Jan Casadei, PhD, retired from the federal government in February 2019 after 28 years working with the Cancer Therapy Evaluation Program (CTEP). Dr. Casadei’s areas of expertise cover Food and Drug Administration (FDA) regulations, policies, and guidelines for the conduct of clinical studies with investigational agents. She became Chief of the Regulatory Affairs Branch (RAB) in 2008. Jan discusses RAB’s role in clinical trials and the evolution of regulatory affairs over the years.

What led you to NCI and CTEP?

After receiving my doctoral degree in biochemistry from the University of Pennsylvania, I worked in a small biotech company from 1986-1991. This was during the volatile 1980s when funding for scientific research was not easy to receive. My husband, who is also a scientist, was already at NIH, and I heard of an NIH job fair that offered interesting opportunities with more stability. I applied for a job in regulatory affairs at CTEP and was interviewed by Jay Greenblatt, PhD, Associate...
Chief, Regulatory Affairs, who retired in 2005. I knew nothing about regulatory affairs then, but something about it sounded appealing — I stayed in CTEP's RAB for 28 years!

**What is RAB's role within CTEP and the clinical trials enterprise?**

One of RAB's primary roles is to be CTEP/DCTD's interface with the FDA. RAB consists of the Drug Regulatory Group and the Agreement Coordination Group. The Drug Regulatory Group has extensive expertise in FDA's IND regulations and guidances, serving DCTD as a regulatory resource and FDA liaison. Towards that end, this group maintains collegiality and constant communications between NCI staff and FDA. This mutually-beneficial relationship between the two government agencies - wherein FDA provides regulatory insight, and CTEP provides clinical trial experience - facilitates the development of promising investigational agents. This group coordinates the standing quarterly meeting between CTEP/DCTD and the FDA and communicates with the FDA on a weekly basis (e.g., addressing FDA queries quickly and accurately). The Drug Regulatory Group is responsible for all submissions made to the approximately 175 DCTD-sponsored INDs, yielding approximately 1,000 IND amendments each year. They ensure the accuracy and control of IND Safety Reports, protocol amendments, and Annual Reports. The other half of RAB, the Agreement Coordination Group, develops and negotiates agreements to support collaborative non-clinical and clinical studies. This is primarily done via a CRADA mechanism, but other types of agreements are also used (e.g., Clinical Trial and Material Transfer Agreements). Dr. Sherry Ansher provides details on this group in the accompanying newsletter article.

RAB maintains a dialogue with the FDA for each clinical trial intended to support a product's FDA approval. We orchestrate the End-of-Phase 2 meeting with the FDA to ensure the study design of these trials will support an indication, should the trial be positive. This meeting is a collaboration between FDA, CTEP [IND Sponsor], NCI's National Clinical Trials Network (NCTN), and the pharmaceutical sponsor [marketing applicant]. RAB brings these stakeholders together to inform FDA of the study details and to ask licensing-support questions. The pharmaceutical company leads the marketing efforts should a clinical trial yield positive outcome(s), but RAB continues to interact with the company to facilitate the marketing application process. Should FDA, PMDA (Japan), or EMA (Europe) schedule a Sponsor Inspection during this licensing process, RAB plays a key role. One example of this situation is the approval of Unituxin to treat neuroblastoma in children. RAB co-led the simultaneous FDA-EMA Sponsor inspection of this therapy, ensuring that all documentation requested by the inspectors was made available, and ensuring that all inspector questions were addressed by pertinent parties.

**What has changed in regulatory affairs over the years?**

For decades, specific federal regulations (21 CFR 312) dictated the structure of IND applications; more recently, the FDA mandated that all commercial INDs (the majority of CTEP-held INDs) be restructured in the CTD (common technical document) format and be submitted electronically, with an implementation deadline of May 5, 2018. The goal was to format IND applications similarly to the Marketing Application, thereby allowing for a more streamlined process from initiation of clinical trials through submission of a marketing application. All CTEP-held IND applications are now submitted electronically in the CTD format, allowing for quicker FDA reviews and less environmental impact.

Also, the FDA Office of Hematology and Oncology Products reorganized in 2011. As a result, FDA restructured the review of INDs to be based on tumor type, rather than on the drug product. In practice, this meant a new IND for each new tumor type to be studied, increasing CTEP's IND portfolio several-fold.

Lastly, RAB's expertise has advanced alongside the evolution of biomarker-driven clinical trials. RAB met the challenge of learning more about
Jan Casadei, PhD - continued

the regulation of biomarker assays as devices (specifically, *in vitro* diagnostics). The Drug Regulatory Group now works not only with FDA’s Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), but also with the Center for Devices and Radiological Health (CDRH) and its Office of In Vitro Diagnostics and Radiological Health (OIR). OIR/CDRH is an essential partner in evaluating CTEP-sponsored biomarker studies. The Drug Regulatory Group organizes pre-submission meetings with OIR/CDRH to delineate the use of a biomarker test within the context of the clinical study and its impact on patient risk. The Agreement Coordination Group negotiates any necessary agreements should there be a collaborating device company involved.

What have you enjoyed most during your time in RAB?

The analytical part of my work (applying facts and prior experience to solve regulatory and other hurdles), working with a wide spectrum of agents, and taking on more responsibility over the years have been rewarding elements of this job. Additional positive factors are NCI’s mission and my CTEP colleagues. The staff in CTEP and across DCTD is unsurpassed in their clinical trials and drug development knowledge. Our team works well because we have diverse expertise, but we can’t work alone. FDA is a vital component of our mission to get new treatments to the public. The collegial relationship RAB has nurtured with our FDA colleagues has been especially satisfying.

What do you plan to do once you retire?

I don’t have specific, long-term plans yet, as I’d like to take some time to think about what I want to do next. I plan to give myself 6-months, doing more outdoor activities and revisiting my artwork, especially watercolor, while I make up my mind. I’m also looking forward to visiting with my children and mom (South Carolina, Texas, and New York) more often.

Sherry Ansher, PhD - continued from page 1

into health science administration positions. This led me to join CTEP’s RAB as a coordinator for research and development agreements in 1994. Following the 1995 furlough, I was in this new and recently vacated position and began to define it based on CTEP’s needs. This was a great fit for me because of my scientific background and training at FDA.

What kind of work did you do in RAB when you first joined NCI?

When I arrived at RAB, the field of drug development in industry was burgeoning, and my goal was to strengthen our ability to collaborate with industry. Because of this explosion of drug development, CTEP needed to manage the interactions, expectations, and concerns of industry and clinical investigators. Our pharmaceutical company partners wanted assurance that their rights related to data generated in clinical trials were protected. We instituted NCI standard protocol language that ensured that the institutions, investigators, and Institutional Review Boards all knew that the supplied drugs were coming from the pharmaceutical company. After the language was put in place, the company no longer needed to negotiate with each clinical site to make sure their rights were protected.

What is the role of RAB’s ACG?

CTEP established the ACG in 2007 to streamline the process for negotiation of agreements with pharmaceutical collaborators by introducing model agreements specifically designed for CTEP-sponsored clinical trials. The ACG prepares collaborative agreements and coordinates all the company-investigator interactions to make sure that everyone knows each other’s roles in the clinical trial process. These agreements with our industry collaborators have allowed us to support trials like NCI-MATCH, where
multiple agents are used in one study. It’s a great advantage that members of ACG are embedded here in CTEP – it distinguishes us from a separate technology transfer center.

What are some changes that took place in RAB during your time in CTEP, and how did they influence RAB’s work?

Two major changes took place during my time in RAB. First, we established the CTEP IP (Intellectual Property) Option in 1999, which allows companies to have access to the IP for their compound. This major accomplishment revolutionized our ability to conduct clinical trials with multiple collaborators and ensured protection of the companies’ data and IP. Prior to the IP Option, companies insisted on separate agreements with the institutions first, and this delayed trial implementation. Now, clinical trials start faster, and access to the data and inventions is protected. Another improvement was the establishment of multi-party data language, which was an important milestone that protects each company involved in combination clinical studies. Each company agrees to use trial data to develop only their agent.

RAB’s and ACG’s improvement efforts brought consistency across CTEP’s clinical trial agreement efforts. This is even more important now that there is a new level of data entering the public domain. For example, ACG needed to amend the company agreements following the establishment of the NCTN/NCORP Data Archive, which provides controlled access to a centralized repository of patient-level data from randomized phase 2 and phase 3 clinical trials. The agreements had previously provided the companies’ exclusive use of the patient-level data, and this needed to be adjusted. This has been a recent paradigm shift for companies – patient-level data had always been confidential, but now data are accessible in the Data Archive. We collaborated with Project Data Sphere on the Data Archive, and Dr. Jeff Abrams, who recently retired from CTEP, was its visionary.

In addition to supporting agreements for NCI-MATCH and the NCTN/NCORP Data Archive, ACG has supported several other recently developed programs. For example, CTEP was instrumental in the development of the NCI Formulary, which provides main-member ETCTN or NCTN investigators with rapid access to agents for investigator-held-IND clinical trials or preclinical research. We’ve also worked with the Foundation for the National Institutes of Health to implement the Lung-MAP clinical trial and to set up data use agreements for the Cancer Immune Monitoring and Analysis Centers and Cancer Immunologic Data Commons (CIMACs/CIDC), a network of laboratory centers that supports both adult and pediatric immunotherapy trials. In the early 2000s, CTEP began to include agents for preclinical studies in our portfolio, which are now a mandatory and critical aspect of the program. ACG executes the Material Transfer Agreements for our investigators for these studies, and the company receives the same rights as for clinical studies.

What do you see as the future for RAB, ACG, and for you, now that you’ve retired from the federal government?

We envision more interactions with diagnostic companies. Diagnostics will be an increasingly important part of clinical trials, and these are new collaborations for us. The ACG needs to identify the shared goals of diagnostic companies and pharmaceutical collaborators and develop collaboration templates for diagnostic partners the way we have for our pharmaceutical partners. As for me, although I’ve officially retired from the federal government, I’m working part-time at CTEP as a Scientific Agreement Consultant doing similar work to my previous job. I provide the clinical agreement expertise to the program, and I will help to set up new initiatives. Because of RAB’s unique position, I have a global perspective across CTEP, which helps when new initiatives come along.
In September 2017, NCI funded a Canine Immunotherapy Trials Network consisting of five clinical trial sites (U01) and one coordinating center (U24). These grants, which were funded by the Cancer MoonshotSM, were based on five strategic areas of interest for NCI in precision medicine oncology. In addition to the six funded institutions, staff in NCI’s Comparative Oncology Program, Center for Cancer Research, are integral to this initiative.

The goal of this collaborative network is to promote the development of immunotherapies for several common human cancers - glioma, lymphoma, melanoma, and osteosarcoma - through comparative oncology. Veterinary oncologists and surgeons in the network are now enrolling pet dogs as patients in specific immunotherapy clinical trials. Dog owners or referring veterinarians who are interested in learning more about the studies and how to enroll a dog patient onto a network trial can contact staff at any of the five participating clinical sites.

NCI’s Natural Products Repository is one of the world’s largest, most diverse collections of natural products, containing more than 230,000 unique extracts derived from plant, marine, and microbial organisms obtained from biodiverse regions throughout the world. This national resource is available to the research community for the screening of extracts and the isolation of bioactive natural products. Despite the success of natural products in cancer drug discovery, compatibility issues have made crude natural product extracts challenging for the high-throughput screening (HTS) of these extracts in targeted assay systems.

To address these limitations and make the NCI’s Natural Products Repository more amenable to HTS, NCI developed the NCI Program of Natural Product Discovery (NPNPD) Prefractionated Library. This project, which was partially funded by the Cancer MoonshotSM, initiated the prefractionation of extracts using an automated, high-throughput robotics platform capable of generating a library of 1,000,000 partially purified extracts. Publicly available in January 2019, the NPNPD is a research resource for the scientific community that is free of charge and open to screening against any disease target. Read more about this important source of new drugs and drug leads in a recent publication in ACS Chemical Biology and in the NCI’s Cancer Currents blog, “Nature’s Bounty: Revitalizing the Discovery of New Cancer Drugs from Natural Products.”
News about DCTD Programs and Activities

Program Updates

NCI’s Experimental Therapeutics (NExT) Program Project Launches into Space

On May 4, 2019 the Space X CRS 17/Falcon 9 rocket launched containing several NIH-supported research projects. In addition to four National Center for Advancing Translation Sciences (NCATS) projects on bioengineered devices called “tissue chips,” one project joining the mission is supported by the NExT Program’s Chemical Biology Consortium. The goal of the 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.

A New NCI-NRG Precision Medicine Clinical Trial Treats Patients with ALK-positive Non-Small Cell Lung Cancer

NCI and NRG Oncology, a member of NCI’s National Clinical Trials Network (NCTN), are leading a precision medicine clinical trial in patients with late-stage, ALK-positive non-small cell lung cancer (NSCLC), whose tumors are resistant to previous ALK inhibitor therapy. This is a phase 2 trial with nine treatment arms, and patients are treated based on the genetic alterations of their tumors, which are identified by tumor biopsy performed at the time of progression. The goals of the trial are to compare the response rates in ALK-positive patients with and without ALK-resistant mutations and to evaluate the effectiveness of liquid biopsies to detect ALK alterations in circulating tumor DNA and corroborate those results with the tumor biopsy.

NCI Announces New Tissue Procurement Study to Inform Cancer Drug Resistance

The NCORP Tissue Procurement Protocol will assess if researchers can obtain and analyze tissue and blood samples at baseline and upon disease progression from patients with advanced cancer being treated with approved molecularly targeted therapies at community sites. The goals are to analyze the specific genes that may affect the growth and spread of the tumor and determine if the patient’s treatment influences the genomic make-up of the tumor cells and resistance to therapy.

This effort, which is being developed by DCTD and the Division of Cancer Prevention, will collect tumor biopsy and blood biospecimens and associated data to help answer pressing questions in cancer research. It is a project within the Cancer MoonshotSM and will help to inform the Cancer MoonshotSM Biobank.

next page ...
A New Look for the NIH Genotype-Tissue Expression (GTEx) Project from the Cancer Diagnosis Program’s (CDP) Biorepositories and Biospecimen Research Branch (BBRB): Comprehensive Web Pages for Quick and Easy Access to Samples

The GTEx Project was developed to help researchers better understand the relationship between genetic variation and gene expression in normal human post-mortem tissue to determine how these differences influence susceptibility to disease. CDP’s BBRB managed the collection of tissue and blood specimens for GTEx from nearly 1,000 deceased donors who were identified through organ and tissue transplant programs. GTEx has created a comprehensive public resource for the research community to evaluate tissue-specific gene expression and regulation in these different tissues and disease types. Investigators can request residual samples from the biobank, access the histology database, and more, on BBRB’s new GTEx web pages.

Publications and Outreach

Peer-reviewed Publications


NCI Cancer Currents Blog Posts

**New Drugs, New Side Effects: Complications of Cancer Immunotherapy; Elad Sharon, MD, MPH, Cancer Therapy Evaluation Program; May 10, 2019.**

**Some Children with Liver Cancer May Need Less Chemotherapy, Study Suggests; Nita Seibel, MD, Cancer Therapy Evaluation Program; May 9, 2019.**

**Making Cancer Clinical Trials Available to More Patients; Percy Ivy, MD, Andrea Denicoff, RN, MS, Grace Mishkin, MPH, and Fernanda Arnaldez, MD, Cancer Therapy Evaluation Program; March 7, 2019.**

**Nature’s Bounty: Revitalizing the Discovery of New Cancer Drugs from Natural Products; Barry O’Keefe, PhD, Developmental Therapeutics Program; March 22, 2019.**

**Scientists Mine for Potential Drugs in the Berkley Pit and Other Industrial Sites; Barry O’Keefe, PhD, Developmental Therapeutics Program; Chemical & Engineering News; May 6, 2019.**

**FDA Strives to Expand Trial Enrollment; Percy Ivy, MD and Fernanda Arnaldez, MD, Cancer Therapy Evaluation Program; Cancer Discovery; April 24, 2019.**

**Malignant Neoplasm Label May Affect Patient Perceptions and Treatment Decisions; Elise Kohn, MD, Cancer Therapy Evaluation Program; Reuters; April 5, 2019.**

**Maintenance Rucaparib Controls Some Pancreatic Cancers; Alice Chen, MD, Developmental Therapeutics Clinic; Cancer Discovery; April 2, 2019.**

**Federal Study Gives New Options for People with Rare Cancers; Elad Sharon, MD, MPH, Cancer Therapy Evaluation Program; Associated Press; April 1, 2019.**

**Tuberculosis Can Emerge After Cancer Immunotherapy; Elad Sharon, MD, MPH, Cancer Therapy Evaluation Program; The Scientist; April 1, 2019.**

**Cancer Immunotherapy May Have a Dark Side; Elad Sharon, MD, MPH, Cancer Therapy Evaluation Program; Science; March 29, 2019.**

**NCI-MATCH Results Offer Clues for the Use of Agents across Tumor Types; Lyndsay Harris, MD, Cancer Diagnosis Program; OncLive; February 1, 2019.**
DCTD-supported research was presented at the recent AACR Annual Meeting 2019 in Atlanta, GA. View the full list of DCTD staff presentations and DCTD-supported research and see the photo highlights below.

Dr. Malcolm Smith, Cancer Therapy Evaluation Program, stands by a poster about the Pediatric Preclinical Testing Consortium.

Dr. Yvonne Evrard, Developmental Therapeutics Program, speaks about the NCI Patient-Derived Models Repository.
News about DCTD Programs and Activities - continued

Dr. Elad Sharon, Cancer Therapy Evaluation Program, speaks at a Meet-the-Expert session at the NCI Exhibit Booth

(l to r): Drs. Arjun Mittra and Sabrina Khan, Developmental Therapeutics Clinic, at the poster session

(l to r): Drs. Robert Meehan, formerly of the Developmental Therapeutics Clinic, and Drs. Geraldine O’Sullivan Coyne and Alice Chen, Developmental Therapeutics Clinic, at the poster session
Second Interdisciplinary Conference on Cancer, Autoimmunity, and Immunology Held at NIH

The American Association for Cancer Research (AACR) joined NCI, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Institute of Allergy and Infectious Diseases this year to convene the “NIH-AACR Cancer, Autoimmunity, and Immunology Conference” on April 15-16, 2019 in Bethesda, MD. The archived meeting can be viewed by NIH Videocast (Day 1 and Day 2). This conference follows the first Cancer, Autoimmunity, and Immunology Conference in 2018, with its accompanying proceedings published in the Journal of Immunology.

Norman Coleman, MD, Radiation Research Program, was selected to give the 16th Warren K. Sinclair Keynote Address at the 2019 Annual Meeting of the National Council on Radiation Protection and Measurement. His talk was entitled, “Frontiers in Medical Radiation Science.”

New DCTD Funding Opportunities and Funding Information

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