Malcolm Smith, MD, PhD, arrived at NCI in 1988 to pursue a fellowship in pediatric hematology/oncology and has continued to work at NCI since then. He provides highlights from a 30-year history of NCI-supported pediatric oncology research and a perspective on the importance of collaboration to advance patient care.

**What types of pediatric oncology research programs were in place at NCI when you joined the Cancer Therapy Evaluation Program (CTEP)?**

When I arrived at CTEP in 1990, NCI supported four separate pediatric oncology research groups to perform clinical trials. These groups merged into the current Children’s Oncology Group (COG) in 2000. Although early-phase clinical trials were well established for adult cancers, there wasn’t an early-phase clinical trials program in place for children. Recognizing this need, I worked with others at NCI to start the first pediatric phase 1 consortia in the early 1990s, which subsequently became the COG Phase 1 Consortium in 2001 and is now the **Pediatric Early Phase Clinical Trials Network (PEP-CTN)**. The PEP-CTN includes 21 core member pediatric oncology programs in the US and works to conduct “first-in children” studies of novel anticancer agents so that the most promising can then be studied in more definitive clinical trials through COG.

**What other pediatric oncology programs were developed during your time at NCI?**

The most compelling theme I associate with working at NCI is our unique ability to collaboratively address unmet needs in pediatric oncology, which has resulted in the implementation of several key programs in the last 30 years. For example, in the late 1990s, the need for a more focused clinical trials activity for pediatric brain tumors was recognized, so my colleagues and I worked together to develop the
Pediatric Brain Tumor Consortium (PBTC). This is a collaborative effort involving a set of large academic institutions to rapidly conduct phase 1 and 2 clinical trials in children with primary central nervous system tumors.

In the mid-2000s, sporadic and limited pediatric preclinical cancer data were available. We needed a more systematic approach to preclinical testing and more comparative data sets for making prioritization decisions. Many more agents are developed for adults with cancer than can be studied in children, and quality preclinical data can help in selecting the most promising agents to bring forward for pediatric clinical trials. To address this need, NCI funded the Pediatric Preclinical Testing Program for ten years, which evolved into the current Pediatric Preclinical Testing Consortium.

As precision medicine started to gain momentum, genomics flourished, and The Cancer Genome Atlas (TCGA) was established for adults in 2005. We realized we needed to do something similar for children. We worked with the NCI Office of Cancer Genomics and with COG to implement the TARGET genomics program - Therapeutically Applicable Research to Generate Effective Treatments – the pediatric equivalent of TCGA. The TARGET program has successfully met its goal of obtaining detailed molecular characterization of the genomes, transcriptomes, and epigenomes of tumors from pediatric patients.

What are some examples of clinical trials that have positively impacted pediatric patient outcomes?

A lot has changed over the last few decades in pediatric cancer patient care. Through our strong working relationship with research teams at COG, we’ve supported phase 3 clinical trials for patients with different types of cancer. A number of these trials were positive and resulted in new and improved treatments that have redefined the standards of care for a range of childhood cancers. Having those positive clinical trials and seeing their impact on improved survival rates for children with cancer is a great reward of working at CTEP.

NCI has unique opportunities to conduct important clinical trials even when there is little or no profit motive. Two examples of this are the development of nelarabine for T-cell acute lymphoblastic leukemia and dinutuximab for neuroblastoma. In these instances, NCI took the lead and conducted clinical trials that were needed for regulatory approval. In the case of dinutuximab, no pharmaceutical company was involved at the time, and NCI manufactured and distributed the agent.

What are some important current and future initiatives in pediatric oncology?

Grant funding through the Cancer Moonshot℠ is important to our current research efforts. The Moonshot is supporting the Fusion Oncoproteins in Childhood Cancers Consortium that is focusing on specific drivers of childhood cancers. This is a pediatric precision medicine initiative trying to identify treatment approaches for gene changes that are unique to these childhood cancers. As most childhood cancers don’t have the genomic changes relevant to targeted agents developed for adult cancers, it is critical that we learn how to target these pediatric-specific cancer drivers so that precision medicine principles can
be broadly applied for childhood cancers. In addition, a Pediatric Immunotherapy Discovery and Development Network is researching immunotherapy targets for children. Adult immuno-oncology approaches often aren’t relevant to pediatrics, so NCI has an essential role in trying to identify therapeutic strategies that apply to pediatric-specific antigens.

We are looking ahead to see how discoveries from ongoing activities can be translated into more effective treatments. One example is the PBTC’s work on selumetinib for the treatment of low-grade glioma. As a result of the PBTC phase 1-2 trial of selumetinib, COG is now conducting phase 3 trials to determine if selumetinib can be a new standard-of-care for children with some types of low-grade glioma. Other potential areas of translation come from the PPTC, where clinical trials for T-cell acute lymphoblastic leukemia (T-ALL) or mixed-lineage leukemia (MLL) are in development based on PPTC results. These trials will determine if the preclinical results can be successfully translated to the clinic.

There are also opportunities to make data more useful and accessible to the research community. The Childhood Cancer Data Initiative (CCDI) plans to improve the way we generate and deliver data to researchers. There are also efforts to improve biospecimen collection and to try to use specimens to learn why some treatments fail in patients who have relapsed (STAR Act).

As we pursue these projects, I am grateful for the many talented, dedicated, and committed colleagues that I have both within and outside of NCI. Our shared mission is to improve the way we treat childhood cancers and to help children survive and live good lives as adults. Not many jobs get to do that.

**Spotlight – Updates from the NCI Patient-Derived Models Repository (PDMR)**

The NCI PDMR is a publicly accessible, national repository for early-passage, molecularly characterized patient-derived models developed from patients with solid tumors.

The PDMR released its first PDX models in May 2017, its first patient/PDX-derived cell cultures (PDCs) and cancer-associated fibroblasts (CAF) in September 2018, and its first molecularly characterized PDOrgs in May 2019. Release of the PDOrg cultures provides a more complex preclinical translational model for researchers who have limited access to animal facilities.

Currently, 248 PDX models, 75 PDCs, 135 CAF cultures, and 54 PDOrgs from a variety of cancer types are available for investigators to request for their research.

**PDMR Facts**

- Models are generated from tumor tissues collected from patients at NCI-designated Cancer Centers, NCI’s Developmental Therapeutics Clinic (DTC), participating sites within NCI’s Experimental Therapeutics Clinical Trials Network (ETCTN), NCI’s Community Oncology Research Program (NCORP), Specialized Programs of Research Excellence (SPOREs), and other participating centers.
Researchers not interested in performing wet lab studies can mine the metadata associated with the models using the PDMR database.

The PDMR continually adds new models to the database. In 2018, several new cancer types were added to the PDMR collection, including some rare cancers.

The PDMR is actively working to establish matched PDX – PDOrg – PDC model sets, wherever possible, so researchers can pursue basic and translational biologic questions across these model types.

The PDMR includes genetic ancestry for all public models and germline sequence for a subset of the models.

<table>
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<th>PDORg</th>
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Alert from the PDMR: A Newly Described Mouse Parvovirus Is a Risk to Patient-derived Xenograft Models

A recent publication (Roediger, 2018) describes a new atypical strain of mouse parvovirus, Mouse Kidney Parvovirus (MKPV), which was reported to be present in over 15% of the authors’ tested samples. In-house screening at NCI-Frederick demonstrated the presence of MKPV in a subset of animal colonies. Tumor fragments were found to be positive for MKPV and capable of transmitting the infection to mice receiving cryopreserved fragment implants. If tumor fragments are not screened for MKPV prior to implantation, closed colonies are at risk for infection. The NCI PDMR has confirmed its distribution material is MKPV negative.

Existing tests for Mouse Parvovirus 1-5 (MPV 1-5) do not detect MKPV; therefore, mouse colonies previously tested for MPV 1-5 should be tested for MKPV.
The NCTN is one of the largest, publicly-funded cancer research networks in the world. It is a collection of organizations and clinicians that coordinates and supports cancer clinical trials at more than 2,200 sites across the US, Canada, and internationally. The system provides for an annual enrollment of about 17,000-20,000 participants on cancer treatment and imaging trials.

Early in 2019, the NCTN’s annual budget increased from $151 million to $171 million, and the awards were given for six years, rather than five. In addition, 32 academic institutions received a Lead Academic Participating Site grant, an increase from 30 in 2014.

The network’s organizational structure is ideal for screening large numbers of people with cancer for participation in precision medicine clinical trials. The NCTN is currently supporting several precision medicine trials, including, Lung-MAP, NCI-MATCH, NCI-COG Pediatric MATCH, and the NCI-NRG ALK Protocol.

NCTN continues to be a national leader in conducting clinical trials that change practice in both common and rare cancers, as well as in special populations. A few examples of NCTN trials with recently reported findings that have impacted clinical care are:

Formed in 2014 after a transformation of NCI’s Cooperative Group program, the NCTN is one of the largest, publicly-funded cancer research networks in the world. It is a collection of organizations and clinicians that coordinates and supports cancer clinical trials at more than 2,200 sites across the US, Canada, and internationally. The system provides for an annual enrollment of about 17,000-20,000 participants on cancer treatment and imaging trials.

The following websites provide commercial testing resources and further information: IDEXX BioAnalytics, Taconic, and Charles River Laboratories.

For additional information on the steps NCI-Frederick has taken to monitor for MKPV and other pathogens, please contact:

Melinda Hollingshead, DVM, PhD, Branch Chief, Biological Testing Branch, Developmental Therapeutics Program, DCTD, NCI, NIH (melinda.hollingshead@nih.gov).
### Trial Assigning Individualized Options for Treatment (TAILORx)

**NCI Press Release**

Most women with early breast cancer do not benefit from chemotherapy.

### Ibrutinib and Rituximab Compared with Fludarabine Phosphate, Cyclophosphamide, and Rituximab in Treating Patients with Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

**NCI Press Release**

Ibrutinib plus rituximab was superior to standard treatment for patients age 70 and younger with previously untreated chronic lymphocytic leukemia.

### Sorafenib Tosylate in Treating Patients with Desmoid Tumors or Aggressive Fibromatosis

**NCI Press Release**

Sorafenib improves progression-free survival for patients with rare sarcomas.

### Combination Chemotherapy in Treating Young Patients with Newly Diagnosed Acute Lymphoblastic Leukemia

**Publication**

A combination therapy developed for children could also be given to older adolescent and young adult patients with newly diagnosed acute lymphoblastic leukemia, setting a new standard of care.

### Irinotecan Hydrochloride and Temozolomide with Temsirolimus or Dinutuximab in Treating Younger Patients with Refractory or Relapsed Neuroblastoma

**Publication**

Relapsed and refractory neuroblastomas in children had a greater response to the combination of irinotecan-temozolomide-dinutuximab than to irinotecan-temozolomide-temsirolimus, resulting in a new standard of care.

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**News about DCTD Programs and Activities**

### Program Updates

**Molecular Radiation Therapeutics Clinical Working Groups Generate Preclinical Data to Support Clinical Trials**

The Molecular Radiation Therapeutics (MRT) Clinical Working Groups within DCTD’s Radiation Research Program (RRP) work to design and develop sound clinical trial concepts with robust preclinical data. The MRT was established after a 2011 RRP workshop concluded that preclinical data supporting the design of radiation-drug combination trials was integral to the success of the trial. The RRP MRT Clinical Working Groups help fill this gap by providing a collaborative platform with NCI scientific staff, including DCTD’s Developmental Therapeutics Program and Cancer Therapy Evaluation Program and the NCI Center for Cancer Research, as well as external experts in academia and industry. The MRT also plays a major role in developing radiosensitizers as part of the NCI Experimental Therapeutics (NExT) Program. The MRT’s efforts have led to several clinical trials, publications, and scientific workshops.
MRT Mission

Facilitate the generation of preclinical data that will support clinical trials with radiation modifiers

MRT Goals

- Serve as a common platform to discuss preclinical translational ideas with a high likelihood for development into clinical trial concepts, including:
  - evaluation of conventional Phase I and 2 endpoints
  - development of novel endpoints (novel imaging, biomarkers of response and toxicity, and patient-reported outcomes)

- collaborate with individual institutions, industry partners, consortia, and groups within NCI’s National Clinical Trials Network to help conduct clinical concepts

MRT Disease Site Working Groups

- Brain Metastasis and Glioblastoma Multiforme
- Colorectal Cancer
- Sarcoma
- Lung Cancer
- Radiation and Immune Modulation
- Upper Gastrointestinal
- Hepatocellular Carcinoma
- Grid, Lattice, Flash and Microbeam Radiotherapy

Recent Publications Resulting from MRT Clinical Working Groups


The NCI Formulary Offers Rapid Access to Anti-Cancer Agents for Preclinical Studies

- The NCI Formulary currently has 30 agents (with more under negotiation) available for preclinical studies. Formulary agents, even those originating from different companies, can be easily obtained for preclinical combination studies.
News about DCTD Programs and Activities...

- **To Researchers:** NCI would like to know what agents, targets, and pathways are relevant to your research. If the Formulary does not currently have agents of interest to you, please contact us to provide suggestions for new agents: NCIFormulary@mail.nih.gov.

- The Formulary also offers agents to qualified investigators for clinical trials, under investigator-held INDs, at main member sites of either the NCTN or ETCTN.

- The Formulary is one of NCI’s initiatives in support of the Cancer MoonshotSM, allowing greater collaboration and faster development of new therapies for patients.

- Other sources of agents/compounds available from NCI for preclinical studies, by approved request, can be found through the Cancer Therapy Evaluation Program or the Developmental Therapeutics Program.

A New Immunotherapy Phase 2 Clinical Trial Opens in the NCI Developmental Therapeutics Clinic

A new **phase 2 clinical trial** recently opened in the NCI Developmental Therapeutics Clinic to treat patients with advanced solid tumors. The primary outcome is to measure the safety of the immunotherapy drug, durvalumab (an anti-PD-L1 antibody), in combination with different FDA-approved chemotherapy agents. Combining immunotherapy with chemotherapy may improve how immune cells respond and attack tumor cells. Additional research will include pharmacodynamic studies on the tumor tissue to determine the effects of the combination on the tumor’s immune microenvironment, if the patient’s response to therapy correlates with any genetic aberrations in their tumor or activation of their T cells, and if there is any relationship between the immune status of the tumor and overall mutational load (quantity of mutations found in the tumor).

Publications and Outreach

**Peer-reviewed Publications**

Jim Doroshow, MD, Director, DCTD, was the guest editor for a special edition of *The Cancer Journal* (2019 Jul/Aug;25(4): 243-304) on precision oncology. The following publications in this edition were written by DCTD staff:

- Doroshow JH. **Introduction by the Guest Editor:** Oncologic Precision Medicine and the Use of Basket and Umbrella Clinical Trials.

- Doroshow DB and Doroshow JH. **From the Broad Phase II Trial to Precision Oncology:** A Perspective on the Origins of Basket and Umbrella Clinical Trial Designs in Cancer Drug Development.


- Karlovich CA and Williams PM. Clinical Applications of Next-Generation Sequencing in Precision Oncology.


News about DCTD Programs and Activities ... continued

- Mittra A and Moscow JA. Future Approaches to Precision Oncology-Based Clinical Trials.


News about DCTD Programs and Activities ... continued

NCI Cancer Currents Blog Posts

Laser-Based Device Detects and Kills Melanoma Cells in the Blood, Study Finds; Miguel Ossandon, PhD, Cancer Diagnosis Program; July 25, 2019.


Helping Dogs – and Humans – with Cancer: NCI’s Comparative Oncology Studies; Toby Hecht, PhD, Translational Research Program, and Connie Sommers, PhD, Developmental Therapeutics Program; July 10, 2019.

A physician and assistant at the University of Minnesota examine a dog patient.

Interviews, Press, and Social Media

US Scientists Save Vanishing Plants & Animals for Global Medical Research; Barry O’Keefe, PhD, Developmental Therapeutics Program; CGTN; August 2, 2019.

Focusing on Proton Therapy; Jeff Buchsbaum, MD, PhD, Radiation Research Program; Cancer Today; Summer 2019.


Pediatric MATCH Trial Finds More Frequent Targetable Genetic Alterations in Pediatric Cancers Than Predicted; Nita Seibel, MD, Cancer Therapy Evaluation Program. ASCO Press Release; May 15, 2019.


Conferences and Meetings

Chemical Biology Consortium Symposium

The Chemical Biology Consortium (CBC) in the NCI Experimental Therapeutics (NExT) Program operates as a collaborative network of 7 Dedicated and 15 Specialized Centers across the U.S. that support the advancement of NExT drug discovery projects, provide scientific leadership, and provide technologies to projects.

The CBC brought together chemical biologists and molecular oncologists from government, industry, and academia to address unmet therapeutic needs in oncology at the second NCI Chemical Biology Consortium Symposium. The CBC Symposium, sponsored by NCI, convened on July 10, 2019 at Vanderbilt University in Nashville, TN. Members of the CBC and the scientific community met to discuss emerging concepts, novel technologies, and
therapeutic strategies in drug discovery and development, with an emphasis on bridging the gaps between discoveries in academic settings and translation or advancement of those hypotheses into novel therapeutics.

**Lung Cancer SPORE Workshop**

The Translational Research Program held a lung cancer SPORE workshop on June 13-14, 2019. The meeting brought together lung cancer investigators, staff from NCI and the Department of Defense, and patient advocates. In addition to a Keynote Presentation by Lieping Chen, MD, PhD, Yale School of Medicine, nine scientific sessions included topics such as: immunotherapy, therapeutic resistance, and molecular profiling and biomarkers. See the agenda and highlights from the meeting.

**Workshop on Imaging Inflammation and Its Resolution in Health and Disease**

A trans-NIH Organizing Committee convened a “Workshop on Imaging Inflammation and Its Resolution in Health and Disease” on June 10-11, 2019. This meeting focused on aligning research efforts toward the development and application of *in vivo* imaging-based tools and techniques to monitor an individual's inflammatory and resolution state at the organ levels for better clinical decisions and treatment planning. The scientific sessions included the following: clinical challenges and needs, state-of-the-art imaging tools, cross validations, and human applications. See the agenda, and read highlights from the meeting.
News about DCTD Programs and Activities ... continued

American Society of Clinical Oncology Annual Meeting

DCTD staff presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, IL. See the list of DCTD-supported research presentations and photo highlights below.

Percy Ivy, Cancer Therapy Evaluation Program

Naoko Takebe (right), Developmental Therapeutics Clinic

Geraldine O’Sullivan Coyne, Developmental Therapeutics Clinic

Cecilia Monge Bonilla, Developmental Therapeutics Clinic

Jerry Collins, Developmental Therapeutics Program, and Arjun Mittra, Developmental Therapeutics Clinic

Chris Karlovich, Frederick National Laboratory for Cancer Research
Quantitative Imaging Network Annual Meeting

The Cancer Imaging Program’s Quantitative Imaging Network (QIN) held its annual meeting on May 21-22, 2019. The QIN creates and validates quantitative imaging software tools to support clinical decision making during clinical trials. During the QIN’s annual meeting, its members provide updates on the development of clinical imaging tools. Read about the QIN and highlights from the meeting.

Clinical advisors evaluate QIN tools.

Co-Clinical Imaging Research Program Network Annual Meeting

The Cancer Imaging Program convened its second Co-Clinical Imaging Research Program (CIRP) Network Annual Meeting on May 20, 2019. The CIRP Network is a trans-NCI initiative launched in 2015 designed to:

- provide the broader cancer community with web-accessible research resources for quantitative imaging of co-clinical trials (defined as: in parallel or sequential investigations in patients and mice or human-in-mouse models)
- encourage consensus on how quantitative imaging methods are optimized to improve the quality of imaging results for co-clinical trials

The CIRP’s annual meeting brought the four U24 teams together from Washington University at St. Louis, Duke University, Vanderbilt University, and University of Pennsylvania, along with other stakeholders from academia, industry, and federal agencies. The theme for this meeting was “Biology Meets Imaging,” with a mission to review program progress, identify
challenges in developing best practices for animal models and for co-clinical quantitative imaging, and collect suggestions and recommendations.

The meeting was comprised of:

- presentations from the four CIRP teams on their research projects
- presentations from the three working groups on animal models and co-clinical trials, imaging acquisition and data processing, informatics, and outreach

As a research resource program, CIRP seeks to leverage existing NCI resources and programs to ensure best practices, effective outreach, and service improvement.

### NCI Workshop on Artificial Intelligence in Radiation Oncology

The Radiation Research Program convened the “NCI Workshop on Artificial Intelligence in Radiation Oncology” on April 4-5, 2019. A goal of the meeting was to discuss how the latest capabilities of artificial intelligence and machine learning can address the clinical needs of radiation oncology. For example, this technology could help facilitate cancer diagnosis, assess radiation treatment response, and data-mine Big Data for clinical and imaging databases from NCI clinical trials and publicly accessible archives. See the agenda and highlights from the meeting.

### New DCTD Funding Opportunity and Funding Information

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