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.
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 (NF1) 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 NF1 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 NF1 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 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.

- 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)

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 US4 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


NEWS ABOUT DCTD PROGRAMS AND ACTIVITIES ... continued


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.

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.

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

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 Michaele Christian Oncology Drug Development Award was given to Timothy Yap, MBBS, PhD, MD Anderson Cancer Center.
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

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<td>Small Cell Lung Cancer (SCLC) Consortium: Biology, Therapy and Resistance (Clinical Trial Not Allowed)</td>
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