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

December 7, 2021
1:15 p.m.–2:15 p.m. EDT
Virtual Meeting

SUMMARY

Subcommittee Members
Dr. Timothy J. Ley, Chair
Dr. Peter Adamson (absent)
Dr. Francis Ali-Osman
Dr. Rose Aurigemma, Executive Secretary
Dr. Anna D. Barker
Dr. Howard Fingert
Dr. Andrea Hayes-Jordan (absent)
Dr. Scott W. Hiebert
Dr. Nikan Khatibi
Dr. Nancy J. Raab-Traub

Other Participants
Dr. Chandraknath Are, Board of Scientific Advisors (BSA)*
Dr. Nilofer S. Azad, NCAB*
Dr. Suzanne J. Baker, BSA*
Dr. John D. Carpten, NCAB
Dr. Andrew T. Chan, BSA*
Dr. Nelson J. Chao, BSA*
Dr. Gloria D. Coronado, BSA*
Dr. Luis Alberto Diaz, Jr., NCAB*
Dr. James H. Doroshow, National Cancer Institute (NCI)
Dr. Christopher R. Friese, NCAB*
Dr. Paulette S. Gray, NCI
Dr. Dorothy K. Hatsukami, BSA
Dr. Amy B. Heimberger, NCAB*
Dr. Trey Ideker, BSA*
Dr. Michelle M. Le Beau, BSA
Dr. Douglas R. Lowy, NCI
Dr. Anne Lubenow, NCI
Dr. Edith Mitchell, President's Cancer Panel
Dr. Karen M. Mustian, BSA*
Ms. Thu Nguyen, NCI
Mr. Ricardo Rawle, NCI
Dr. Norman E. Sharpless, NCI
Dr. Dinah Singer, NCI
Dr. Sharad K. Verma, NCI
Dr. Ashani T. Weeraratna, NCAB*
Dr. Max S. Wicha, NCAB
Dr. Karen M. Winkfield, NCAB*
Ms. Joy Wiszneauckas, NCI
Dr. Amanda Webb, The Scientific Consulting Group, Inc., Rapporteur

***pending appointment**

Welcome and Introduction to the Day's Topic
Dr. Timothy J. Ley, Subcommittee Chair, Washington University in St. Louis

Dr. Timothy J. Ley, Subcommittee Chair, welcomed all participants and noted that this Subcommittee has been charged with addressing two priority topics. The first priority topic, cell therapy, was discussed in previous meetings and has led to many interesting and effective recommendations for the NCI. The second priority topic, rational drug design, was the focus of today's meeting. Rational drug design is a complex topic, and progress in this area likely will require advancements in infrastructure.

Presentation on NCI Review of Rational Drug Discovery
Dr. Rose Aurigemma, Associate Director, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis

Dr. Rose Aurigemma began her presentation by providing an update on the Subcommittee's first priority topic: cell therapy. The NCI has hosted two workshops addressing this topic—the NCI Workshop on

Cell-Based Immunotherapy for Solid Tumors, and the 2nd NCI Workshop on Cell-Based Immunotherapy for Solid Tumors. The second workshop was well attended and generated many recommendations from experts in the field. A report from the workshops was published in July 2021: "Challenges and next steps in the advancement of immunotherapy: Summary of the 2018 and 2020 National Cancer Institute workshops on cell-based immunotherapy for solid tumors."

Areas of unmet need that were identified during the workshops include additional preclinical and translational research to address cell therapy for solid tumors, the ability to perform small proof-of-concept studies on the topic, the enhancement of cell-manufacturing technologies, the identification of biomarkers and image-based detection of response to therapies, the standardization of cell product characterization via a core laboratory, quality-control testing for cell therapy–related reagents that are needed for manufacturing, and additional guidance for investigators preparing investigational new drug application submissions.

The NCI has established cell therapy resources at the Frederick National Laboratory for Cancer Research (FNLCR) and still is adding technologies, facilities, and capacity in this area. Current technologies include genetically modified autologous cells, as well as lentivirus and gamma retrovirus vectors; G-Rex manufacturing platforms and CRISPR-based gene-editing technologies will be added in the future. The current facility at the FNLCR contains two Good Manufacturing Practice (GMP) suites, and the new facility will contribute an additional three GMP suites. The current capacity of these cell therapy resources enables the completion of 4 cell therapy products per month and 4 viral vector campaigns per year; the future added capacity is expected to increase outputs to 12 cell therapy products per month and 8 virus vector campaigns per year. In addition, a cell therapy core service is in development. This core will provide quality systems and regulatory affairs guidance, multisite trial GMP production support, clinical trials coordination, and data coordination.

Dr. Aurigemma then discussed the primary focus of her presentation: information related to intelligent drug discovery based on biochemistry, structure, and mechanisms, including artificial intelligence (AI)–driven drug discovery (i.e., rational drug design, the Subcommittee's second priority topic).

The NCI organized a virtual Workshop on Rational Drug Design on 18–19 October 2021, inviting subject-matter experts from academia, industry, and federal agencies. The workshop comprised four sessions: (1) Structural Biology, (2) Machine Learning/Artificial Intelligence in Discovery, (3) Novel Therapeutic Modalities, and (4) Target Interrogation. Nearly 700 people attended the workshop, which comprised 18 presentations and four discussions. During this workshop, attendees reviewed the four topic areas to better understand the state of the field. Through that process, they identified gaps in knowledge, resources, and technologies, as well as critical barriers to advancing rational drug discovery. In addition, they determined opportunities for the NCI to better support the extramural community, thereby accelerating the discovery of new cancer treatments. A video recording of the workshop can be found at https://events.cancer.gov/dctd/drugdiscovery/meeting-recordings.

General challenges identified during the workshop included difficulties related to data sharing, a lack of data reproducibility, the need to unify the research community, and the challenging transition from idea to product. Gaps and opportunities to close those gaps also were identified, which included opportunities to better leverage structural biology knowledge and related tools, provide additional support in the areas of small-molecule chemistry and novel modalities, enhance target evaluation, and overcome AI and machine learning (ML) challenges in discovery.

Dr. Aurigemma noted that the NCI can support innovation by funding high-risk and novel approaches at the earlier stages of innovation. The NCI could fund research on cancer targets that are not druggable and invest in the development of relevant assays and tools. The NCI also could support innovation with

increased investment in modalities that are not reversible inhibitors or occupancy-driven pharmacology. In addition, the NCI could increase investigators' access to resources by establishing a centralized medicinal chemistry core, facilitating the acquisition of translational resources, assisting sample- and grid-optimization processes for cryogenic electron microscopy (cryo-EM), and providing access to technologies related to fragment-based drug design and DNA-encoded libraries.

Additionally, the NCI could provide technology and training support, particularly in the areas of improving cell models and organoid screening capabilities, utilizing computational resources for protein prediction and design, supporting new modalities and platforms in AI/ML, and funding training in specific disciplines. Moreover, the NCI can foster collaboration in the field by leading workshops and other platforms of interaction among investors and stakeholders, promoting open data and knowledge sharing, incentivizing data and research quality improvements, and coordinating confirmatory studies.

Presently, the NCI offers support for the extramural community via funding, resources, facilities, and other efforts. For example, the FNLCR has a cryo-EM facility that can be accessed by the extramural community via an application process. The NCI Experimental Therapeutics Program (NExT) includes the Chemical Biology Consortium, which offers a wide array of drug-discovery expertise and resources for extramural researchers. The Drug Synthesis and Chemistry Branch includes a synthetic laboratory in the FNLCR, and the NCI Open Chemicals Repository includes more than 200,000 open compounds that are available to the community. The Developmental Therapeutics Program maintains this set of open compounds, as well as the NCI-60 Human Tumor Cell Lines Screen, an *in vitro* screening system.

The Natural Products Branch provides additional extramural support by producing prefractionated natural product extracts, more than 300,000 of which have been released to the public. This Branch has established collaborations through which it is providing these prefractionated natural product extracts to extramural investigators who study them and provide any "hits" for further study back to the Branch for further isolation. This screening capability is a powerful process. The Biological Testing Branch provides further extramural support via animal studies and *in vivo* screening, as well as via the Patient-Derived Models Repository, through which models can be accessed at https://pdmr.cancer.gov.

Additional support can be provided by expanding access to discovery resources, expanding access to medicinal chemistry services, standardizing language and terminology for AI/ML processes, sponsoring training programs in AI/ML for "wet laboratory" researchers, investing in large and publicly available screening data sets, coordinating confirmatory studies, improving domain expertise and accurate data for AI/ML, expanding the use of AI/ML in drug discovery, and coordinating grants. The NCI can further foster collaboration and community building by leading workshops, colloquia, case studies, and special topic lectures in drug discovery to enhance community building; increasing opportunities to access drug development resources; and promoting data sharing by encouraging and optimizing existing portals, as well as by rewarding data sharing practices via funding mechanisms.

Dr. Aurigemma closed her presentation by discussing next steps. In the upcoming months, the NCI will assess the challenges and opportunities for each area covered in the Workshop on Rational Drug Design to achieve the following outcomes:

- Formulate a list of possible actions that will assist the extramural community with rational drug design research.
- Prioritize possible actions for feasibility, cost, and strength of impact on the field.
- Return with an analysis of potential paths to assist the extramural stakeholders in the rational discovery of new cancer therapeutics.

Discussion of Report on Rational Drug Discovery: Next **Steps**
Dr. Timothy J. Ley, Subcommittee Chair, Washington University in St. Louis

Dr. Ley thanked Dr. Aurigemma for her presentation and asked the other Subcommittee members for their comments on the presented information.

Dr. Ley began the discussion by asking whether the cryo-EM and NExT library screening program resources need more support. Dr. Aurigemma noted that NCI programs often require that investigators apply for the program and complete a process, such as peer review, before access is granted. These processes provide metrics for and limit accessibility. Dr. Ley noted that additional information on the demand for these resources and the process by which the resources are accessed could be helpful to the Subcommittee. Dr. Aurigemma stated that she will acquire and share more details on the process with the Subcommittee members.

Dr. Sharad K. Verma noted that gaps or bottlenecks in the area of medicinal chemistry were noted during each of the four sessions of the Workshop on Rational Drug Design, indicating a critical need to focus on filling the gaps in that area. Dr. Verma also noted the importance of training more clinician–scientists in the areas of synthetic or medicinal chemistry.

Dr. Max S. Wicha mentioned that a full team of people with different areas of expertise is needed to target cancer cells and the cancer microenvironment using rational drug design approaches.
Dr. Aurigemma added that the area of rational drug design requires extensive and widespread expertise and suggested that the NCI consider ways to foster gatherings of these experts. Dr. Wicha stated that this provides an opportunity to establish multidisciplinary funding mechanisms encouraging the joining of these areas of expertise.

Dr. Howard Fingert recommended that the NCI expand existing resources to make speedy and actionable progress in the area of rational drug design. He suggested that the NCI work to improve the quality of data-sharing initiatives by building upon work that already is being performed in this area. He also recommended that the NCI strengthen the training of academic researchers who are working in the areas of early-to-late-stage clinical development. Dr. Fingert asked whether the topic of training could be part of the discussion in the upcoming summit on this topic in the United Kingdom.

Dr. Francis Ali-Osman referenced recent evidence indicating that stem cells migrate toward tumors. He asked whether the NCI was developing cell therapy technologies utilizing this feature of stem cells.
Dr. Aurigemma responded that NCI's work is driven largely by proposals and input from extramural and intramural investigators. The NCI has not received any proposals suggesting use of that stem-cell feature for cell therapy, but the NCI is open to all modalities for treatment. Dr. Norman E. Sharpless, Director, NCI, added that chimeric antigen receptor (CAR) T cell–based projects are planned first, because this area reflects the highest demand. Other types of cells can be explored if a demand arises, and vector-production processes can be used for other projects that are of interest to the community.

Dr. Ley mentioned that DNA-encoded libraries have received relatively little focus at the NCI and in academia; an NCI investment in this area could greatly benefit investigators because these libraries have huge potential in the area of drug development.

Dr. Ley asked Dr. Trey Ideker for his thoughts on how drug targets are developed via multi-omic approaches. Dr. Ideker responded that drug target development will be served by AI/ML, but AI/ML has the potential to have a major role in many additional areas. Indicating what these areas are would be helpful in future discussions with the Subcommittee.

Dr. Scott W. Hiebert stated that his research group is designing protein degraders to target individual proteins using proteolysis-targeted chimeras (PROTACs). Because the PROTAC degraders enable investigators to pull in targeted components for degradation, they provide great potential to suppress oncogenes. Dr. Hiebert's group can employ drugs against targeted genes to remove proteins in as little time as an hour, which enables the group to perform preclinical work in this area. Dr. Ley responded that it is important both to develop therapies for targets and to ensure that the identified targets are the correct ones for the investigators' intentions. Dr. Hiebert stated that conducting basic work in this field could greatly increase the collective understanding of signal transduction pathways in the context of rational drug design. This work will lead to a stronger understanding of transcriptional networks and how oncogenes function within these networks. Dr. Ali-Osman asked whether this work would facilitate the targeting of hard-to-target mutations that drive the oncogenic process. Dr. Hiebert answered that it would, adding that this process requires only that the targeting end of the molecule in use adhere to the protein selectively; the success of this process would be easy to confirm by determining whether the protein disappeared via Western blot. Dr. James H. Doroshow noted that projects in this area and using these methods have been very encouraging, and he added that the Outside Special Emphasis Panel has been favorable to review of those kinds of projects. Dr. Wicha commented that basic researchers are needed to develop this, along with clinical researchers, because understanding transcription factors requires a deep understanding of epigenetics and gene regulation. In addition, transcription factor–binding sites, as well as chromatin accessibility, must be accounted for when determining which factors to target, because targeted factors also must be accessible in the development of successful therapies.

In response to a question from Dr. Ley, Dr. Michelle M. Le Beau stated that many of the areas discussed represent current areas of need at her Cancer Center. Presently, her Center lacks the bandwidth and infrastructure to address these areas, and NCI support would beneficial.

Dr. Sharpless said that the NCI has invested significantly in the natural products library to fractionate these extracts, identify active molecules, identify active metabolites, and provide this information in a user-friendly screening format. The NCI would like to see more academic use of this information, but he asked the Subcommittee members whether they think the NCI should be actively investing in encouraging academic use of the natural products library and data. Dr. Verma stated that the NCI is filling a large void for the community, which remains interested in identifying the basis for drugs from natural product libraries. Dr. Ley added that maintaining natural products libraries also has provided justification for the preservation of biologically rich areas, such as the rainforest. Dr. Sharpless stated that the chemical space of most big pharmaceutical companies' work is very limited, but natural products are much more chemically diverse. Maintaining these products is valuable. Dr. Ali-Osman suggested that other NIH Institutes and Centers could be interested in utilizing NCI's natural product library. Dr. Sharpless agreed but noted that he would prefer that the library be used for more cancer-related work.

Dr. Ley emphasized that pharmacology training has not been emphasized in medical and Ph.D. programs. He noted also that individual Cancer Centers lack the capacity and resources to address these large concepts and tasks. Thus, it is critical that the NCI develop centralized resources to help individual investigators and programs assemble the multidisciplinary teams necessary to complete this work effectively.

Other Items
Dr. Norman E. Sharpless, Director, NCI

Dr. Sharpless thanked participants for their attendance, comments, and questions. He also thanked Dr. Aurigemma for her presentation.

Dr. Sharpless emphasized that the topic of rational drug design is of great interest to the NCI. He mentioned that the NCI is beginning to work in the areas of medicinal chemistry and the use of novel ML approaches to facilitate drug design. Dr. Sharpless noted also that the NCI also might need to begin work in the areas of central planning and structural biology capabilities. Identifying individuals with the necessary expertise to drive high-quality work in this area is challenging, which underlines a critical and specific training need. The other critical need is the collection of high-quality data sets; the NCI is working to contribute to the development of new data sets, as well as the utilization of already-collected data.

Dr. Sharpless stated that he was looking forward to the joint board meeting in the coming days.

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

Dr. Ley adjourned the meeting at 2:17 p.m. EST.

Dr. Timothy Ley Chair	Date	Dr. Rose Aurigemma Executive Secretary	Date