Department of Health and Human Services
National Institutes of Health
National Center for Advancing Translational Sciences

29th Meeting of the
Cures Acceleration Network Review Board

Minutes of Virtual Meeting
December 13, 2019

The National Center for Advancing Translational Sciences (NCATS) Cures Acceleration Network (CAN) Review Board convened a virtual meeting, in open session, at 11 a.m. EST on December 13, 2019. 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.

Following the meeting, the CAN Review Board met to plan and discuss the activities and logistics for establishing an *ad hoc* CAN Review Board Working Group.

CAN REVIEW BOARD MEMBERS PRESENT

Chair

G. Lynn Marks, M.D., Senior Advisor, Tunnell Government Services, Inc.

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, National Institutes of Health (NIH)

Board Members

Theodore Holman, Ph.D.
Richard E. Kuntz, M.D., M.Sc.
Geoffrey Shiu Fei Ling, M.D., Ph.D.
Brad A. Margus, M.B.A.
Kalpana M. Merchant, Ph.D.
Valerie Montgomery Rice, M.D.
Megan O'Boyle
Alan D. Palkowitz, Ph.D.
Todd B. Sherer, Ph.D.

Representative Members

Michael Rosenblatt, M.D., Flagship Pioneering
Elizabeth Stoner, M.D., MPM Capital

Ex Officio Members

Christopher P. Austin, M.D., Director, NCATS
Rachel Ramoni, D.M.D., Sc.D., Chief Research and Development Officer, Office of Research and Development, U.S. Department of Veterans Affairs (VA Research)
Frank F. Weichold, M.D., Ph.D. (for Brett P. Giroir, M.D.), U.S. Food and Drug Administration (FDA)

OTHERS PRESENT

NCATS leadership and staff

I. CALL TO ORDER AND OPENING REMARKS: G. Lynn Marks, M.D., Senior Advisor, Tunnell Government Services, Inc. Chair, CAN Review Board; Ronald J. Bartek, M.A., Co-founder and Founding President, FARA, Vice Chair, CAN Review Board

G. Lynn Marks, M.D., and Ronald J. Bartek, M.A., called the meeting to order and extended a welcome to the 29th meeting to CAN Review Board members and others participating by telephone or WebEx. Dr. Marks reviewed the agenda.

II. MEETING RULES AND CONFIRMATION OF DATES FOR FUTURE NCATS ADVISORY COUNCIL AND CAN REVIEW BOARD MEETINGS: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, CAN Review Board

Anna L. Ramsey-Ewing, Ph.D., reviewed the procedures for the meeting. In the discussion sessions following the presentations, only CAN Review Board members would be able to participate verbally, and they would have to dial in to participate by phone. Dr. Ramsey-Ewing noted that other participants could submit questions or comments using the Q&A box in WebEx or by sending an email.

Dr. Ramsey-Ewing confirmed the schedule of NCATS Advisory Council and CAN Review Board meetings in 2020 and 2021:

- 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)

III. DIRECTOR'S REPORT: Christopher P. Austin, M.D., Director, NCATS

Christopher P. Austin, M.D., began by welcoming new Advisory Council and CAN Review Board member Theodore R. Holman, Ph.D. He expressed appreciation to Valarie Montgomery Rice, M.D., President and Dean, Professor of Obstetrics and Gynecology and Reproductive Endocrinology and Infertility, Morehouse University, who recently completed her 4-year term as a member of the Advisory Council and CAN Review Board. Dr. Austin then gave a brief update on the fiscal year (FY) 2020 budget, ongoing programs and other NCATS activities.

FY 2020 Budget and Congressional Briefings and Visits

Dr. Austin reminded the CAN Review Board members that NCATS was operating under a continuing resolution (CR) that funded the government through December 20, 2019, at FY 2019 levels; this was the second CR of 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; the Senate Appropriations L–HHS Subcommittee released its spending bill on September 18, 2019 but had not voted. Both bills showed budget increases for NCATS above the FY 2019 enacted budget, but these were projected amounts and were subject to change. Congress announced a preliminary, high-level budget agreement on December 12, 2019. Appropriators will be working to draft a 12-bill omnibus; a smaller number of appropriation bills grouped in a minibus also have been considered.

Dr. Austin joined Francis S. Collins, M.D., Ph.D., Director, NIH, and four other NIH Institute and Center (IC) directors in testifying at the September 25, 2019, House Appropriations L–HHS Subcommittee hearing on "Investments in Medical Research at Five Institutes and Centers of the National Institutes of Health." Dr. Austin had the opportunity to discuss the CAN-supported projects and ways that NCATS and its mission complement industry efforts.

One week prior to the hearing, House Appropriations L–HHS Subcommittee Chair and long-time supporter of the NIH and NCATS, Rep. Rosa DeLauro of Connecticut, visited the NIH and spoke with NCATS and other ICs' trainees about their experiences.

Rare Diseases Clinical Research Network (RDCRN) Program Update

Dr. Austin reported that the RDCRN, which was established by Congress in 2002, began a fourth 5-year cycle of funding (i.e., RDCRN4) to support existing and new consortia; NCATS and nine other ICs co-fund the program. The criteria for the consortia are that they must focus on three or more diseases addressing a common biological or medical characteristic and must have two or more studies (one observational) ongoing. Each consortium is composed of multiple sites in the U.S. and internationally, as well as one or more patient advocacy groups. Twenty consortia, including approximately 400 sites, comprise RDCRN4.

New features of RDCRN4 are the single institutional review board, external advisory committee and a strong emphasis on data sharing. In addition, a Data Management and Coordinating Center (DMCC) is being hosted by the NCATS cloud computing services, and an NIH program team composed of representatives from across the 10 IC partners will be developing standard operating procedures and other common templates. Five new areas of emphasis were added to the RDCRN: congenital infections, leukodystrophies, myasthenia gravis, disorders of glycosylation and phenylketonuria.

Events and Workshops

Dr. Austin described NCATS activities supporting rural health, including participation in the November 21, 2019, National Rural Health Day—an annual event hosted by the Federal Office of Rural Health Policy.

- **Inaugural NIH Rural Health Seminar.** NCATS and the Clinical and Translational Science Awards (CTSA) Program, in collaboration with the National Institute of Mental Health and National Institute on Minority Health and Health Disparities, co-sponsored a rural health seminar on November 18, 2019. Ten other ICs contributed. Participants (in-person and via webcast) discussed ways that clinical and translational innovations could improve rural health outcomes.

Dr. Michael G. Kurilla, Director, Division of Clinical Innovation (DCI), NCATS, was an invited speaker. Dr. Austin expressed appreciation to Dr. Xinzhi Zhang, Program Director, Division of Clinical Innovation (DCI) and CTSA Program Officer, for leading this effort.

- **National Rural Health Day Photo Contest.** On November 21, 2019, NCATS hosted a rural health day photo contest in which the CTSA Hubs showcased their clinical and translational efforts supporting underserved populations in rural communities. The winners—first (Oregon Health & Science University), second (Indiana University) and third (University of Arkansas for Medical Sciences) place—were announced.

- **NCATS CTSA Rural Health Website.** Dr. Austin conveyed NCATS' commitment to improving the disproportionate effect of health issues in rural America. NCATS has organized the CTSA Program's rural health efforts on a new rural health website that other researchers and the public can access: ncats.nih.gov/ctsa/projects/RuralHealth.

The Helping to End Addiction Long-term℠ Initiative, or NIH HEAL Initiative℠, Pain Management Effectiveness Research Network (Pain-ERN or ERN) Update

Dr. Austin reminded participants of the overarching goals of the NIH HEAL Initiative Pain-ERN: to prevent and manage pain and reduce the risk of addiction by comparing the effectiveness of existing therapies with novel approaches to delivering those therapies; strengthen and inform current acute and chronic pain guidelines; provide patients and practitioners a suite of effective strategies to alleviate pain and reduce reliance on opioids; and improve quality of life for affected patients and their families.

The Pain-ERN is being run through the NCATS Trial Innovation Network (TIN), which is providing data, clinical and biostatistical coordination in support of four clinical trials and also is supporting study recruitment. The clinical trials are being conducted primarily at CTSA Program hubs. Two additional trials will be conducted in existing clinical trial networks—the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network (MFMU) and the National Cancer Institute's Community Oncology Research Program (NCORP). The TIN and ERN study teams began weekly meetings in October 2019 to finalize protocols, establish data safety monitoring boards, and address institutional review board needs. The TIN meets with the NCORP and MFMU investigator teams monthly. The first trans-ERN meeting was held on November 15, 2019, to discuss scientific aims and goals of the studies as they relate to the NIH HEAL Initiative and to strategize about ways to collaborate across trials.

Discussion

Dr. Marks asked how the NCATS CAN projects (e.g., the Tissue Chip for Drug Screening program) and other NCATS programs would fit in with the rural health efforts. Dr. Austin explained that the common theme in rural health is low population density, and communities face issues involving social determinants of health and access to health care. The CTSA Program's rural health innovations, such as telehealth and machine learning, could help clinicians working in these isolated areas, and leveraging the CTSA long-standing community engagement programs can help with implementation and dissemination.

Ronald J. Bartek, M.A., asked about details of the report language regarding the House and Senate proposed appropriations/budgets for the CAN (up to $80 million and $60 million, respectively), as indicated on the presentation slide. The use of the term "up to" is unclear. Dr. Austin noted that NCATS

had requested increased flexibility in deciding the percentage of the total budget that would support CAN and non-CAN projects. Instead of a percentage, the appropriators appear to have indicated "up to" values, but Dr. Austin has not received any information about the report language.

IV. STATUS OF CAN REVIEW BOARD PROJECTS: G. Lynn Marks, M.D., Senior Advisor, Tunnell Government Services, Inc.Chair, CAN Review Board; Ronald J. Bartek, M.A., Co-founder and Founding President, FARA, Vice Chair, CAN Review Board; P.J. Brooks, Ph.D., Program Director, Office of Rare Diseases Research (ORDR), NCATS; Bobbie Ann Mount, Ph.D., Program Officer, New Therapeutic Uses Program, NCATS

Dr. Marks introduced the two topics for presentation: CAN project updates on gene therapy and drug repurposing.

CAN Project Proposal 1: Gene Therapy

Mr. Bartek summarized the CAN Review Board's six gene therapy issues (rare diseases related) that were identified in the August 20–21, 2018, jointly sponsored NCATS/FDA workshop on gene therapy for rare diseases. The crosscutting theme is immunogenicity and the related factors for addressing it, such as standardized predictive measures, assays for potency, scientific tools to inform clinical design, manufacturing and gene therapy programs.

A series of workshops was launched to address these issues and provide an opportunity for NCATS and the CAN Review Board members to participate as speakers. Four such workshops were convened in 2019, and two will be hosted in 2020.

- NCATS and FDA will co-host the "Workshop on Expanding Adeno-Associated Virus (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.

Mr. Bartek remarked on an anticipated outcome of the January 2020 workshop on expanding AAV manufacturing: developing actionable gene therapy projects that address and offer solutions to the six issues that the CAN Review Board identified as shaping advanced technologies in gene therapy for rare diseases.

P.J. Brooks, Ph.D., pointed out that many of the workshops have been organized in collaboration with other groups that have a shared interest in gene therapy for rare diseases. The ORDR is staying up to date on the existing initiatives so that efforts are not duplicated. Regarding the January 2020 meeting, Dr. Brooks encouraged CAN Review Board members and their colleagues who are working in the area of AAV manufacturing, particularly on nontraditional approaches, to submit an abstract. From these submissions, two speakers will be invited to present their ideas to representatives from industry, academia, NIH and the FDA.

CAN Project Proposal 2: Repurposing Generic Drugs

Bobbie Ann Mount, Ph.D., focused her presentation on recapping the CAN Review Board workshop "Repurposing Off-Patent Drugs: Research and Regulatory Challenges," which was held December 5–6, 2019, and was co-sponsored by the FDA, NCATS and the Reagan-Udall Foundation for the FDA. Dr.

Austin opened the workshop by stating the goals and outcome. The workshop focused on the challenges in trying to find a new use for an existing drug with limited patent life and limited regulatory exclusivity. On the first day, participants surveyed the landscape of those challenges, and the speakers were tasked to identify solutions. Building on that framework, participants spent the second day in breakout groups focused on prioritizing the problems, identifying solutions, setting a research agenda, and addressing any associated problems. Dr. Mount emphasized that the research agenda is not an NCATS agenda alone and that it requires a team approach and health care ecosystem.

Dr. Mount continued that a patient advocacy group representative gave the call to action in highlighting the challenges individuals face when no treatment options are available for a disease and clinicians' access to drug safety data is limited. Potential solutions were given addressing the areas of incentives, data access, real-world evidence (in addition to clinical trial data) and data accessibility. She summarized subsequent discussions on data as levels of evidence needed for preclinical work, translation to the clinic, and the clinical experience spectrum. All stakeholders' (e.g., patients, providers and/or drug owners) perspectives were captured. Representatives from the regulatory (FDA), economics (Faster Cures) and payor (Aetna, Centers for Medicare & Medicaid Services [CMS]) sectors discussed the overarching challenges.

NCATS and FDA co-developed a solution, the CURE ID computer application (app), which Dr. Mount invited Noel Southall, Ph.D., Acting Director, Division of Pre-Clinical Innovation (DPI) Informatics, to describe. Dr. Southall explained that DPI Informatics has been collaborating with FDA's Office of Medical Policy Initiatives to develop a local internet-based entity for clinicians to share their off-label experiences, which often are not known to the clinical community. FDA wanted to highlight this problem and provide a potential solution for the community, resulting in the launch of the CURE ID app, which has been well received. CURE ID can be accessed from the NCATS website (cure.ncats.io) or downloaded as the mobile app.

In closing, Dr. Mount remarked on the success of the workshop and noted that the meeting proceedings are archived in an NIH videocast. The next steps include generating a written report and synthesis of the meeting's second day and presenting during a future Advisory Council and CAN Review Board meeting a list of priorities identified in the breakout sessions to assist the research/clinical communities in finding solutions to rapidly treat patients. In addition, NCATS is recruiting task force volunteers, establishing goals and working groups and is developing public engagement and communications action plans that the task force will use.

Discussion

Geoffrey Shiu Fei Ling, M.D., Ph.D., asked whether CMS had been engaged in the gene therapy for rare diseases discussions and whether CMS is participating in the January 2020 workshop. Mr. Bartek confirmed that invitations had been extended to CMS to attend. Even though CMS is not in the AAV manufacturing field, Dr. Austin wondered if CMS representatives should be invited as speakers at the January 2020 workshop; ORDR staff will follow up on this possibility.

Dr. Marks commented on an effective and successful meeting on drug repurposing. He shared that the main message, from his perspective, is determining the least amount of data necessary for changing treatment guidelines and providing essential information to healthcare professionals to impact new therapies for patients.

Mr. Bartek noted a strong emphasis in discussions he attended at the meeting was that the current model does not incentivize drug development for nonpatent drugs.

Rachel Ramoni, D.M.D., Sc.D., commented on discussions in the meeting about a model that, in her perspective, is innovative. The FDA and/or the VA would package the clinical data not the drug manufacturers. Dr. Ramoni also called attention a strong interest in drug repurposing at the National Institute of Aging regarding the lack of treatment for Alzheimer's and dementia-related diseases.

ACTION ITEM: Dr. Brooks will ensure that ORDR considers inviting CMS representatives to speak about their perspectives on the proposed CAN gene therapy project at the January 2020 "Workshop on Expanding AAV Manufacturing Capacity for Rare Disease Gene Therapies."

V. CAN PROGRAM UPDATES: P.J. Brooks, Ph.D., Program Director, ORDR, NCATS; Christine M. Colvis, Ph.D., Director, Drug Development Partnership Programs, NCATS; Danilo A. Tagle, Ph.D., M.S., Associate Director for Special Initiatives, Office of the Director, NCATS

Platform Vector Gene Therapy (PaVe-GT) Project

Dr. Brooks explained that the PaVe-GT project addresses a critical need—designing efficient and affordable gene therapy clinical trials to investigate multiple diseases at once using AAV vectors, rather than the current approach of investigating one disease at a time. The pilot project is a public platform vector gene therapy trial that will be conducted at the NIH Clinical Center. The pilot will evaluate four genetic diseases using the same AAV vector serotype, route of administration, and production and purification method across studies. The therapeutic gene constructs will be disease-specific. All trial data will be publicly available, including FDA communications.

The PaVe-GT concept was approved by the CAN Review Board on December 15, 2017, as a collaborative mechanism and intramural demonstration project that would leverage the expertise of the intramural investigators and the NIH Clinical Center. Dr. Brooks detailed the project status. Two collaborating investigators have been identified, one at the National Institute of Neurological Disorders and Stroke (NINDS) and the other at the National Human Genome Research Institute (NHGRI). The plan is to investigate four target diseases of low-penetrance disorders with no commercial interest using the AAV-9 vector. Preclinical studies are in progress. The Initial Targeted Engagement for Regulatory Advice on CBER (Center for Biologics Evaluation and Research) Products (commonly called INTERACT) meeting with FDA is planned for early 2020. Contracting services for good manufacturing practice AAV vector production remains a challenge because of supply and demand issues.

Biomedical Data Translator (Translator)

Christine M. Colvis, Ph.D., provided an update on the NCATS Translator, a tool that enables computational assisted exploration of existing knowledge by integrating information from multiple data sources and mining that data to construct new research hypotheses. Currently more than 100 data sources have been incorporated. Scientists using the data translator are motivated by the spectrum of research questions that can be asked and solved, from a simple (e.g., what?) to a complex (e.g., why?) query. The Translator 3-year feasibility assessment in the research community is concluding. Investigators (e.g., computer scientists, informaticists and data scientists) were encouraged to take risks in the prototype development phase and were told that failure is an option and that the lessons learned would reveal the boundaries and inform the next iteration.

Dr. Colvis described examples demonstrating the transformative potential of Translator for assessing undiagnosed or rare diseases. In one case study, a Translator investigator shared that a patient weighing 78 pounds at age 19 had from age 4 experienced multiple vomiting episodes daily, and there were no effective treatments. Using these data, Translator, in seconds, searched all 29.1 million PubMed abstracts and found an obscure case report treatment option, as well as evidence for a molecular mechanism based on chemotherapeutic research in rats. The outcome was a successful treatment for nausea (isopropyl alcohol), allowing the patient to resume a normal life. Translator was next used as a research tool to determine the nausea treatment's mechanism of action, thereby connecting the knowledge.

To explain to the broader research community the use and capabilities of Translator, investigators developed Tidbits (ncats.nih.gov/tidbit/tidbit_01.html), use cases that tell a compelling story and demonstrate the unique power of the tool. Dr. Colvis pointed out that less than 2 years from when the initial awards for the reasoning tool were issued in January 2018, the Translator program has made significant progress and investigators have developed shared standards. Public opinion likens Translator to a Google for biomedical research, with additional capabilities to make a connection within the various information sources.

The Translator program products—including the knowledge graph standards, application programming interfaces and the source code—have been added to the public domain GitHub repository. In December 2018, the CAN Review Board approved establishing an NCATS Biomedical Data Translator Consortium, and the funding opportunity announcement was released on September 27, 2019. Applications are being reviewed, and awards will be announced in January 2020.

A Specialized Platform for Innovative Research Exploration (ASPIRE)

Danilo A. Tagle, Ph.D., M.S., provided an overview and update of the ASPIRE program. He reminded the CAN Review Board members that the ASPIRE initiative was first proposed in September 2017 to address key translational challenges: (1) the uninterrogated vast chemical space (10^{63}) of potential pharmacologically active molecules, (2) the undrugged biological space (5×10^5), and (3) an outdated reaction toolkit for accessing the relevant chemical space. To address these issues, NCATS convened the "Workshop on Automated Chemical Synthesis" on October 19–20, 2017, to identify the associated research opportunities, challenges and roadblocks. Participants identified technical (e.g., lack of big data and standards) and cultural challenges, including lack of collaborations and data sharing. Subsequently, NCATS officially launched ASPIRE; however, at the time, CAN funds were limited. In 2018, a pilot ASPIRE program was funded by the NIH HEAL Initiative through prize competitions.

To prepare for a successful prize competition, NCATS defines the problem, sets the appropriate prize amount, follows the SMART (Specific, Measurable, Achievable, Realistic, and Timetable) principles, and encourages team building and networks. Dr. Tagle described the three steps of prize competitions for ASPIRE—ideation, design and reduction-to-practice—and detailed the recent ASPIRE Design Challenges. Stage 1—Design Challenges for Translational Innovation in Pain, Opioid Use Disorder, and Overdose—is funded by the NIH HEAL Initiative. Five challenges comprise Stage 1: Challenge 1, Integrated Chemistry Database; Challenge 2, Electronic Synthetic Chemistry Portal; Challenge 3, Predictive Algorithms; Challenge 4, Biological Systems; and Challenge 5, Integrated Solution, in which applicants can propose integrating two or more of the four Challenge solutions.

The Stage 1 ASPIRE NIH HEAL Initiative Challenge was run through challenge.gov and offered a total prize of $2.5 million. The initial review identified 29 submissions that met the design criteria. These submissions subsequently were scored in a two-stage selection process based on innovation and challenge-specific and programmatic feasibility. The 17 winners were announced at the October 28, 2019, award ceremony, which also doubled as a teambuilding/networking event. Dr. Tagle acknowledged the winning design teams and noted that the next step, Stage 2, Reduction-to-Practice, has not been decided.

Tissue Chips for Drug Screening Program

Dr. Tagle highlighted that Tissue Chips (or Microphysiological Systems [MPS]) for Drug Screening was the first CAN-funded program for NCATS. The goals are (1) to develop an *in vitro* platform that uses human cells and tissues and (2) to combine with advances in stem cell biology, microfluidics and bioengineering to evaluate the efficacy, safety and toxicity of promising therapies. The platform will contain all 10 human physiological systems and is intended to be modular and reconfigurable. The program meets the CAN Review Board metrics for success for high-risk projects; collaborators include NIH, FDA, the Defense Advanced Research Projects Agency (DARPA), pharmaceutical companies and other stakeholders.

Tissue Chips 1.0 to Predict Drug Safety, which ran from FY 2012 to FY 2017, was a partnership among NCATS, DARPA and FDA; had 19 projects; and resulted in 506 publications and review articles. The current Tissue Chips Consortium has grown in partnerships and scientific scope since 2017, and NCATS is central to the operations and plays a leadership role. New features include the addition of Tissue Chips Testing Centers (TCTCs), the MPS Data Center, and disease modeling and efficacy testing. Startup companies are provided resources, as well as the Tissue Chips in Space program. More than 2,000 companies are in the process of commercializing their products, many of which are spinoff companies from the Consortium academic institutions. Dr. Tagle elaborated on how the TCTCs and MPS Database Center are building confidence in MPS in the research community.

The NIH Tissue Chips 2.0 for Disease Modeling and Efficacy Testing will run from FY 2018 to FY 2022; is a collaboration of 10 ICs, including NCATS; and funds 13 awards. The initial 2-year awards (Phase 1) support developing *in vitro* disease models using primary tissue or induced pluripotent stem cells derived from patient cells on a tissue/organ-on-chips platform, determining the disease relevancy of the models, and testing candidate drug effectiveness. In years 3 to 5 (Phase 2), investigators will use the models for efficacy and safety testing of therapeutic compounds. In another disease modeling activity and use of tissue chip technology, NCATS is partnering with NASA and the International Space Station (ISS) National Laboratory and Center for the Advancement of Science in Space (CASIS) on studies modeling aging-related conditions in microgravity to provide insights that could improve health on Earth.

Dr. Tagle noted that CAN funding has been limited and has never fully funded Tissue Chips during the 7 years of the program. In FY 2012, NCATS invested $9.8 million, and the NIH Common Fund and other ICs collectively invested $5.2 million. Given the growing partnerships and investments beyond NCATS, Dr. Tagle suggested that the CAN Review Board in a future meeting consider discussing an exit strategy for NCATS. To summarize FY 2019 funding, Tissue Chips investments totaled $40 million, of which NCATS invested $16.5 million, other ICs $18.8 million, the NIH HEAL Initiative $6.9 million, and NASA $1.2 million. The ISS National Laboratory and CASIS provide in-kind support of $8 million per launch.

ACTION ITEM: At a future meeting, the CAN Review Board is encouraged to consider discussing an exit strategy for NCATS to reduce its investments in the Tissue Chips for Drug Screening program.

Discussion

In response to questions on the anticipated clinical trial platform for the PaVe-GT in terms of determining the first therapeutic dose and whether the platform provides the opportunity to enroll participants with prior AAV-9 exposure for trials, Dr. Brooks replied that the first dose as therapeutic is a goal, but noted that the clinician would be the one making those decisions. The cutoff for preexisting exposure to AAV-9 is to be determined and addressing the immune response will be uniform across diseases. Anne Pariser, Ph.D., added that the field is moving toward taking aim for an efficacious dose from the beginning of the study.

Alan D. Palkowitz, Ph.D., asked how the ASPIRE Design Challenges would be linked to derive a solution to the problem. Dr. Tagle explained that the team-building exercise at the award ceremony was the initial step to encourage communication between the multidisciplinary teams and also build partnerships and collaborations. Stage 2 of the Challenge will solicit submissions on solutions for the four areas; demonstrating feasibility and developing a prototype will be key for competitors.

Dr. Ramoni asked how the VA could participate in the Tissue Chips for Drug Screening program, leveraging its ongoing studies. She explained that VA Research is transitioning from using animal models and called attention to a large-scale military toxic exposures research effort. Both appear to be opportunities for the Tissue Chips program. Dr. Tagle replied that VA representatives were invited to participate in the Consortium meetings, but at the time had conflicting schedules. He explained that the invitation to partner with the Consortium remains open. He noted that the U.S. Environmental Protection Agency (EPA) also is moving away from animal models and is hosting the "Alternative Test Methods and Strategies to Reduce Vertebrate Animal Testing" meeting on December 17, 2019, which might be applicable to VA Research. Dr. Ramoni invited Dr. Tagle to the VA Office of Research and Development to present on Tissue Chips.

ACTION ITEM: Dr. Tagle will plan a visit to the VA and meet with Dr. Ramoni to discuss collaborating on the Tissue Chips for Drug Screening program.

In response to a question on success in the private sector in terms of owning their own tissue/organ chips, Dr. Tagle replied that the goal is to have the TCTC resources widely accessible to the broader scientific community.

VI. CLEARANCE OF CONCEPTS

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

Microphysiological Systems Scientific Conference: International Standardization and Harmonization of Microphysiological Systems: Danilo A. Tagle, Ph.D., M.S., Associate Director for Special Initiatives, Office of the Director, NCATS

Dr. Tagle presented a concept for sponsoring an MPS scientific conference to promote international standardization and harmonization of MPS. Several recent activities warrant development of an international standard. In fact, the MPS technology has expanded internationally, and progress has been

significant in developing MPS for a number of human organs and organ systems. Tissue chips and other 3-D models are converging in application.

The goals are to lay the groundwork for an orderly transition of MPS strategic, organizational and funding aspects to other stakeholders; convene annual scientific conferences; use these forums as the main conduit of information, technology and data sharing; and establish a training environment for the next generation of MPS scientists.

NCATS anticipates that the outcome—an international scientific conference devoted to MPS—will be self-sustaining through registration fees and sponsorship after a brief period of CAN support. One major effect will be an increased awareness in the research community about the potential use of tissue chips in drug development as an approach that more accurately reflects the human response when compared to existing *in vitro* and *in vivo* animal models.

Discussion

Dr. Palkowitz expressed his strong support for the concept and commented on the timeliness and impact of building a multidisciplinary community of users, particularly with the successful examples of MPS currently being showcased.

Mr. Bartek asked about the state of MPS internationally. Dr. Tagle said that the activities in Europe are primarily centered in Germany, the Netherlands, Switzerland, and the United Kingdom and are beginning to equal those of the United States. NCATS staff visited the Japan Agency for Medical Research and Development (AMED), which has since launched a program similar to NCATS and has funded seven projects. NCATS also had discussions with China, which is interested in establishing a tissue chips space program. In addition, NCATS is planning trips to South Korea.

Members unanimously approved the Microphysiological Systems Scientific Conference concept.

VII. ESTABLISHING A CAN REVIEW BOARD WORKING GROUP: G. Lynn Marks, M.D., Senior Advisor, Tunnell Government Services, Inc., Chair, CAN Review Board; Ronald J. Bartek, M.A., Co-founder and Founding President, FARA, Vice Chair, CAN Review Board

Dr. Marks presented the charge for the proposed CAN Review Board Working Group. NCATS is seeking recommendations from the CAN Review Board regarding how to better leverage the power of CAN and its authorities established under the 2011 Patient Protection and Affordable Care Act. Four specific areas of activities include (1) review and assess the CAN authorities, (2) provide input on project prioritization and phase-out, (3) identify long-term sustainability strategies, and (4) identify factors to enhance stakeholder engagement. Dr. Marks explained that the Working Group has the option to establish subgroups to assist in the activities if needed. After deliberations, the Working Group will provide its recommendations to the CAN Review Board, which then will vote. The approved recommendations will be forwarded to the NCATS Director, who may either accept or decline, with explanations and a response provided to the CAN Review Board.

The Working Group membership will include representatives with expertise comparable to the CAN Review Board and may include *ad hoc* members. The Designated Federal Officer will be the CAN Review Board Executive Secretary. Regarding the process, deliverables and timeframe, the Working Group will meet in-person or via videoconference, plans to record all sessions, will make the membership roster

public, and prepare a final report for submission to the CAN Review Board. Meetings are expected to begin in late January 2020 and conclude in the late fall of 2020.

Mr. Bartek remarked on the opportunity for the Working Group to deliberate and make recommendations to the NCATS Director regarding advancing mature projects to real-world use so as to rapidly provide treatments for patients.

Discussion

Dr. Ramsey-Ewing clarified that the CAN Review Board Working Group will not offer advice to NCATS on maximizing the use of existing authorities and explore authorities of NCATS' counterparts. Recommendations will be provided to the CAN Review Board.

Joni L. Rutter, Ph.D., emphasized focusing on strategies to advance NCATS projects and their associated discoveries to a broader application, which does not happen automatically as the project matures.

VIII. WRAP UP: G. Lynn Marks, M.D., Senior Advisor, Tunnell Government Services, IncChair, CAN Review Board; Ronald J. Bartek, M.A., Co-founder and Founding President, FARA, Vice Chair, CAN Review Board; and NCATS Leadership

Dr. Marks asked the members for feedback on whether the Director's reports and program updates for these meetings were providing the necessary information the Board needs to hear for making decisions and providing advice to NCATS.

IX. ADJOURNMENT OF THE CAN REVIEW BOARD MEETING

Dr. Marks and Mr. Bartek thanked the participants and presenters for their time and engagement, and they acknowledged the work of the NCATS staff in organizing the meeting. They adjourned the meeting at 2:28 p.m. EST.

X. CAN REVIEW BOARD Working Group Planning Meeting

This portion of the CAN Review Board 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).

CAN Review Board members discussed activities for establishing an *ad hoc* CAN Review Board Working Group.

XI. CERTIFICATION

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

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

Date

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

Date