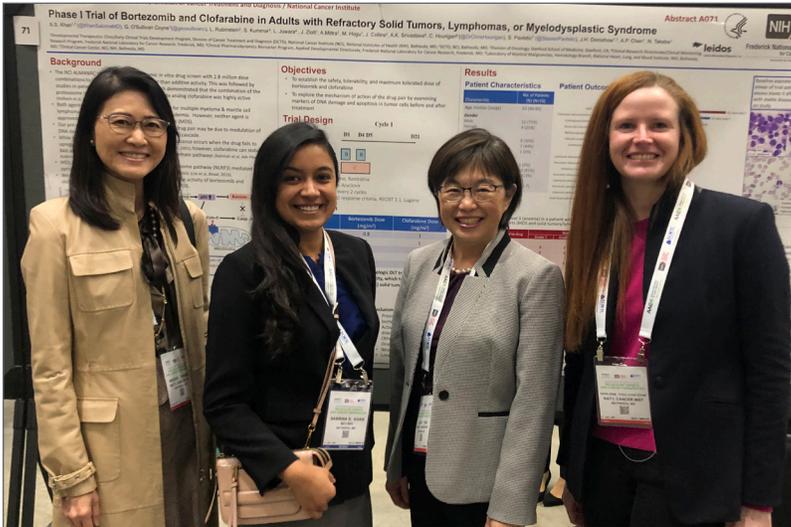


L to R: Barbara Conley, Alice Chen, Lyndsay Harris, and Elad Sharon at the NCI-MATCH poster

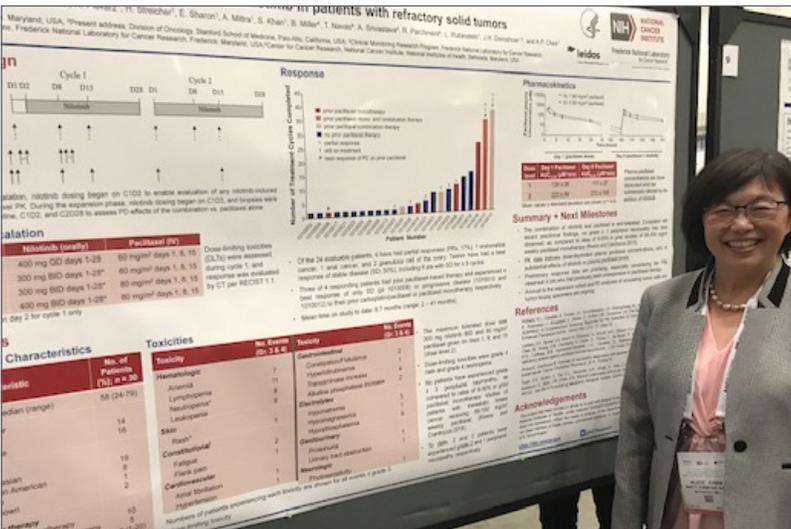


L to R: Robert Kinders, Elad Sharon, and Geraldine O'Sullivan Coyne at the beta-catenin poster

NEWS ABOUT DCTD PROGRAMS AND ACTIVITIES ... continued



L to R: Naoko Takebe, Sabrina Khan, Alice Chen, and Geraldine O'Sullivan Coyne at the bortezomib/clofarabine poster



Alice Chen at the paclitaxel/nilotinib poster

Cancer Therapy Evaluation Program’s Early Drug Development (EDD) Meeting

The **2019 EDD Meeting** was held on October 17-18, 2019. The focus of the EDD meeting is to enhance communications between the NCI and the network of CTEP-supported Experimental Therapeutics Clinical Trials Network (ETCTN)-funded early clinical trial investigators.

Presentation sessions included talks on biomarker assay development projects, resources available to the extramural scientific community, radiopharmaceutical agents, and CTEP-sponsored early-phase clinical trials. The 13th Annual Michael Christian Oncology Drug Development Award was given to Timothy Yap, MBBS, PhD, MD Anderson Cancer Center.



Timothy Yap, Michael Christian Oncology Drug Development Award recipient, gives his talk, “Targeting the DNA Damage Response in Oncology.”

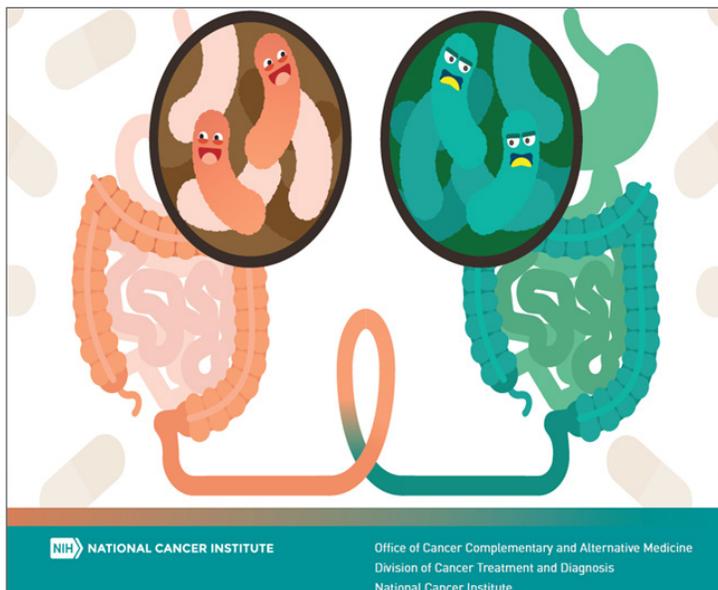
2019 Annual Principal Investigators Meeting of the NCI Alliance for Nanotechnology in Cancer

The NCI Alliance for Nanotechnology in Cancer, which consists of the Centers of Cancer Nanotechnology Excellence, Innovative Research in Cancer Nanotechnology, Cancer Nanotechnology Training Centers, and The Nanotechnology Characterization Laboratory, held its **14th Annual Principal Investigators Meeting** in September. More than 100 investigators, including Principal Investigators, project leaders, post-doctoral fellows, and federal employees attended.



Outstanding Poster Presentation Awardees (L to R): Yazhen Zhu, UCLA; Gang Han on behalf of Nhung Nguyen, University of Massachusetts; Yara Kadria-Vili, Rice University; Andrew Lee on behalf of Shuya Wang, Northwestern University
Not pictured: Luman Liu, Iowa State University

Workshop on Reproducibility of Fecal Microbiota Transplants in Cancer Therapeutics



To explore the potential role that fecal microbiota transplants (FMT) and pre/probiotics may play in cancer therapeutics and to address reproducibility and safety to inform translational human studies

and clinical trials, NCI convened a “**Strategic Workshop on Rigor and Reproducibility: Precision Fecal Microbiota Transplant and Microbiome Cancer Therapeutics**” on September 5, 2019.

The goals of the workshop were to:

- assess the current state of clinical research and clinical trials involving FMT and microbiome-based cancer therapeutics
- discuss the knowledge gaps and future opportunities in the field
- provide feedback to NCI and NIH regarding future priority areas to enhance precision- and mechanism-based rigor and reproducibility of defined microbiome-based therapeutic clinical research for cancer and other diseases

New DCTD Funding Opportunity and Funding Information

TITLE	ANNOUNCEMENT NUMBER	OPENING DATE	EXPIRATION DATE	ACTIVITY CODE
NCI Clinical and Translational Exploratory/ Developmental Studies (Clinical Trial Optional)	PAR-19-356	September 18, 2019	July 21, 2022	R21
Small Cell Lung Cancer (SCLC) Consortium: Biology, Therapy and Resistance (Clinical Trial Not Allowed)	PAR-19-361	October 12, 2019	March 12, 2022	U01