Department of Health and Human Services
National Institutes of Health

National Center for Advancing Translational Sciences Advisory Council
and
Cures Acceleration Network Review Board

Minutes of Joint Meeting
September 19, 2019

The National Center for Advancing Translational Sciences (NCATS) Advisory Council and the Cures Acceleration Network (CAN) Review Board held a joint meeting in open session on September 19, 2019, convening at 10:06 a.m. EDT in Conference Room 620/630, Building 35, on the National Institutes of Health (NIH) main campus. Christopher P. Austin, M.D., NCATS Advisory Council chair, and G. Lynn Marks, M.D., CAN Review Board chair, led the meeting. In accordance with Public Law 92-463, the session was open to the public.

Prior to the joint meeting, the NCATS Advisory Council met in closed session from 8:30 a.m. to 9:30 a.m. for the review and consideration of grant applications.

NCATS ADVISORY COUNCIL MEMBERS PRESENT

Chair

Christopher P. Austin, M.D., Director, NCATS

Executive Secretary

Anna L. Ramsey-Ewing, Ph.D., Director, Office of Grants Management and Scientific Review, NCATS

Council Members

Ronald J. Bartek, M.A.
Daniel L. Hartman, M.D.
Richard E. Kuntz, M.D., M.Sc.
Brad Margus, M.B.A.
G. Lynn Marks, M.D.
Valerie Montgomery Rice, M.D. (by telephone)
Megan O'Boyle
Alan D. Palkowitz, Ph.D.

Representative Members

None present

***Ex Officio* Members**

Naomi Tomoyasu, Ph.D. (for Rachel Ramoni, D.M.D., Sc.D.), U.S. Department of Veterans Affairs (VA)
Frank F. Weichold, M.D., Ph.D. (for Norman E. Sharpless, M.D.), U.S. Food and Drug Administration (FDA)

CAN REVIEW BOARD MEMBERS PRESENT

Chair

G. Lynn Marks, M.D., Senior Advisor, Tunnell Government Services, Inc. and Chair, CAN Review Board

Vice Chair

Ronald J. Bartek, M.A., Co-Founder and Founding President, Friedreich's Ataxia Research Alliance (FARA)

Executive Secretary

Anna L. Ramsey-Ewing, Ph.D., Director, Office of Grants Management and Scientific Review, NCATS

Board Members

Daniel L. Hartman, M.D.
Richard E. Kuntz, M.D., M.Sc.
Brad Margus, M.B.A.
Valerie Montgomery Rice, M.D. (by telephone)
Megan O'Boyle
Alan D. Palkowitz, Ph.D.

Representative Members

Kiran Reddy, M.D., Praxis Precision Medicines, Inc. (by telephone)
Michael Rosenblatt, M.D., Flagship Pioneering
Elizabeth Stoner, M.D., MPM Capital

***Ex Officio* Members**

Richard Dickinson, Ph.D., National Science Foundation (NSF)
Naomi Tomoyasu, Ph.D., (for Rachel Ramoni, D.M.D., Sc.D.), VA
Frank F. Weichold, M.D., Ph.D. (for Norman E. Sharpless, M.D.), FDA

Others Present

Anne Berry, M.P.P., Association of American Medical Colleges
Catherine E. Krebs, Ph.D., Physicians Committee for Responsible Medicine
NCATS leadership and staff

I. CLOSED SESSION OF THE NCATS ADVISORY COUNCIL

This portion of the Advisory Council meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code, and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

Advisory Council members discussed procedures and policies regarding voting and the confidentiality of application materials, committee discussions, and recommendations. Members did not participate in the discussion of and voting on applications from their own institutions or other applications in which there was a potential conflict of interest, real or apparent.

II. ADJOURNMENT OF CLOSED SESSION OF THE NCATS ADVISORY COUNCIL MEETING

Christopher P. Austin, M.D., adjourned the closed session of the NCATS Advisory Council meeting at 9:30 a.m. EDT.

III. CALL TO ORDER, OPEN SESSION

Dr. Austin and G. Lynn Marks, M.D., called the meeting to order. Dr. Austin welcomed members and guests to the 22nd meeting of the NCATS Advisory Council and the 28th meeting of the CAN Review Board. He reminded attendees that the open session was being videocast. Dr. Marks extended a welcome on behalf of the CAN Review Board, and Dr. Austin introduced the members of the Council and the Board and previewed the meeting agenda.

IV. CONFIRMATION OF DATES FOR FUTURE MEETINGS: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council and CAN Review Board

Anna L. Ramsey-Ewing, Ph.D., confirmed the schedule for the meetings of the NCATS Advisory Council and CAN Review Board for 2019, 2020 and 2021:

- December 13, 2019 (virtual meeting; CAN Review Board only)
- January 16, 2020 (virtual meeting)
- May 14, 2020
- September 17, 2020
- December 11, 2020 (virtual meeting; CAN Review Board only)
- January 14, 2021
- May 20, 2021
- September 23, 2021
- December 10, 2021 (virtual meeting; CAN Review Board only)

V. APPROVAL OF MINUTES: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council and CAN Review Board

Members unanimously approved the minutes from the May 2019 joint meeting.

VI. INTRODUCTION OF NEW STAFF: Randall J. Redmond, Deputy Executive Officer, NCATS; Jessica Faupel-Badger, Ph.D., M.P.H., Director, Education Branch, Office of Policy, Communications and Education, NCATS; Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council and CAN Review Board

Randall J. Redmond introduced Zoe-Ann Copeland as Chief, Administrative Services Branch (ASB), who has served on detail to NCATS since 2017—first as Senior Advisor to the Executive Officer, and then as Acting Chief, ASB in the Office of Administrative Management. Ms. Copeland comes to NCATS from the National Institute of Biomedical Imaging and Bioengineering (NIBIB), where she was the Deputy Executive Officer.

Jessica Faupel-Badger, Ph.D., M.P.H., introduced Amanda Vogel, Ph.D., M.H.S., as new staff in the NCATS Education Branch, Office of Policy, Communications and Education. Dr. Vogel had been at the National Cancer Institute (NCI) for 10 years and had held positions in the Center for Global Health and the Behavior Research Program within the Division of Cancer Control and Population Sciences.

Dr. Ramsey-Ewing announced the appointment of Crina Frincu, Ph.D., as the inaugural NCATS Scientific Initiative Management Officer in the Office of Grants Management and Scientific Review. Dr. Frincu

comes to NCATS from the National Institute of Dental and Craniofacial Research (NIDCR), where she was a Scientific Review Officer.

VII. DIRECTOR'S REPORT: Christopher P. Austin, M.D., Director, NCATS, Chairperson, NCATS Advisory Council

Dr. Austin began by expressing his appreciation to Sharon F. Terry, M.A., President, Genetic Alliance, who recently completed her 4-year term as a member of the CAN Review Board.

Fiscal Year 2020 Budget and Legislative Updates

Dr. Austin provided an update on the current state of the NCATS budget for fiscal year (FY) 2020. The House Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies (L–HHS) approved its spending bill in June 2019, including a $2 billion increase over the FY 2019 enacted budget for the NIH and a $39 million increase for NCATS. The Senate Appropriations L–HHS Subcommittee released its spending bill on September 18, 2019, including a $3 billion increase for the NIH and a $43 million increase for NCATS. Dr. Austin remarked that these amounts are projected and are subject to change. Congressional leaders are considering a continuing resolution that would fund the government through November 21, 2019, if the budget is not approved before the fiscal year ends on September 30, 2019.

On September 25, 2019, the House Appropriations L–HHS Subcommittee will convene a hearing on "Investments in Medical Research at Five Institutes and Centers of the National Institutes of Health." Five directors of NIH Institutes and Centers (ICs) who do not routinely attend the Appropriations Subcommittees briefings—representing NCATS, NIBIB, the National Center for Complementary and Integrative Health (NCCIH), the National Institute on Minority Health and Health Disparities (NIMHD), and the National Library of Medicine (NLM)—will join Francis S. Collins, M.D., Ph.D., Director, NIH, at this hearing.

Events and Workshops

- **HHS Innovation Day.** Dr. Austin highlighted the success of NCATS during the HHS Innovation Day, held on June 12, 2019. The Ignite Accelerator IDEA Incubator Program granted four awards to NIH investigators, three of them to NCATS teams. The winning NCATS projects were: No Disease Left Behind: Empowering Patients to Take Action; Choose Happiness!; and Web-Based Knowledge Integration to Support Public Health Response Coordination.

- **Machine Intelligence in Healthcare Workshop.** NCATS co-hosted this event with NIBIB and NCI on July 12, 2019. Participants discussed strategies to overcome challenges in incorporating artificial intelligence technology within health care. NCATS is currently preparing a white paper summarizing the outcomes of this meeting, which is expected to be completed in early 2020.

- **The Role of the NIH in Drug Development Innovation and Its Impact on Patient Access: A Workshop.** In a talk at the event, held July 24–25, 2019, Dr. Austin conveyed the critical functions of the NIH within the larger context of drug development and marketing, which he described as a "multi-sector process."

Diversity and Representation in NIH Meeting Panels

Dr. Collins issued a statement on June 12, 2019, "Time to End the Manel Tradition," in which he pledged NIH's support for diversity in panels of invited speakers and disavowed continuing the "manel" (i.e., all-male speaking panel). Dr. Austin issued a similar statement in the July 2019 NCATS e-newsletter, affirming his commitment to supporting diverse and inclusive meetings and conferences.

Translational Science Education and Training Highlights

Dr. Austin presented a short video defining the role of translational scientists and the basic concepts and challenges of translational science. He credited Christine M. Cutillo, Office of Policy, Communications and Education, as the lead on the project.

NCATS staff members participated in an effort by Translation Together, a global translational collaborative group they co-founded with the European Advanced Translational Research Infrastructure in Medicine, to publish an article, titled "The Fundamental Characteristics of a Translational Scientist," in the May 2019 issue of *ACS Pharmacology & Translational Science*. The article defines the aims and attributes of a translational scientist with the intent of defining and advancing the field.

Division of Pre-Clinical Innovation (DPI)

Dr. Austin reported that NCATS investigators have been evaluating chemical probes for novel targets, expanding the scope of the 3D tissue models, and collaborating in drug discovery.

- **BNP-NPR1 itch signaling pathway.** A team of NCATS researchers, working in collaboration with the NIDCR and Lehigh University, identified a receptor, NPR1, that can be targeted for treatment of chronic itch. Their findings were published in the July 2019 issue of *Science Translational Medicine.*

- **3D tissue modeling.** In collaboration with the National Eye Institute (NEI), NCATS researchers worked to construct a 3D tissue model for atopic dermatitis, addressing the challenges inherent in 3D modeling, which include cell sourcing, tissue complexity and data management.

- **Drug discovery.** Dr. Austin noted that existing therapies for sickle cell disease and thalassemias remain inaccessible to many patients. NCATS researchers, in collaboration with Susan Perrine, M.D., Boston University School of Medicine, are working to repurpose the drug benserazide for treatment of several blood disorders.

Cures Acceleration Network (CAN) Projects

Dr. Austin highlighted two ongoing CAN projects, including the implementations and recent activities.

- **Tissue Chip Project.** NCATS initiated the Tissue Chip Project in 2012 and is playing a critical role in catalyzing this field. The partnerships are growing, and investments are extending beyond NCATS. In fact, the tissue chip technology—microphysiological systems (MPS) disease models—is being implemented in other NIH ICs, other HHS and non-HHS agencies, and other countries (e.g., Asia, Europe and Australia). Interest in the MPS disease models continues to increase.

- **Tissue Chips in Space.** The tissue chips from the May 2019 NASA space launch have been recovered successfully and are now being tested at the International Space Station (ISS) National

Laboratory for different biological markers. The next space flight is being planned for either 2020 or 2021, during which researchers will test the physiological effects of different chemical compounds on the chips.

Dr. Austin participated on a panel entitled "Future of Regenerative Medicine in Space" at the 2019 ISS Research and Development Conference. He reminded Council/CAN Review Board members that he serves as the NIH/HHS liaison to NASA. In that capacity, NCATS has co-hosted multiple meetings and workshops with NASA, the ISS National Laboratory, other NIH ICs, and other HHS OpDivs, which have resulted in several new space-related programs.

Clinical and Translational Science Award Program

Dr. Austin provided an overview of the Clinical and Translational Science Awards (CTSA) Program infrastructure and highlighted recent program awards from FY 2019: CTSA Program Hub Awards, Enhancing Network Capacity Awards and Collaborative Innovation Awards. He also noted the recent support for seven KL2 Career Development Program scholars by the NCCIH and NIBIB.

- **CTSA Program Feedback Campaign.** The CTSA Program is seeking input from stakeholder communities on program objectives, operations, outcomes and future Requests for Applications. NCATS has an issued a Request for Information; responses are due by October 25, 2019, and a town hall session will be held in January 2020.

The Helping to End Addiction Long-term℠ Initiative, or NIH HEAL Initiative℠

Dr. Austin outlined the role of NCATS in the NIH HEAL Initiative as encompassing three areas: Pre-Clinical Research in Pain, Clinical Research in Pain Management, and Expanding Therapeutic Options. He provided an update on NCATS activities that support the HEAL Initiative.

- **Pain Management Effectiveness Research Network (Pain-ERN).** The clinical trials will be conducted in the CTSA Program, and the NCATS Trial Innovation Network will provide data, clinical and biostatistical coordination, and support for study recruitment. Two additional trials have been incorporated into the Pain-ERN: the NICHD Maternal-Fetal Medicine Units Network and the NCI Community Oncology Research Program. Individual clinical trial awards are anticipated late September 2019, trial planning is expected in October 2019, and a Pain-ERN kick-off meeting is scheduled for November 2019.

- **Drug Development and Testing Platform.** One aspect of NCATS' pre-clinical research in pain to support HEAL focuses on developing new chemical structures to modulate novel targets. In its approach to efficiently identify novel targets for pain, NCATS is making use of a prize challenge—A Specialized Platform for Innovative Research Exploration (ASPIRE). The ASPIRE Design Challenges task researchers with proposing innovative and catalytic approaches to identified problems related to the opioid crisis. Winners for Phase 1 (Feasibility) will be announced on October 28, 2019. The Phase 2 (Reduction-to-Practice) Challenge are expected to commence in early FY 2020.

Discussion

Brad Margus, M.B.A., asked whether NCATS outlines long-term projections for drug development, as is common practice in commercial industry. Dr. Austin explained that the ability to take risks without any commercial concept from the beginning is central to the focus of much of the work within NCATS. He

added that his goal is to develop a platform with assets that are potentially useful to as many people as possible.

Frank F. Weichold, M.D., Ph.D., commended NCATS for its work. He noted that the FDA's collaboration with NCATS provides valuable opportunities to align resources and act synergistically. Dr. Austin responded that NCATS proudly takes a different approach from other NIH ICs; much like engineers, translational scientists begin with the end goal in mind and work backwards. Dr. Austin also spoke on the importance of CAN RB' representatives from outside the NIH.

VIII. CURES ACCELERATION NETWORK REVIEW BOARD UPDATE: G. Lynn Marks, M.D., Chairperson, CAN Review Board; Anne Pariser, M.D., Director, Office of Rare Diseases Research, NCATS; Ronald J. Bartek, M.A., Co-Founder and Founding President, FARA, Vice Chairperson, CAN Review Board; Bobbie Ann Mount, Ph.D., Program Officer, New Therapeutic Uses Program, NCATS

Dr. Marks introduced the topics for presentation: two CAN project proposals (gene therapy and drug repurposing) and a discussion concerning the establishment of a CAN Review Board Working Group. He provided an overview of the CAN project process and underscored the importance of investing time into understanding issues, listening to stakeholders and mapping out approaches.

CAN Project Proposal 1: Gene Therapy

Ronald J. Bartek, M.A., described the proposal's beginnings, referencing a 2-day NIH conference that identified several factors that appeared to confound investigators across the field of gene therapy. In response, the CAN Review Board has proposed six focus areas that encompass the most prevalent issues in gene therapy, including standardization, immune responses, manufacturing efficiency and clinical design. The goal of the proposed project is to apply translational science to providing platform solutions for investigators. Mr. Bartek reiterated that the involvement of NCATS serves to ensure that the developed technologies will be applicable across the field.

The team developed a series of workshops and conferences to further explore the common issues within gene therapy and to discuss potential solutions.

- NCATS hosted the "Workshop on Central Nervous System Immunogenicity Considerations for Adeno-Associated Virus (AAV)–Mediated Gene Therapy" on June 11, 2019. The event was well attended, and publication of the workshop proceedings is in progress.

- The National Academies of Sciences, Engineering, and Medicine will host "Exploring Novel Clinical Trial Designs for Gene-Based Therapies: A Workshop" on November 13, 2019. NCATS is providing input to the agenda planning committee and will give a presentation during the workshop.

- NCATS and the FDA will co-host the "Workshop on Expanding AAV Manufacturing Capacity for Rare Disease Gene Therapies" on January 28–29, 2020.

- An NCATS "Workshop on Systemic Immunogenicity Considerations" is scheduled for July 7–8, 2020.

CAN Project Proposal 2: Repurposing Generic Drugs

Bobbie Ann Mount, Ph.D., described the drug repurposing proposal. She noted that drug repurposing is particularly challenging because it encompasses many different issues that cannot be resolved by a single entity. Dr. Mount highlighted an upcoming meeting, "Repurposing Generic Drugs: Research and Regulatory Challenges," which be held on December 5–6, 2019. The meeting will focus on the roadblocks to using generic drugs, as well as drugs with a limited patent life and limited regulatory exclusivity, for unmet medical needs. Participants will work to identify strategies for addressing the obstacles.

Dr. Mount stated that partnerships with other government agencies, including the FDA, are critical. She noted that NCATS is interested in situations where not enough data exist yet for a generic drug to be used off-label; meanwhile, the FDA is interested in situations in which physicians prescribe drugs off-label. Dr. Mount also explained that no clear regulatory guidelines exist for drug repurposing. She identified data accessibility, clinical practices, funding, ownership and participation incentives as overarching issues that require further exploration.

Discussion

Elizabeth Stoner, M.D., asked how the team would define success. Dr. Mount replied that specific goals will be developed within a series of workshops, which likely will stem from topics raised in breakout sessions during the initial meeting. Dr. Mount explained that the first meeting is intended to serve primarily as an educational resource.

Dr. Austin added that a funding initiative would constitute a tangible success for the project. He also highlighted the fact that drug repurposing, like many other issues that NCATS faces, constitutes a multi-step process with many rate-limiting factors; researchers must choose which factor to approach first.

Dr. Weichold highlighted the need for a discussion on economic issues related to drug repurposing. Dr. Mount responded that multiple stakeholder organizations will likely form a collaboration and identify who can solve which problems. Dr. Marks agreed that this project will require teamwork across multiple groups.

Daniel L. Hartman, M.D., added that it would be interesting to hold a discussion on the economics of a repurposed drug, noting that much of the groundwork involving synthesis and characterization already has been completed. Dr. Hartman also raised the question of whether the repurposed drug needs to be registered, because 50 percent of drugs being prescribed are off-label. Dr. Weichold emphasized the importance of product labels for public impact, noting their implications for safety and effectiveness.

Leveraging CAN Authorities: A Proposal to Establish a CAN Review Board Working Group

Dr. Marks and Mr. Bartek participated via teleconference in a discussion with NCATS management, including Dr. Austin, Joni L. Rutter, Ph.D., and Dr. Ramsey-Ewing, about establishing a CAN Review Board Working Group to advance the Board's mission. The discussion focused on the evolution of the Board to support maturation of CAN programs and activities. Although NCATS and the CAN Review Board have been successful in driving new science and platforms to advance translational science via the CAN authorities, a key question remains: How can NCATS employ the CAN authorities better to hasten adoption of the cutting-edge science that it fosters?

NCATS is seeking recommendations from the CAN Review Board on how to better leverage the power of CAN and its authorities established under the 2011 Patient Protection and Affordable Care Act. Dr. Marks explained that four specific areas of inquiry include (1) review and assessment of the CAN authorities, (2) project prioritization and phase-out, (3) long-term sustainability and (4) stakeholder engagement.

Speaking from NCATS' perspective, Dr. Rutter called attention to the 2012 Institute of Medicine report "Accelerating the Development of New Drugs and Diagnostics: Maximizing the Impact of the Cures Acceleration Network" and discussed how subsequently, NCATS has done an incredible job developing CAN projects that are now maturing. She added that NCATS values the input of the CAN Review Board in considering stakeholder interest, both at the beginning of a project and during its development. Dr. Rutter emphasized that the Board's input will be important for both new and ongoing projects, and Dr. Marks noted the critical need to consider real-world applications while developing projects.

Discussion

Alan D. Palkowitz, Ph.D., noted that having a discussion of this topic is timely, and he emphasized that new technologies bring a need for broader implementation and education.

Dr. Hartman posed the question of what strategies can be used to increase the adoption of innovative technologies. Naomi Tomoyasu, Ph.D., replied that the VA also has been asking these questions. She added that VA investigators are required to work with policymakers, and an implementation plan is now a required component of VA trial proposals.

Dr. Marks looks forward to partnering with Dr. Rutter and stated that he will bring this proposal to the CAN Review Board meeting in December. Dr. Austin expressed appreciation to the Board for taking on this challenge.

Action Item: Dr. Marks will bring the proposal of establishing a CAN Review Board Working Group to the December 13, 2019, CAN Review Board virtual meeting.

IX. OFFICE OF RARE DISEASES RESEARCH UPDATE*:* Anne Pariser, M.D., Director, Office of Rare Diseases Research, NCATS

Anne Pariser, M.D., described the mission of the Office of Rare Diseases Research (ORDR), emphasizing that its goal is to improve the research environment for all rare diseases. She explained that the ORDR facilitates coordination between multiple stakeholders in the rare diseases community through its three branches: Knowledge/Data, Research/Collaboration and Community Engagement. Dr. Pariser explained that while a rare disease is defined as a condition affecting fewer than 200,000 persons in the United States, the distribution of diseases is highly skewed toward low-prevalence conditions (i.e., affecting 350–3,500 people, or even fewer). Researchers traditionally consider diseases individually, but Dr. Pariser explained that the large number of rare diseases necessitates a more efficient approach, which ORDR is addressing actively.

Rare Diseases Clinical Research Network

Dr. Pariser pointed out that the majority of the ORDR's budget is allocated to the Rare Diseases Clinical Research Network (RDCRN), which was established in 2002 under the Rare Disease Act. The RDCRN serves two purposes: to facilitate research through the establishment or continuation of clinical research consortia and to help physicians, scientists and multidisciplinary teams work together with

patient advocacy groups. The first RDCRN consortia were established in 2003 and approximately 140 patient advocacy groups are associated with the ORDR's 21 consortia. Many of the RDCRN consortia are located at a CTSA Hub institutions and this platform is enabling cutting-edge clinical trials. Nine NIH ICs co-fund and manage the RDCRN.

Through its three award cycles (RDCRN 1–3), the RDCRN has served more than 56,000 patients, published nearly 2,000 journal articles and supported more than 300 trainees. The fourth award cycle (RDCRN4) will emphasize the collaborative nature of the network, as well as readiness for clinical trials. Dr. Pariser stated that additional focus is placed on data sharing and standards, noting that the ORDR Data Management Coordinating Center (DMCC) was recently migrated to the NCATS-hosted cloud computing services.

Genetics and Rare Diseases (GARD) Information Center Programs

Launched in 2003 following a congressional mandate, the GARD Information Center initially began as a call-in/write-in center. Now maintained as a searchable website since 2008, GARD's key feature is its accessibility; information on diseases is written in plain language and designed for the public. The website currently hosts content describing approximately 6,500 diseases and is visited by 15.3 million users per year. New to GARD in 2017 were the Toolkit for Patient-Focused Therapy Development that serves as a resource for patient groups and research programs and the Rare Diseases Registry Program (RaDaR), which provides information for building patient registries and has received positive user feedback. The RaDaR website was relaunched in FY 2019. A future vision for GARD—Deep Zebra—involves the use of informatics solutions to improve accuracy while keeping up with new content. The goals of Deep Zebra include enhancements to customer service, data accuracy/interoperability and data access/reach.

NCATS Platform Vector Gene Therapy

The NCATS Platform Vector Gene Therapy (PaVe-GT) Project is a CAN project that represents a collaboration among the ORDR, the NCATS Therapeutic Development Branch, the NCATS Office of Strategic Alliances, the National Human Genome Research Institute and the National Institute of Neurological Disorders and Stroke. PaVe-GT provides a platform to support testing of multiple gene therapies and diseases at once. Because many diseases can be treated with gene therapy, PaVe-GT operates within the hypothesis that addressing abnormalities within the same cell types may serve as a more efficient way to treat diseases. The pilot project involves development of a treatment plan for four diseases; while the target gene differs, the protocols and viral vectors are the same between the diseases. An umbrella trial is conducted in which participants are assigned a specific arm of therapy, based on the specific molecular makeup of the underlying disease. In addition, the AAV Manufacturing Efficiency Initiative is currently in development and aims to increase efficiency of production of clinical-grade AAV by 10- to 100-fold.

Dr. Pariser highlighted other grant programs, engagement and new activities.

- **The Clinical Trial Readiness grants (R21 and R03)** provide funding to address critical needs in trial readiness, including biomarker identification, outcome measures and trial design. Applications are due October 24, 2019.

- **Rare Disease Day at NIH (RDD)**, an annual event at the NIH, has attracted increased interest from community members in recent years. The event is designed to increase awareness about rare diseases, the people they effect and research performed at the NIH.

- **The Burden of Rare Disease Project** was launched recently to provide objective data (e.g., burden) on the health care system and patients and to focus on issues of misdiagnosis and system utilization.

Dr. Pariser requested input from the Council and Board on ORDR's programmatic priorities, critical areas that might have not been addressed, and concerns within the field that require more (or less) attention than currently is provided.

Discussion

Michael Rosenblatt, M.D., noted that the definition of "disease" is unclear and asked how the ORDR is addressing this question within their project designs. Dr. Pariser agreed that the definition is not ironclad but represents an evolving area of discussion. She emphasized that the ORDR typically sorts diseases according to their genetic underpinning.

Megan O'Boyle observed that the umbrella approach is logical but acknowledged that funding opportunities for that type of research often are limited. She stated that collaborations will be critical to program success and offered the idea of a global unique identifier system—the absence of which means that individuals often are counted multiple times across databases, leading to skewed results. Additionally, Ms. O'Boyle pointed out that rare diseases often are underdiagnosed because of limited access to genetic testing, which is particularly pronounced within minority communities. She suggested that the field would benefit from the participation of other NIH ICs through mandated collaborative efforts.

Dr. Weichold echoed Ms. O'Boyle's suggestion that unique global patient identifiers are critical to decision-making for health and wellness, and he asked the ORDR to continue prioritizing data liberation. He noted that although these problems are particularly pronounced for rare diseases, the issues are present across the scientific community. He also raised the issue of drug pricing.

Mr. Margus suggested that the ORDR act as a catalyst for the FDA, noting that some regulatory processes can be impractical for smaller diseases. He stated that trial designs are prohibitively expensive and suggested pooling studies as one possible solution. Dr. Pariser replied that the FDA Center for Biologics Evaluation and Research (CBER) has been supportive of this concept. The ORDR and CBER are communicating on how to be engaged and help address these issues.

Observing that research can be broken down into three steps—identification, diagnosis and treatment—Dr. Hartman asked how the ORDR budget is allocated, given that many rare disease patients are seldom provided a diagnosis in the current system. Dr. Pariser discussed efforts to leverage existing databases and identify undiagnosed individuals who are likely to have a particular disease. This approach will require developing multiple machine-based algorithms and will bring together new technologies, such as facial recognition and augmented reality, to identify possible patients. Richard E. Kuntz, M.D., M.Sc., suggested working with Google Health for search patterns.

Mr. Bartek proposed the idea of whole-genome sequencing as part of the newborn screening paradigm to assist researchers in identifying more patients. Michael G. Kurilla, M.D., Ph.D., described how prenatal testing is changing in North Carolina; parents are given the option to undergo additional screening. He explained that the goal is to see how many people opt in over time so that when testing for a disease becomes available, a database of possible patients exists.

Dr. Rosenblatt expressed concerns about patient privacy, citing instances where personal identifying data may be compromised. Ms. O'Boyle clarified that patients provide their information voluntarily and that the information used is designed to match to the patient's unique identifier without revealing his or her identity to other parties.

Dr. Austin posed a theoretical question of how an extra $5 million should be allocated within the ORDR. Ms. O'Boyle proposed applying the additional funds to increase genetic testing; Mr. Bartek suggested making improvements to patient identification and diagnosis.

Dr. Rosenblatt suggested considering the issue of therapeutic development in translational and practical terms. He proposed that ORDR focus on a few diseases for FDA approval, rather than collecting a massive dataset without clear plans for treatment, which would be strategic for increasing funding.

X. CLEARANCE OF CONCEPTS

The Council and Board received presentations on two new projects that NCATS is considering for funding. At the end of each presentation, the members discussed the proposal and voted on whether to approve NCATS' moving forward with the initiative.

Rare Diseases Are Not Rare! Challenge 2.0: Alice Chen Grady, M.D., Program Officer, ORDR, NCATS

Alice Chen Grady, M.D., explained that the first NCATS rare diseases prize competition, Challenge 1.0, sought creative ways to raise awareness about rare diseases and the need for expanded research, new treatments and patient support. The competition opened in 2018, and nearly 50 submissions were received. Participation was widespread and generated innovative works of art that educated the public about rare diseases. Details on the three winning submissions and honorable mentions can be found on the NCATS website: https://ncats.nih.gov/funding/open/rare-diseases-challenge/winners.

The overarching goals of Challenge 2.0 are to change the public perception of "rare" and foster collaborations across the rare disease community. Metrics for success will be defined in advance and could possibly inform ORDR public-facing programs. Children can directly submit entries with the appropriate consent. In addition to increasing public awareness about rare diseases, the many people affected, and common challenges encountered, NCATS could use the Challenge 2.0 submissions to strongly convey the message about the ongoing need for rare diseases research and new treatments. This concept builds on the success of the NCATS 2018 prize competition and aligns with some ongoing rare diseases activities, such as the patient organization-sponsored competitions and the emphasis of the NCATS RDCRN to study multiple diseases at a time and include patient groups as partners in research.

Discussion

Mr. Bartek congratulated NCATS on the program and lauded ORDR for the resources that were developed as outcomes to Challenge 1.0. He encouraged developing an added robust dissemination plan for the next phase that extends beyond advertising on the NCATS website and using existing platforms, such as RDD, to launch the Challenge. He proposed that submissions, assessments and evaluations be moved to later in the fiscal year, providing more time for participants to develop their submissions. Mr. Bartek also suggested working on a dissemination plan that would engage a broader audience, including various communications networks (e.g., television).

Ms. O'Boyle recommended promoting the message (nationally) that one in 10 people has a rare disease. After learning that the total cost of the Challenge 1.0—$5,000—includes the first- and second-place prize awards, she commented on the minimal costs to achieve this level of public outreach about rare diseases. Ms. O'Boyle also suggested providing examples in which research and development of a drug for a rare disease has led to treatment for a common disease.

Dr. Rosenblatt articulated two goals of such a rare disease Challenge: caucusing the community and increasing awareness on the national level. Soliciting the best product (i.e., messaging), rather than constraining submissions to originate only in the community setting, could help with dissemination, locally and nationally. Another dissemination approach would be to contact large U.S. advertising agencies about *pro bono* messaging campaigns. Dr. Grady explained that constraints on the minimum age requirement have been removed for this next phase and noted that the Challenge 1.0 submissions were not limited to any specific groups or scientific disciplines—the majority of interest came from the lay community.

Although increasing awareness about rare diseases has been effective in the public and private sectors, Mr. Margus wondered whether these efforts—including the Rare Diseases Are Not Rare Challenges—were prompting constituents to contact legislators about increasing set-asides in funding for rare disease research or causing an influx of researchers to study these diseases and conduct new clinical trials. Dr. Grady noted the plans to extend the rare disease Challenges beyond increasing awareness to addressing solutions.

Dr. Austin explained that the ORDR's initial efforts on increasing awareness emanated from discussions with policymakers, internal and external to the NIH, who are not fully aware of the position of rare diseases in the context of a public health crisis; NCATS will need to consider a proactive plan in making this case.

Dr. Weichold pointed out the opportunity to link rare diseases to educational aspects (e.g., lessons learned or personalized medicine), which could lead to increased funding.

Action Item: Dr. Austin and the ORDR will consider developing a proactive plan to broadly address rare diseases, including an analysis of health care costs and evaluations on loss of productivity to patients and their families.

Members unanimously approved the Rare Diseases Are Not Rare 2.0 concept.

Microphysiological Systems (MPS) Database Center: Danilo A. Tagle, Ph.D., M.S., Associate Director for Special Initiatives, Office of the Director, NCATS

Danilo A. Tagle, Ph.D., presented the concept re-issue to continue the Microphysiological Systems (MPS) Database Center (DC) currently hosted and managed by the University of Pittsburgh Drug Discovery Institute. Dr. Tagle noted that establishing the MPS Database Center was first approved on September 7, 2017, by the Council and Board as database support for the Tissue Chip Program. The MPS Database—which is the central archive for aggregate pre-clinical, clinical and experimental MPS data generated in the Tissue Chips Testing Centers (TCTCs)—also is being used by developers and other stakeholders, including the pharmaceutical industry. To date, the database contains 58 MPS (i.e., tissue chips) experimental models covering 11 organ systems, which were developed at 14 TCTCs. Data from 171 studies are being housed, including images and videos deposited by eight data developers. Dr. Tagle emphasized that all data submitted to the MPS DC will be made publicly available to the research community.

Since November 2018, the MPS database usage has steadily increased: 109 users are currently registered and, on average, 86 new users view or download data each month. The MPS database has the potential to transition to a self-sustaining business model after the 2-year funding cycle. Dr. Tagle summarized the ongoing research activities in this area and noted that the MPS Database Center is a collaborative partnership between NCATS, the FDA and the MPS affiliate of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ).

Discussion

Dr. Palkowitz recommended continuing this project, which will become a major data repository for validation sets, foster communication with the broader community, and serve as a key point of stakeholder engagement. He asked whether information other than datasets, such as use cases to inform and transform the drug discovery process, could be captured in the MPS database, especially as this technology converts to being more common and is integrated into research programs. Adoption and uptake or engagement by the pharmaceutical industry, which is a diverse community, can be an indication of future utilization. Dr. Tagle explained that each model system is specific and can serve as its own use case. The end users actively are accessing the database and are interested in the available disease models, promising compounds and assays. The interaction with the pharmaceutical companies have been productive, and discussions are ongoing with MPS IQ about incorporating their datasets into what is amounting to a clearinghouse.

Action Item: Dr. Tagle (Special Initiatives) will consider using the MPS database as a basis to facilitate implementation of the MPS technology.

Dr. Marks expressed his long-time support for the MPS concept, which is leading the field to a new predictive model in recapitulating human diseases and away from only using animal models, which can be unreliable. He asked about plans for continued data inputs, dissemination and sustainability, particularly with the collaborative partnerships. Although the interest of the pharmaceutical industry is significant, Dr. Tagle pointed out that legal issues need to be addressed regarding data sharing; NCATS is facilitating these discussions, which will take time. In addition, data inputs from the TCTCs, tissue chip developers and the FDA are anticipated. The next 2 years of NCATS investments are necessary to support these activities and allow time to formulate a sustainability plan.

In response to questions by Dr. Weichold on intersection with other databases, such as the FDA Global Substance Registry System (G-SRS), as well as fees for service and open access, Dr. Tagle noted that MPS Database-G-SRS interactions are already in progress, open data from the FDA are being incorporated, and access is tiered—data is held privately for 1 year. Responders to the concept funding opportunity announcement will be asked to provide input on open access and ways to sustain it.

Dr. Rosenblatt asked whether correlative data (e.g., *in vivo* animal data with tissue chip data) were being collected to address safety and toxicity. Dr. Tagle replied that the private sector has funded activities focused on correlative datasets in animal models, but the major emphasis of the MPS database and NCATS funding is on human cells and tissues. Tissue chip experiments have confirmed drug toxicity in humans.

Members unanimously approved the Microphysiological Systems Database Center concept re-issuance.

XI. MAKING CLINICAL RESEARCH INFORMATICS COLLABORATIVE: Ken Gersing, M.D., Director of Informatics, Division of Clinical Innovation, NCATS

Ken Gersing, M.D., presented the first in a series of discussions to the Advisory Council and CAN Review Board about the NCATS Division of Clinical Innovation (DCI) informatics activities and initiatives. Focusing on machine learning and artificial intelligence, he emphasized that translational science depends on the interoperability of data and elaborated on the data life cycle—collecting, sharing and using data—and the associated informatics tools and resources.

Unlike other HHS agencies, including the Office of the National Coordinator (ONC) for Health Information Technology and the FDA, the NIH has not had well-established clinical research data standards for data collection. On July 30, 2019, the NIH endorsed the use of Fast Healthcare Interoperability Resources (FHIR®), a standard owned and maintained by Health Level 7 International, recommending that research information should use a standard. DCI Informatics and CTSA National Center for Data to Health (CD2H) are partnering with the Centers for Disease Control and Prevention, FDA, NCI, NLM and ONC on the HHS FHIR Harmonization Project. A prototype is expected to be released by the end of the 2019 calendar year.

Dr. Gersing explained that the Findable, Accessible, Interoperable, Reusable (FAIR) data principles govern data sharing across the NIH and align with practice in other federal agencies. NCATS funding supports the CD2H Data Management and Sharing Plan in all areas of FAIR but does not include investigator attribution. He emphasized that data sharing using FAIR increases data use, visibility and accessibility of research and ultimately credits investigators for their work.

Data usage in the NCATS cloud is active within the CTSA Program and will likely be mandated in the future. The cloud encourages collaboration and democratization and is secure. Dr. Gersing described two informatics tools currently being used in the cloud.

- **Software as a Service (SaaS).** SaaS via the cloud provides a central location for software—such as the Centers for Medicare & Medicaid Services (CMS) Strategic Partners Acquisition Readiness Contract (commonly called SPARC)—to be shared across CTSA hubs. The SaaS model allows comparisons across CTSAs, reduces cost, improves security and promotes collaboration.

- **NCATS Sandboxes.** The Sandboxes are collaborative algorithm-development projects engaging scientists to work together on disease topics they routinely address separately. Three areas of focus are machine learning for mortality prediction, natural language processing, and data quality. Algorithms developed within a Sandbox are competed in the CTSAs, and those that score best are deposited in the CTSA applications store to be shared across the CTSA community, at no cost.

In closing, Dr. Gersing highlighted the CD2H projects and data interoperability initiatives and solicited feedback from the Council and Board on the electronic health record (EHR) FHIR project, the CTSA cloud initiative, and ways to accelerate the CD2H process.

Discussion

Dr. Weichold expressed his support for this project, which is critical to addressing one of the key issues affecting the data ecosystem (i.e., interoperability), and suggested leveraging FDA clinical data sources. Dr. Gersing clarified that the FHIR harmonization project focuses on the line-level data rather than aggregate data.

Dr. Kuntz asked about plans for mapping the Epic Systems Corporation (Epic) EHR fields to FIHR. Dr. Gersing noted that ONC and CMS are mandating that EHR vendors, including Epic, transfer data using the FIHR Bulk Data Extraction feature, which is a special initiative for public health information. DCI Informatics is working with ONC to implement a similar feature (Bulk FHIR) in the HHS FHIR harmonization project; the first data set, U.S. Core, has been completed.

In response to a question from Dr. Stoner on expanding beyond the CTSAs, Dr. Gersing explained that the role of the CD2H is to establish data use agreements among the CTSA hubs, which is a difficult task. The DCI is considering an arrangement similar to the SMART IRB Reliance Agreement (the Streamlined, Multisite, Accelerated Resources for Trials IRB Reliance platform) that would be applicable to the broader community. The main objective is to function as a transport mechanism mimicking a federated analytic model.

Mr. Bartek asked to what extent technologies such as FIHR could be used for supporting other programs, such as the RDCRN data. Dr. Gersing pointed out that CTSA informatics tools and resources are shared and can be used across NCATS. Data from registries and repositories can be accessed by FIHR, but other factors such as cost will need to be considered. Mr. Bartek also noted the need to include clinical laboratory data in a standardized, accessible and interoperable manner that encompasses the audit trail (i.e., chain of processing to storage).

XII. OPEN DISCUSSION

Dr. Austin opened up the discussion to other topics of interest and invited the Council and Board to comment on other content NCATS could present at these meetings.

Ms. O'Boyle asked whether the Undiagnosed Diseases Network (UDN) is within the NCATS sphere of activities. Dr. Austin noted that the UDN is a Common Fund program, but NCATS is represented. Discussions are ongoing pertaining to UDN's continuation past its current funding structure, which is a substantial NIH investment that NCATS would not be in a position to sustain.

Dr. Marks wondered about the impact of the decisions being made regarding NCATS funding and the results and suggested a dialog on the process. Dr. Austin noted that he generally reports on funding decisions, which usually are about the physical trail of the dollars, at the January meetings of the Council and Board. The impact and result of those decisions are observed years later. Dr. Austin will consider ways to present this information that would be more useful to the ongoing and new Council and Board members.

Action Item: Dr. Austin will consider a discussion at the January 2020 Council and Board meeting about NCATS' funding decision-making process, the responses and the outcomes.

Dr. Kurilla commented on the timeframe between the CD2H concept approval and the results from that investment, some of which were presented at today's meeting. Dr. Ramsey-Ewing explained that the interval between concept approval and NCATS' issuing a FOA reflects the time it takes to mature the concept, which is in its early stages, and consider the best funding mechanisms. The date a concept is approved is provided to the *en bloc* panels, but the roster of Council and Board members often changes prior to any results' being reported. Dr. Austin added that presentations on initiatives by NCATS Offices and Divisions can reflect the concept's start date and other activities leading up to the results.

Action Item: NCATS staff will include concept history in presentations reporting on initiatives or product development.

Dr. Palkowitz commented that providing added information on the interactions with other groups, internal and external, and the application of tools and technologies across the various NCATS programs would be helpful.

Dr. Tomoyasu asked about the possibility of NCATS' developing rapid funding mechanisms that would be applicable to the VA intramural research structure. Dr. Austin referred to noteworthy examples of various NCATS short-term funding structures, including the 6-month funded CAN projects, the milestone-driven projects (e.g., Tissue Chip Program), and non-Hub CTSA awards. Generally, the turnaround time for results is short, and a project failure discontinues that research program. Dr. Kurilla added that some CTSAs partner with the VA on research projects.

Mr. Margus remarked on how the CTSA Program still is not fully understood and commented that a tutorial might be helpful. He also suggested a Council brainstorming session on the obstacles to drug development and reporting back at a future meeting. Dr. Austin supported this idea and will also consider ways that NCATS could present data in an understandable way.

Action Item: Dr. Austin will consider how best NCATS could present all data in an understandable way to the Council and Board.

XIII. ADJOURNMENT OF THE OPEN MEETING

Dr. Austin thanked all participants for their input. Drs. Austin and Marks adjourned the open portion of the meeting at 4:27 p.m. EDT.

CERTIFICATIONS

We hereby certify that, to the best of our knowledge, the foregoing minutes and supplements are accurate and complete.

Christopher P. Austin, M.D.
Chair, NCATS Advisory Council;
and
Director, National Center for Advancing Translational Sciences, NIH

Date

Anna L. Ramsey-Ewing, Ph.D.
Executive Secretary, NCATS Advisory Council;
Executive Secretary, Cures Acceleration Network Review Board;
and
Director, Office of Grants Management and Scientific Review, NCATS

Date

G. Lynn Marks, M.D.
Chair, Cures Acceleration Network Review Board;
and
Senior Advisor, Tunnell Government Services

Date