

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

**September 1, 2020**  
**4:45–5:45 p.m. EDT**  
**Virtual Meeting**

**SUMMARY**

Subcommittee Members

Dr. Timothy Ley, Chair  
Dr. Peter C. Adamson  
Dr. Francis Ali-Osman  
Dr. Rose Aurigemma, Executive Secretary  
Dr. Anna D. Barker  
Dr. Howard J. Fingert  
Dr. Andrea Hayes-Jordan  
Dr. Scott W. Hiebert  
Dr. Nancy J. Raab-Traub

Other Participants

Dr. Jerry Collins, National Cancer Institute (NCI)  
Dr. James D. Doroshow, NCI  
Dr. Paulette S. Gray, NCI  
Dr. Nikan Khatibi, NCAB (pending)  
Dr. Douglas R. Lowy, NCI  
Mr. Ricardo Rawle, NCI  
Dr. Norman E. Sharpless, NCI  
Dr. Dinah S. Singer, NCI  
Ms. Joy Wiszneauckas, NCI  
Dr. Amanda Webb, The Scientific Consulting Group, Inc., Rapporteur

**Welcome and Charge to the Subcommittee**

*Dr. Timothy Ley, Subcommittee Chair, Washington University in St. Louis, and Dr. Norman Sharpless, Director, NCI*

Dr. Timothy Ley, Subcommittee Chair, welcomed the participants and reviewed the meeting’s agenda.

Dr. Norman Sharpless described the charge of the Experimental Therapeutics Subcommittee. He emphasized that it is incredibly important for the NCI to learn about new and rapidly emerging areas of science where the NCI portfolio needs to be expanded. He noted that these areas of interest need to be identified immediately so the NCI can start steering processes in the correct direction in a timely manner.

This effort relates to the specific charge of this subcommittee: “to help the National Cancer Institute identify high-priority research opportunities in the area of experimental therapeutics.”

Dr. Sharpless elaborated on this charge, stating that the subcommittee should identify areas where the NCI portfolio should be increased or changed, areas where the special capabilities of the NCI would be especially helpful (e.g., via their ability to work with other parts of the United States government, their ability to fund projects without regard to market size, and their ability to convene stakeholders), and areas where there is high potential to provide meaningful benefits for patients.

Dr. Sharpless provided some examples of the types of activities that the subcommittee can do. For example, the subcommittee can ask the NCI for data, ask the NCI to impanel a working group and add *ad hoc* members who can better address topics of interest with specific expertise, and advise the NCI on the need for additional emphasis on a specific scientific area or new NCI infrastructure.

Dr. Sharpless also provided examples of areas where the NCI has faced challenges with regards to developmental therapeutics that the subcommittee may want to address, including novel medicinal chemistry; cellular immunotherapy and vector production; other complex biologics; the “bespoke” medicines problem; and precision prevention efforts.

Dr. Sharpless concluded by emphasizing the need to identify scientific opportunities that the NCI likely will hear about soon.

### *Discussion*

Dr. Ley noted that the NCI portfolio likely is fixed in size, which would mean that adding more topics of interest would require the removal of other topics. Dr. Ley asked Dr. Sharpless if the subcommittee’s charge, then, should include an evaluation of fixed components within the portfolio regarding their present usefulness in the context of therapeutics development.

Dr. Sharpless acknowledged the validity of Dr. Ley’s concern but noted that NCI’s larger concern—and, thus, the ideal focus of these short subcommittee meetings—is on identifying new scientific topics that should be prioritized for further study.

Dr. Francis Ali-Osman commented that he would like to let the science direct the topic. He stated that the research and discussions will lead the program in a way that best serves the science.

Dr. Anna Barker agreed with Dr. Ali-Osman’s point, stating that she thinks the subcommittee should focus on supporting and expanding the NCI’s programs.

### **Review of Expertise and Special Interest(s) in the Subcommittee’s Mission**

*Dr. Timothy Ley, Subcommittee Chair, Washington University in St. Louis*

Dr. Ley asked each of the subcommittee members to briefly introduce themselves and provide an overview of the areas of expertise and interests that make them an asset to this subcommittee.

Dr. Ley began by introducing himself, stating that his expertise is largely discovery-focused and specific to epigenetics and genomics. He has focused on identifying which genes are most relevant, which genes are good targets, which pathways are good targets, and which mechanisms are most crucial for the pathophysiology of acute myeloid leukemia. He is interested in target discovery and mechanisms of action, which can lead to the development of drugs that can affect target pathways.

Dr. Rose Aurigemma, Executive Secretary, has been working in therapeutics development. She started in the Developmental Therapeutics Program (DTP) in the Biological Resources Branch of the NCI, worked in infectious disease drug development for seven years, and has been working in cancer drug development for a cumulative 15 years. She is a virologist and recently has returned to the NCI. She is the Deputy Associate Director in the developmental therapeutics program of the Division of Cancer Treatment and Diagnosis (DCTD).

Dr. Peter Adamson has worked in childhood cancer drug development. He moved from academia recently to become the Global Head of Oncology Development at Sanofi, which has given him industry perspective.

Dr. Francis Ali-Osman has a background in neuro-oncology treatment and drug resistance mechanisms, which has led to an interest in targeted drug discovery. He stated that this is an exciting time, with developments in immunotherapy providing unique opportunities to advance the field.

Dr. Anna Barker worked as a post-doctoral researcher and, eventually, the Senior Vice President at the Battelle Memorial Institute, where she directed the anchoring of the Drug Discovery Program at the NCI. This program resulted in the development of many natural products. She has extensive drug development knowledge, has been trained in organic chemistry and immunotherapy development, and has worked as an immunologist. She also started a biotechnology company where she focused on reactive oxygen species. Dr. Barker also helped to set up the CTD<sup>2</sup>: Cancer Target Discovery and Development program at the NCI. Currently, Dr. Barker is most interested in chemical genomics and the use of biomarkers in chemotherapy and immunotherapy.

Dr. Howard Fingert is a hematologist-oncologist who trained at the NCI medicine branch and pediatric branch. He completed his post-doctorate training at Harvard University and was a faculty member at Massachusetts General Hospital and the Dana-Farber Cancer Institute. He has experience in industry and has held grants focused on translational research leading to phase I clinical trials. He is interested in public-private partnerships and the structural and infrastructure components that affect the quality of clinical trials.

Dr. Andrea Hays-Jordan's subspecialty is in molecular biology. Her work has included translational research on sarcomas and pediatric cancers.

Dr. Scott Hiebert is focused on the discovery of therapeutic targets of epigenetic and transcriptional sites. He is an end-user who loves to work with small molecules that inhibit epigenetic targets and is particularly impressed by proteolysis targeting chimeras (PROTACs). He suggested that the NCI should make its portfolio of PROTACs widely available to facilitate research discoveries.

Dr. Nancy Raab-Traub is a virologist who works on the Epstein-Barr virus, which causes tumors. She is interested in understanding the etiology of virally associated cancers and how that etiology extends to other cancers. She is interested in therapeutics that target essential viral mechanisms or proteins and pathways that are affected by cancer-driving viruses.

Dr. Ley noted that this subcommittee represents broad expertise and is a great place to begin. He introduced Dr. Aurigemma, who provided an overview of the therapeutics development programs in DCTD.

### **Overview of the NExT Program and the Developmental Therapeutics Program**

*Dr. Rose Aurigemma, Executive Secretary, DCTD*

Dr. Aurigemma provided a DCTD briefing to the NCAB subcommittee on experimental therapeutics. She noted that the committee has not met in 9 years, so much of information needed to be summarized in her presentation very broadly and briefly. The topics included in this presentation were an overview of the NCI Experimental Therapeutics (NExT) program, an overview of the DTP, and the determination of topics that the subcommittee would like to discuss in future meetings.

Dr. Aurigemma displayed a list of the DCTD organization programs and branches, pointing out that the Cancer Imaging Program (CIP), Cancer Therapy Evaluation Program (CTEP), DTP, Radiation Research Program, and Developmental Therapeutics Clinic are involved actively with the NExT support program.

Dr. Aurigemma then emphasized that NExT is not a grant mechanism and does not provide funding, but it does provide support in advancing a product to the clinic and providing patient benefit. NExT provides access to NCI resources and experience and was launched in 2009 to integrate separate DCTD programs. Innovators and investigators can apply via a simple application that has three submission dates per year, and those applicants who are chosen remain key members of the team advancing the proposed ideas.

When NExT was conceived, the Chemical Biology Consortium (CBC) also was set up as the discovery engine that increased the flow of early-stage drug candidates into the DCTD therapeutics pipeline by leveraging research knowledge from biotechnology companies and academia. This discovery engine was set up such that it provided the opportunity for the extramural community to participate in a collaborative drug-discovery partnership with the NCI. The pilot program for the CBC was expanded 2016 with 23 dedicated and specialized centers that provide unique expertise, resources, and capabilities supporting various components of the drug discovery and development process.

The NExT Early Development component largely is covered under the DTP, and the CIP, with support from the Pharmacodynamics Assay Development & Implementation Section (PADIS), the National Clinical Target Validation Laboratory, and the Clinical Assay Development Program. Dr. Aurigemma noted that access to PADIS, specifically develops assays focused on measuring drug effects.

If a NExT project enters the clinical development stage, it can be tested in a network of clinical trial sites managed by CTEP. These projects also can be tested at the DCTD Developmental Therapeutics Clinic (DTC) or via the NCI Experimental Therapeutics Clinical Trials Network and the NCI National Clinical Trials Network. The partnership between DTC and the Pharmacokinetics Laboratory enables investigators to look at the drug metabolism, drug exposure, and the pharmacodynamic properties of agents in clinical trials.

Dr. Aurigemma emphasized the fact that innovators can enter at any point in the NExT pipeline, from early discovery to clinical development. She noted that projects tend to come from the biotechnology industry as frequently as they come from academia and stated that the NCI maintains a balance between the discovery, preclinical development, and clinical development projects within the NExT pipeline.

NExT applications are received three times per year and are reviewed by a Special Emphasis Panel, which is an outside body responsible for reviewing and ranking projects. Highly ranked projects move on to internal review at the NCI, where they are evaluated based on such considerations as project feasibility, funding availability, and applicability within program priorities. Once a project passes these steps, it is approved, and the NCI begins work on the project.

The DTP has resources that support the extramural community to advance new therapeutic concepts toward clinical use. These resources are provided via ten branches along the regulatory critical path from bench to bedside, which Dr. Aurigemma discussed in detail.

The new Information Technology Branch creates and maintains databases generated by DTP efforts. This branch has the goal of developing a dashboard integrating these databases to facilitate data analytics and data mining efforts to speed drug discovery and development.

The Drug Synthesis and Chemistry Branch oversees the NCI chemical repository, which contains more than 200,000 compounds. This branch sends, receives, synthesizes, and tests thousands of chemicals each year. Members of this branch also optimize synthetic routes for manufacturing that can be scaled up for future development.

The Pharmaceutical Resources Branch solves formulation issues, develops clinical dosage forms, solves solubility issues, produces clinical products at good manufacturing practice (GMP) grade, and performs analytical chemistry tests required to release these products for clinical use.

The Molecular Pharmacology Branch is where the NCI-60 tumor cell line screening is housed. Recently, this branch also has focused on developing a high-throughput screening platform (384-well screening) and organoid and spheroid screening processes.

The Natural Products Branch holds a large repository of natural product extracts. This branch recently has been focused on creating pre-fractionated extract libraries that can be distributed and used to speed the identification of active compounds and aid in drug discovery.

The Biological Testing Branch is charged with conducting the *in vivo* testing of all of these anti-cancer candidates. In addition to maintaining tumor models that they distribute to investigators performing their own research, this branch is developing a Patient-Derived Models Repository. They also collaborate with the Molecular Characterization Laboratory and PADIS to perform mouse studies evaluating combinatorial treatments or new therapeutics and the resulting pharmacodynamic effects.

The Toxicology and Pharmacology Branch oversees studies to support the drug development portfolio. They also house the Investigational Toxicology Laboratory, which is developing specialized toxicity assays specific to target organs.

The Biological Resources Branch has a grant portfolio focused on the development of novel biologics and oversees the Biopharmaceutical Development Program. This program has many areas of focus, including cell banking, process development, GMP manufacturing, and analytical methods. Recently, they also have been involved in adoptive cell therapy and virus vector manufacturing for investigators, and they are working on CRISPR-based gene-editing techniques that will support cell therapy efforts.

The Preclinical Therapeutics Grants Branch works on grant management and grant administration and advises a large community of investigators. They oversee small molecule and natural product discovery and development, and they handle nanotechnology therapies and the target validation aspects of drug development.

The Immuno-oncology Branch oversees immunotherapy, comparative oncology, and immune modulators.

Dr. Aurigemma showed several images of a newly renovated suite that has been set up for cell therapy production and will be functional in the fall. She also stated that they are renovating more space because they currently have only one virus production suite and one cell therapy suite. These additional renovations will make more resources available for researchers, and they hope to achieve numerous campaigns to make virus vectors, introduce CRISPR technology to their arsenal, and make cell therapy products to support clinical trials.

The NCI has a large DTP grants portfolio, which is overseen by three branches: the Preclinical Therapeutics Grants Branch, Biological Resources Branch, and Immuno-oncology Branch. Dr. Aurigemma noted that the overall DTP portfolio is made up of 886 active awards, most of which are funded by R01 awards. She showed that the awards in these portfolios can be sorted based on different criteria, including organ systems, primary topic areas of studies, popular targets, and iSearch terms.

Dr. Aurigemma ended her presentation by asking the subcommittee members for their input on what information they would like to see in future meetings.

### **Ongoing and New Business**

*Dr. Timothy Ley, Subcommittee Chair, Washington University in St. Louis*

#### *Consideration of Topics for Future NCI Experimental Therapeutics Support*

Dr. Ley stated that they have 10 topics of interest that would be reasonable to pursue within the context of this subcommittee. Because there is not enough time to discuss all of these topics, he asked each committee member to review this list and send three or fewer topics that they want to prioritize to Dr. Aurigemma via email by the close of business the next day, September 2, 2020.

The proposed topics are—

1. Intelligent drug discovery
2. Agnostic screens of massive compound libraries
3. Screens to repurpose existing drugs
4. Artificial intelligence–driven drug discovery
5. COVID-19 effects on drug discovery
6. Cellular immunotherapies and other complex biologics for cancer
7. Ultrapersonalized therapies
8. Evaluation of existing NCI infrastructure
9. Precision prevention approaches for people with cancer susceptibility
10. Drug discovery for precision medicine targets defined by sequencing and/or pathway studies

### **Adjournment**

*Dr. Timothy Ley, Subcommittee Chair, Washington University in St. Louis*

Dr. Ley adjourned the Subcommittee meeting at 5:45 p.m. EDT.

<u>                    /s/                    </u>	<u>                    9/3/2020                    </u>	<u>                    /s/                    </u>	<u>                    9/3/2020                    </u>
Dr. Timothy Ley Chair	Date	Dr. Rose Aurigemma Executive Secretary	Date