National Cancer Advisory Board (NCAB)
ad hoc Subcommittee on Experimental Therapeutics

29 November 2023
2:05 p.m.–3:05 p.m. EDT
Virtual Meeting

SUMMARY

Subcommittee Members

Dr. Richard J. Boxer, Chair
Dr. Rose Aurigemma, Executive Secretary
Dr. Nilofer S. Azad
Dr. Anna D. Barker
Dr. Andrea Hayes Dixon
Dr. Howard J. Fingert
Ms. Julie Papanek Grant
Dr. Amy B. Heimberger
Dr. Nikan Khatibi
Dr. Susan Thomas Vadaparampil
Dr. Ashani T. Weeraratna

Other Participants

Dr. Chandrakanth Are, Board of Scientific Advisors (BSA)
Mr. Timothy Babich, BSA
Dr. Suzanne J. Baker, BSA
Dr. John D. Carpten, Chair, NCAB
Dr. Mark P. Doescher, BSA
Dr. James Doroshow, National Cancer Institute (NCI)
Dr. Shelton Earp, BSA
Dr. Paulette S. Gray, NCI
Dr. Dorothy K. Hatsukami, BSA
Dr. Ana Maria Lopez, BSA
Dr. Douglas R. Lowy, Acting Director, NCI
Ms. Anne Lubenow, NCI
Dr. Karen M. Mustian, BSA
Ms. Thu Nguyen, NCI
Dr. Barry O'Keefe, NCI
Dr. W. Kimryn Rathmell, BSA
Mr. Ricardo Rawle, NCI
Dr. Beverly A. Teicher, NCI
Dr. Cornelia M. Ulrich, BSA
Dr. Sundar Venkatachalam, NCI
Dr. Samuel L. Volchenboum, BSA
Dr. Stephen L. White, NCI
Dr. Karen M. Winkfield, NCAB
Ms. Joy Wiszneauckas, NCI
Dr. Jason Yovandich, NCI
Dr. Richard C. Zellars, BSA
Dr. Carolyn Fisher, The Scientific Consulting Group, Inc., Rapporteur

Opening Remarks, Recognition of Members, and Charge to the Subcommittee

Dr. Richard J. Boxer, Clinical Professor, David Geffen School of Medicine, University of California, Los Angeles

Dr. Richard J. Boxer, Subcommittee Chair, welcomed all participants to the meeting. He expressed his appreciation of chairing this Subcommittee and that he looks forward to building on the experience of the ongoing members along with the new members. Dr. Boxer explained that this *ad hoc* Subcommittee was established in 2006 for a particular purpose and mission but did not meet periodically for its first 9 years. The group began convening regularly in 2020. During this meeting, the Subcommittee will have a discussion of its mission statement and how it fulfills NCI's needs today. He invited participants to introduce themselves.

Overview of the Developmental Therapeutics Program
Dr. Rose Aurigemma, Associate Director, Developmental Therapeutics Program (DTP), Division of Cancer Treatment and Diagnosis (DCTD), NCI

Dr. Rose Aurigemma provided a detailed overview of DTP and its mission and resources; highlighted recent Subcommittee accomplishments; and led a discussion on the Subcommittee's mission and proposed next steps. One of DCTD's larger programs, DTP's mission is to support and assist the extramural community in promoting translation of new therapeutic concepts toward clinical use. In the preclinical research space, DTP provides grants, services, and resources for translational research and works with the NCI Experimental Therapeutics Program (NExT) program. In 2018, DTP launched the Stepping Stones Initiative to help fill gaps in the translational pathway for new therapeutics for grantees.

DTP consists of 10 branches, three of which comprise the grants portfolio. The Preclinical Therapeutics Grants Branch, the largest component of the portfolio, supports small molecules, natural products, drug target identification, and discovery and development of new therapeutic concepts. The Immuno-Oncology Branch supports immune-oncology, immunotherapy, and a number of networks that the branch oversees. The Biological Resources Branch, which undertakes a number of activities for the cancer research community, has a grants portfolio that primarily covers biotechnology development. This branch also manages a repository of biological reagents that are available to the cancer community and provides related services. Dr. Aurigemma informed the Subcommittee that DTP reached a milestone within its grants portfolio, which spans from discovery to clinical trials: In August 2023, the number of active awards (e.g., R01s, R21s, P01s and U grants) surpassed 1,000—not including no-cost extensions—which the program officers are managing across the three branches.

Seven of the 10 DTP branches provide repository support and services. The Drug Synthesis and Chemistry Branch operates a chemistry laboratory housed at the Frederick National Laboratory for Cancer Research (FNLCR) and manages a large repository of chemical compounds used in *in vitro* screening. Data are publicly available. The Molecular Pharmacology Branch oversees the NCI-60 Human Tumor Cell Lines Screen and is involved in developing other screening technologies, such as for organoids and spheroids, as well as combination screening. The Natural Products Branch has undertaken a major effort to prepare a prefractionated library of natural products or extracts. This branch performs extensive chemistry to help identify novel compounds within those extracts once a positive signal (i.e., hit) has been identified and also manages a repository available to the broader research community. The Information Technology Branch helps manage the copious data that have been collected throughout the years and is actively working to develop a dashboard that can better mine the information within the databases to answer complex questions. The Biological Testing Branch houses animal testing at FNLCR and also oversees the Patient-Derived Models Repository, which is a very valuable resource for the community. The Toxicology and Pharmacology Branch provides Good Laboratory Practice (GLP) and non-GLP pharmacokinetics and toxicology support and performs *in vitro* assays, all via contract services. The Pharmaceutical Resources Branch handles manufacturing of final drug products and of bulk active pharmaceutical ingredients.

Dr. Aurigemma emphasized that because DTP addresses the critical path of advancing new compounds (small molecules and biologics) into U.S. Food and Drug Administration (FDA) Investigational New Drug (IND) readiness, the program is similar to a small drug–development company. She further elaborated on DTP's interactions with two other DCTD programs and resources. Projects can enter the NExT program at any stage of discovery or development and be evaluated for significance, innovation, and readiness. Submissions are accepted three times per year and applications are peer-reviewed by NExT Special Emphasis Panels. The program provides resources for approved studies, not funding to the applicants. The NExT program is composed of three areas. The first area is discovery, which is managed by the Chemistry Biology Consortium. This consortium of academic and research institutions provides

target-validation services, screening, and identification of hit-to-lead compounds. The second area is preclinical development, and DTP provides resources for preclinical evaluation, candidate optimization, and IND-enabling activities. The third area is clinical development, which is overseen by the NCI DCTD Cancer Therapy Evaluation Program (CTEP). The Stepping Stones Initiative is a limited gap-filling resource that is provided to already-funded grantees who may not have funding to cover all the necessary and iterative activities to advance a product to a true lead candidate compound. DTP provides critical data to aid grantees, such as drug formulation to improve bioavailability. The goal is to help the investigator advance the drug and procure additional resources. The main focus is on indications with high unmet research need and institutions that have limited access to drug development tools or resources.

Overview of Recent Subcommittee Accomplishments

Dr. Aurigemma highlighted recent accomplishments across the Subcommittee's three 2020–2022 priority topics. The first priority topic is cell therapy and expanding this capability to the external community. Since the 2020 Subcommittee meeting, NCI sponsored a second workshop on cell-based immunotherapy for solid tumors and published a summary finding paper. NCI also developed a number of initiatives and resources to expand support for cell therapy within the broader cancer research community. Efforts include renovating good manufacturing practice (GMP) suites in the Biopharmaceutical Development Program at the Advanced Technology Research Facility at NCI-Frederick, expanding cell therapy product technology, and exploring other platforms for cell manufacturing. NCI is currently supporting two cell therapy clinical trials, anticipates activating other trials in the next few years, and is working on CRISPR-based gene editing for nonviral cell therapy.

To address the need to conduct small trials that can answer questions quickly, NCI published a request for applications (RFAs) to establish the Cancer Adoptive Cell Therapy Network (Can-ACT). The goals of this RFA are to support cell therapy technologies or clinical trials for adult and pediatric patients with solid tumors; support early-phase trials using the Exploratory and Developmental Phased Award Cooperative Agreements (UG3/UH3); and explore imaging and biomarker development. DTP is partnering with CTEP, the Cancer Imaging Program, Cancer Diagnosis Program, and Translational Research Program to manage the awards. In the first round of funding, four grants have been awarded: three UG3/UH3s for adult cancers and one U24 for the Can-ACT Coordinating Center. NCI will be reissuing the RFA and anticipates receiving proposals for pediatric cancers. The FNLCR is providing development and manufacturing resources for the cell therapy products. Two of the three Can-ACT–funded projects will use resources available through the Immune Cell Network (ICN) Core at the FNLCR, which provides manufacturing and quality-control testing. Efforts also will focus on developing and standardizing the assays necessary to advance cell products into the clinic and to analyze the associated data.

The Subcommittee's second priority topic is rational drug discovery, and NCI organized a workshop in 2021 to hear from the community about the state of this research. Follow-on workshops were sponsored in 2022 on innovative treatment modalities for intractable disease targets and novel chemical approaches for targeting fusion oncoproteins. The recordings and presentation slide decks from these workshops can be accessed on the NCI website. A new initiative focusing on fusion oncoproteins emerged from this workshop series. Notices of funding opportunities were announced in 2023, and awards are anticipated in the summer of 2024.

The third priority topic, supporting translational research training, was discussed in 2022 and is predicated on NCI's serving as a key hub for such training in an electronic format. The Subcommittee discussed existing training available through the NCI Center for Cancer Training on developing clinical protocols and conducting clinical research. DCTD offers translational research training to investigators in the extramural community. In 2021, DCTD hosted a drug development workshop and webinar series titled

How to Advance A Therapeutic Candidate From Bench to Bedside, which consisted of 10 sessions spanning topics from preclinical development to case studies. A second drug development workshop, Specialized Topics in Preclinical Development of Small Molecule Cancer Drugs, convened in 2022 and 2023, focused on special topics that external investigators may not have access to or knowledge of, such as how to design efficacy models or safety studies within their context. Dr. Aurigemma noted that DTP/DCTD provides preclinical development consultation service through the NExT program. The consultations are confidential and provide advice on small molecules, biologics, cell therapies, imaging agents, and nanotechnology products, as well as feedback on advancing products and avoiding potential roadblocks. As of August 2023, DTP has held 209 consultations via Webex, currently averaging one per week. Academic institutions are the main clients, and requests are received from across the United States and around the world. Advertisements during the 2023 annual American Association for Cancer Research (AACR) meeting of DTP's resources and services has increased the requests for consultations.

Discussion of Mission and Proposed Next Steps

Dr. Boxer opened the discussion and noted that he had reviewed the last 4 years of minutes of the Subcommittee meetings and was impressed with some of the key points raised by NCAB members, including Drs. Anna D. Barker, Howard J. Fingert, Amy B. Heimberger, and John D. Carpten. He questioned whether the suggestions had materialized and also whether the minutes conveyed to NCI this Subcommittee's impact, as demonstrated in Dr. Aurigemma's presentation. Dr. Boxer explained that part of the Subcommittee's thought process should focus on whether the mission of this *ad hoc* Experimental Therapeutics Subcommittee as formulated in 2006 is still appropriate for 2023. He requested input in developing a new mission statement and proposing that to NCAB and NCI during the February 2024 NCAB meeting.

Dr. Fingert commended NCI and the experimental therapeutics research, which has adapted well to both new science and regulatory science. The practical workstreams that he sees as the mission of NCAB involve clinical protocols that are intended to help a program become accessible to a larger population, including a commercial partner. Dr. Fingert called attention to gaps in quality that have been recognized in the field, including that more than 50 percent of the proposals from NCI/NIH–funded work often were not reproducible. He emphasized engaging the NCI program directors to share their perspectives on where the quality gaps might lie and encouraged the Subcommittee to think about the metrics for success that it would like to see when reviewing grants. This information would be beneficial to project directors as they interface with investigators.

Dr. Barker suggested that the Subcommittee take a broader view of the entire therapeutics landscape, especially since NCI has a rich history of expertise in drug discovery and development that dates back to the 1970s. NCI was the first to develop the oncology space and has been leading these efforts. DTP recently has increased awareness of its resources by advertising at the AACR annual meetings. She noted that the NCI RAS Initiative is a unique drug discovery effort and a resource this Subcommittee could consider as a case study. Dr. Barker suggested two other areas this Subcommittee could consider: advancing therapeutics with companion diagnostics to facilitate biomarker development and reducing the serious adverse drug events associated with advancing immunotherapeutics for chimeric antigen receptor (CAR) T-cell therapy. She also recommended building on the NCI–FDA relationship.

Dr. Boxer noted that a common theme of this Subcommittee meeting has been that NCI should find a way to partner with FDA and use that relationship to educate applicants who are interested in submitting grants to NCI or their new biologics or small molecules to FDA, thereby facilitating the bench-to-bedside process.

Dr. Andrea Hayes Dixon commented that a major role of this Subcommittee is to use its expertise to act as a bridge with FDA and ask appropriate questions of FDA when regulatory hurdles are observed with particular drug development. She emphasized including such a partnership in the mission of this Subcommittee.

Dr. James Doroshow explained that NCI meets monthly with the FDA to review new clinical trial designs and noted that those two-way conversations are confidential. He also noted two other functions DCTD/NCI provides. First, FDA inspectors are training at the biologics plant at NCI-Frederick to better inform their audits. Second, extramural investigators can leverage the toxicology laboratory at the FNLCR to perform a variety of drug toxicology studies on products in the pipeline, including toxicology studies for CAR T-cells using human induced pluripotent stem cells, for example, providing data that may be used for an FDA IND submission.

Ms. Julie Papanek Grant commended NCI for its vast resources and capabilities in therapeutics. She asked whether the focus of DTP is primarily on discovery or translational toxicology. Dr. Aurigemma clarified that DTP's grants portfolio primarily consists of projects focusing on drug discovery and development. She reiterated that the services DTP provides are optimizing a lead candidate for advancing to the clinic and assisting with solving problems such as optimizing formulations and performing IND-enabling studies. Ms. Grant noted the importance of having an advisory body of consultants with experience in the field who could provide input on any translational gaps and share their knowledge. Dr. Boxer suggested that DTP/DCTD's follow-up interactions with investigators could include providing a link to available consultants and resources. Dr. Barker added that many small oncology companies are failing in drug discovery and development because of the lack of appropriate GLP in the preclinical phase or good clinical practices in the clinical phase. She emphasized educating academicians in these areas, as well as about the regulatory path.

Ongoing and New Business
Dr. Richard J. Boxer

Dr. Aurigemma asked the Subcommittee to consider other priority areas that NCI should explore to help the extramural community in drug discovery as a new mission statement is being developed.

Dr. Boxer explained that he and Dr. Aurigemma will be communicating with the Subcommittee about the new mission statement and that the aim is to have it ready to present at the February 2024 NCAB meeting.

Adjournment

Dr. Boxer adjourned the meeting at 3:00 p.m. EST.

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Dr. Richard J. Boxer Chair	Date	Dr. Rose Aurigemma Executive Secretary	Date