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

February 11, 2021
11:00 a.m.–12:00 p.m. EST
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 Barker
Dr. Howard Fingert
Dr. Andrea Hayes-Jordan
Dr. Scott Hiebert
Dr. Nikan Khatibi
Dr. Nancy J. Raab-Traub (absent)

Other Participants
Dr. Yuan Chang, NCAB
Dr. Jim Doroshow, National Cancer Institute (NCI)
Dr. Marc Ernstoff, NCI
Dr. Paulette S. Gray, NCI
Ms. Thu Nguyen, NCI
Mr. Ricardo W. Rawle, NCI
Dr. Norman E. Sharpless, NCI
Dr. Max S. Wicha, NCAB
Dr. Peter Wirth, NCI
Ms. Joy Wiszneauckas, NCI
Dr. Amanda Webb, The Scientific Consulting Group, Inc., Rapporteur

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, called the meeting to order at 11:00 a.m. EST and welcomed the group to the meeting. He stated that the Subcommittee is charged with providing the NCI with recommendations about research and infrastructure priorities in experimental therapeutics. Within the topic of experimental therapeutics, this Subcommittee has decided to focus on the subtopics of cell-based therapies and intelligent drug design. Today's meeting was focused on cell-based therapies.

Dr. Ley explained that Dr. Rose Aurigemma, Executive Secretary, will present critical background information about cell-based therapies from two workshops organized by the NCI. Recommendations and action items were formulated based on the information and discussions from these workshops. These recommendations are categorized as a set of requests for applications (RFAs) and a set of infrastructure items that could be created within NCI.

Following today's presentation summarizing the informational highlights from the workshops, the Subcommittee will discuss the proposed recommendations and action items. Dr. Ley emphasized that the action items and recommendations proposed today do not need to be approved today.

Presentation on NCI Review of Cellular Immunotherapies
Dr. Rose Aurigemma, Executive Secretary, Division of Cancer Treatment and Diagnosis (DCTD)

Dr. Aurigemma introduced a new staff member: Dr. Marc Ernstoff, M.D., Medical Officer and Chief, ImmunoOncology Branch, DCTD. She described his experience and expertise, emphasizing the value that he will bring to DCTD's Developmental Therapeutics Program (DTP) and thanked him for joining today's meeting.

Dr. Aurigemma described the DTP, a group that supports and assists the extramural community as it develops new therapeutic concepts for clinical use. The DTP includes 10 branches that provide resources facilitating activities along the regulatory-critical path for small molecules, biologics and biopharmaceuticals, and natural products. The DTP also oversees the largest grants portfolio in the NCI that is focused on the discovery and development of new cancer therapies.

Dr. Aurigemma stated that NCI leadership wants to understand how to best drive adoptive cell therapy toward clinical use and patient benefit. To this end, the NCI organized workshops with experts in the field who could remark on the current state of the field and identify knowledge and research gaps that the NCI might be able to address.

She discussed the challenges in the field of cellular therapies that were identified and discussed during the first workshop on cell-based immunotherapy for solid tumors in 2018. These challenges include the need for additional research in the following areas:

- Optimizing solid-tumor targets so that cross-reactivity is avoided and affinity for tumors is strong
- Improving cell trafficking and tumor penetration
- Overcoming the immune-inhibiting tumor microenvironment
- Exploring autologous versus allogenic products
- Establishing *in vivo* gene editing of immune cells

Dr. Aurigemma also elaborated on additional challenges specific to the field of cell therapies. Clinical development of cell therapies is challenging because clinical protocols are costly and highly specialized. Complicated gene transfer and cell production protocols result in significant technological challenges, and the capability to manufacture the vectors and cells necessary for these protocols is limited.

Dr. Aurigemma also noted regulatory challenges. The U.S. Food and Drug Administration (FDA) is becoming more familiar with cell products for liquid cancers, but solid tumors are more challenging; the need to determine where cells are going with regard to the solid tumor itself, as well as the safety issues that come with adoptive cell transfer, have prevented the establishment of flexible and permissive FDA regulatory guidance for solid tumor cell therapies. In addition, because no suitable animal models are available for testing the safety and efficacy of these therapies in an immune environment comparable to that in humans, most of the experimentation and learning needs to happen in the patients themselves, which makes the FDA more rigid in its restrictions and requirements.

Dr. Aurigemma then discussed the recommendations from the 2018 workshop, including that NCI help members of the field manufacture the vectors and reagents they need for their cell therapies. Another recommendation encouraged the NCI to help develop and share standard operating procedures for manufacturing and analytics, which might help members of the field harmonize their work and facilitate the FDA's Investigational New Drug (IND) review process. She also mentioned a need to work with the FDA to harmonize product characteristic specifications; if the NCI could help the field adopt a set of common assays and quality parameters, this could help the FDA speed its review of IND submissions. Workshop attendees recommended that the NCI initiate specific funding for research addressing ideal

target characteristics, critical quality attributes of cell products, noninvasive imaging to assess cell trafficking, clinical trials with data sharing, and validation of useful animal models. Dr. Aurigemma also noted the scarcity of skilled staff capable of making the cells needed in these therapies, leading to a need for better recruitment, training, and retention of a technical workforce.

The second workshop on cell-based immunotherapy for solid tumors took place in December 2020. Many of the challenges discussed during this workshop were similar to those of the 2018 workshop. Similar concerns include solid tumor challenges, such as defining and overcoming the inhibitory tumor microenvironment, improving and measuring cell trafficking and tumor penetration, and improving tumor targeting while reducing off-tumor toxicity. The importance of understanding cell product critical quality attributes was mentioned again in 2020, with emphasis on predicting and controlling adoptive cell activity, persistence and function, and durable anti-tumor immunity. The cell engineering process remains cumbersome and expensive, requiring extensive expertise and Good Manufacturing Practice (GMP) reagents. Available animal models are still poorly representative of the human immune environment with a tumor, which hinders efforts to understand the mechanisms and toxicity of candidate treatments. In addition, noninvasive imaging processes are still needed to understand cell trafficking and to measure the persistence and efficacy of cells used in cell therapies; cells persist in patients for a long time, so it is important to ensure that these cells are still trafficking to the targeted tumor site.

Additional challenges included persistent logistics issues, such as a lack of specialized reagent and equipment availability. High-throughput cell sorters, in particular, are in high demand but expensive to acquire. Dr. Aurigemma also mentioned the persistent need for increased access to manufacturing of GMP vectors, reagents, and cells. Establishing faster and less-cumbersome manufacturing platforms would facilitate research. Researchers also want the ability to perform small proof-of-concept trials to learn how their cell therapies perform in patients. Finally, Dr. Ley remarked on the strong need for better target development for solid tumors.

Dr. Aurigemma then discussed the NCI's development support for cell therapies progress from 2018 to 2021. The NCI has renovated a new cell therapy suite and established the expertise and capability to support two multicenter autologous cell therapy clinical trials. The NCI also is renovating three new areas for manufacturing GMP products. The Institute has provided cell-therapy-related standard operating procedures to a public site and has awarded six grant supplements to Cancer Center and SPORE grantees to develop transformative technology and knowledge that can be applied to the broad adoption of cell therapy for liquid or solid human cancers. The NCI also has developed the capability to manufacture lentivirus and retrovirus products for cell transduction and is currently developing the capability to perform CRISPR/Cas-based editing.

Dr. Aurigemma presented remaining opportunities for the NCI to support research in the area of cell therapies for solid tumors. Such opportunities include funding transformative research on technology development and predictive animal model development. The NCI also could provide resources by facilitating access to NCI Experimental Therapeutics (NExT) support and establishing alternative paths through which investigators can access NCI resources. The NCI could provide critical reagents for manufacturing, cell sorting, and analytical assays; provide gene delivery reagents and technologies; and enable access to essential equipment via equipment purchasing grant supplements. The NCI also could support combinatorial trials and better support clinical trials by establishing a mechanism by which to translate knowledge into small clinical studies. Finally, the NCI could provide regulatory support by developing master protocols that would speed IND submission consultation processes.

Dr. Aurigemma presented recommendations that were classified as having high feasibility. These recommendations include recommendations that the NCI—

- Support standardization of assays and critical quality attributes of cell products
- Develop clinical trial templates for IND submission
- Improve NExT recruitment of high-quality proposals for projects related to cell-based immunotherapy of solid tumors and that include a bridge to small clinical studies
- Provide a testing service for vector and cell products
- Evaluate and make available valuable reagents

Recommendations that were classified as having challenging feasibility include recommendations that the NCI—

- Provide additional support for proof-of-concept clinical trials
- Support increased translational research on tumor targeting, immune cell fitness and persistence and overcoming immunosuppression
- Support the development of novel approaches to cell manufacturing
- Establish a core laboratory for characterizing manufactured products

Dr. Aurigemma presented potential RFA topics, such as identifying solid tumor targets to better destroy tumors while saving normal tissue; evaluating immune cell product fitness, trafficking, and persistence; determining the strategies that are most effective and refining products accordingly; and blocking the tumor immunosuppressive microenvironment in combination with adoptive cell transfer.

Finally, Dr. Aurigemma noted that the NCI could create or provide infrastructure that would offer standardized quality-controlled testing; assist with establishing clinical trials protocols; or serve as a community resource to measure the safety of vectors.

Consideration of Recommendations Re: Cellular Immunotherapies
Subcommittee

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

Dr. Francis Ali-Osman asked how the NCI is determining the potential services that it will provide for investigators. He questioned whether the services provided would be chosen on a case-by-case basis or whether services would be provided only if a critical mass of investigators requests that the same service be offered. Dr. Aurigemma responded that such decisions are still under consideration. She noted that the NCI is considering input from extramural researchers and stakeholders concerning the services and products that would have the most impact in moving the field forward. How investigators access provided resources and services is also still under consideration.

Dr. Ley asked why the NExT mechanism has been falling short in terms of attracting successful and high-quality ideas and research. Dr. Jim Doroshow responded that the NExT mechanism is, in fact, quite successful and attracts between 40 to 50 applications per year. Most of these applications, however, are for small-molecule projects. The central issue is that the new services and facilities that will support biologics projects have only just started and are not yet well known. Dr. Doroshow believes that the NExT mechanism will attract many more biologics projects as more investigators become aware of these new support structures.

Dr. Howard Fingert suggested that the NCI can learn from past partnerships with other groups.

Dr. Ann Barker commented that the Nanotechnology Program Alliance resulted in the Nanotechnology Characterization Laboratory, which made it and NCI the standard site at which materials were qualified. The standards set forth by this alliance were accepted by the FDA, and nanotechnology characterization is still largely performed by this group. Lessons learned from the Nanotechnology Program Alliance may be helpful in establishing similar standards and infrastructure supporting cell-based therapies. Dr. Doroshow concurred and added that much of the information presented by Dr. Aurigemma lends itself to a suite of services supporting cell-based therapies. Cell therapy research could be greatly facilitated if institutions could find this suite of services at a low cost at a standard site.

Dr. Barker noted that the FDA is challenged by the lack of standards or guidelines in the field. She also commented that a main issue in the field is customization. She recommended that cell-therapy investigators consider focusing on receptors that can reduce the degree of specificity required for each patient, and that the NCI consider focusing on these more broadly applicable receptors when developing grants.

Dr. Andrea Hayes-Jordan noted that developing cell therapies for solid tumors is a more complex process because solid tumors exist in very heterogeneous environments. She thus supported the idea of clinical trial templates for solid tumors to reduce the overall complexity of the process. She also emphasized the need to involve more researchers in the study of solid tumors. Dr. Hayes-Jordan asked whether any of the six P30 and P50 grants were specific for solid tumors and whether solicitations for solid tumor cell therapies can be enhanced. Dr. Aurigemma responded that the grant supplements were designed to be broadly applicable to technology involved in any cell therapies and are not tumor-type specific. Dr. Aurigemma agreed that soliciting more solid tumor–specific proposals could be a good idea.

Dr. Fingert noted that clinical trial decision-making is driven largely by partnerships with industry. With that in mind, he recommended that the NCI establish the means of harmonizing efforts with industry. He also mentioned that the FDA is doing regulatory work via a program called Initial Targeted Engagement for Regulatory Advice on Center for Biologics Evaluation and Research Products (INTERACT), which was made to facilitate the development and progression of biologics and cell therapies. He stated that the INTERACT pipeline is overwhelmed because it accepts non-oncology and COVID-19 projects, and he asked if the NCI could potentially serve as a second pipeline that takes on only oncology-based requests.

Dr. Norman Sharpless, Director, NCI, noted that the NCI has worked with the FDA on cell therapies and on establishing FDA guidance on this topic. He noted that some regulatory flexibility exists within the FDA but cautioned that more work is needed in this area. He also noted that few multicenter trials exist in academia and more are needed. Dr. Hayes-Jordan agreed that the field would be well served if the NCI could foster more support for multicenter trials in academia.

Other Items

Dr. Ley asked the Subcommittee members to thoroughly review the provided written report and consider the information presented today. He recommended that this effort be done slowly and methodically and that the Subcommittee meet again to refine and approve the recommendations to the NCI.

Dr. Scott Hiebert agreed with Dr. Ley's suggestion and noted that the Subcommittee should meet again before its next scheduled meeting in June. Dr. Sharpless agreed and urged the Subcommittee members to consider these recommendations very carefully. The Subcommittee members agreed to convening an additional meeting before June.

Dr. Ley mentioned that the Subcommittee could continue to communicate via email and thanked Dr. Aurigemma and her colleagues for their work and presentation.

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

Dr. Ley thanked participants for their contributions and adjourned the meeting at 11:57 a.m. EST.

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