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 May 16, 2019, convening at 8:47 a.m. ET in Conference Room 620/630, Building 35A, 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.

Following the joint meeting, the NCATS Advisory Council met in closed session 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. (by telephone)  
Richard E. Kuntz, M.D., M.Sc. (by telephone)  
Geoffrey Shiu Fei Ling, M.D., Ph.D.  
Brad Margus, M.B.A. (by telephone)  
G. Lynn Marks, M.D.  
Megan O’Boyle  
Alan D. Palkowitz, Ph.D.

**Representative Members**

None

**Ex Officio Members**

Rachel Ramoni, D.M.D., Sc.D., U.S. Department of Veterans Affairs (VA)  
Frank F. Weichold, M.D., Ph.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., Office of the Director, Biomedical Advanced Research and Development Authority (BARDA), Office of the Assistant Secretary for Preparedness and Response (ASPR), U.S. Department of Health and Human Services (HHS); 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. (by telephone) Brad Margus, M.B.A. (by telephone)
Richard E. Kuntz, M.D., M.Sc. (by telephone) Megan O’Boyle
Geoffrey Shiu Fei Ling, M.D., Ph.D. Alan D. Palkowitz, Ph.D.

Representative Members
Kiran Reddy, M.D., Praxis Precision Medicines, Inc.
Michael Rosenblatt, M.D., Flagship Pioneering
Elizabeth Stoner, M.D., MPM Capital

Ex Officio Members
Richard Dickinson, Ph.D., National Science Foundation (NSF)
Rachel Ramoni, D.M.D., Sc.D.
Frank F. Weichold, M.D., Ph.D.

GUEST EXPERTS PRESENT
Theodore (Ted) R. Holman, Ph.D., University of California, Santa Cruz
Andrew W. Lo, Ph.D., Massachusetts Institute of Technology

OTHERS PRESENT
Rachel Levinson, M.A., Arizona State University
Brigid Brennan, J.D., FARA
NCATS leadership and staff

I. CALL TO ORDER, OPEN SESSION
Christopher P. Austin, M.D., and G. Lynn Marks, M.D., called the meeting to order. Dr. Austin welcomed members and guests to the 21st meeting of the NCATS Advisory Council and the 27th 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.

II. 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:

- September 19, 2019
- 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)

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

Members unanimously approved the January 2019 meeting minutes.

IV. INTRODUCTION OF NEW STAFF: Penny Burgoon, Ph.D., Director, Office of Policy, Communications and Education, NCATS; Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council and CAN Review Board

Penny Burgoon, Ph.D., introduced Jessica Faupel-Badger, Ph.D., M.P.H., as the new Education Branch Director. Dr. Faupel-Badger previously was director of training and education in the NCATS Division of Pre-clinical Innovation (DPI) and had directed the Postdoctoral Research Associate program at the National Institute of General Medical Sciences (NIGMS).

Also new to NCATS is Emily Carlson Marti, M.A., Communications Branch Director. Prior to joining NCATS, Dr. Marti was communication lead for the NIH All of Us Research Program (All of Us) and was deputy director and acting director for the NIGMS Office of Communications.

Dr. Burgoon next introduced Meredith Temple-O’Connor, Ph.D., M.S., who is the Science Policy Branch Director. Dr. Temple-O’Connor came to NCATS from her position as senior policy advisor for clinical research at the Eunice Kennedy Shriver National Institute of Child Health and Human Development. She also serves as the NIH Inclusion Policy Officer in the NIH Office of Extramural Research.

Dr. Ramsey-Ewing announced that Alberta Boah, M.A., will be a Grants Management Specialist in the Office of Grants Management and Scientific Review (OGMSR). Ms. Boah came to NCATS from the National Institute of Mental Health (NIMH), has extensive experience in grants management, and is trained in international affairs. She announced a second OGMSR Grants Management Specialist, Sarisa Kowl, who also came to NCATS from the NIMH and has experience in the various grant mechanisms.

V. DIRECTOR’S REPORT: Christopher P. Austin, M.D., Director, NCATS

Dr. Austin began by introducing three new representative members of the CAN Review Board—Kiran Reddy, M.D., M.B.A.; Michael Rosenblatt, M.D.; and Elizabeth Stoner, M.D.—and a new ex officio member, Richard Dickinson, Ph.D. He expressed appreciation to outgoing Advisory Council/CAN members Stephen Spielberg, M.D., and Katherine Ku, J.D., for their service.

Dr. Austin welcomed Joni Rutter, Ph.D., as the new NCATS Deputy Director. Dr. Rutter thanked Dr. Austin for his welcome and noted that her career at the NIH spans 20 years and encompasses both basic and clinical human genetics research and molecular epidemiology in cancer and drug abuse and addiction, lending to both intramural (National Cancer Institute [NCI]) and extramural (National Institute on Drug Abuse [NIDA]) perspectives. The key to advancing science is applying the policy and leadership necessary to build productive collaborations. As prior scientific program director for All of Us, Dr. Rutter thinks that NCATS, in its mission, is the ideal platform to build the translational capacity for All of Us and provide the needed connections to bring the research into practice. She emphasized the importance of
the NCATS Office of Rare Diseases Research (ORDR) in making progress in all areas of translational research and in addressing issues and barriers for these patients, including a member of her immediate family.

**Fiscal Year (FY) 2020 Budget Process**

Dr. Austin reported that the President’s proposed budget was released on March 18, 2019, and begins the NIH/NCATS FY 2020 budget process. The Congressional Appropriations, House and Senate, Subcommittees considered the proposed budget and conducted budget hearings in April 2019. The House Labor, Health and Human Services, Education, and Related Agencies (L-HHS) Appropriations Subcommittee spending bill was approved on April 30, 2019, and was subsequently approved by the full Appropriations Committee on May 8, 2019. The House FY 2020 appropriations include a $2 billion increase to the NIH and a $39.4 million increase to NCATS, a 4.9 percent increase above the FY 2019 enacted budget. The Senate L-HHS Appropriations Subcommittee spending bill is expected in early June 2019.

**Clinical and Translational Science Award (CTSA) Program Highlights**

Approximately 70 percent of the NCATS budget supports the Division of Clinical Innovation (DCI), which includes the CTSA Program. Dr. Austin announced that Barry Coller, M.D., Rockefeller University, is a new CTSA Program Steering Committee (SC) co-chair. In this phase of the CTSA, Drs. Coller and Austin will co-lead efforts to increase, promote, and engage in bidirectional communications across the CTSA Program consortium and NCATS; evolve the CTSA Program Domain Task Forces to the Enterprise Committees; and strongly support the SC Taskforce’s Sustaining the Translational Science Workforce (commonly called STARWORK) in its activities.

The CTSA program has put additional emphasis on developing translational science solutions to the problem of rural health disparities. The opioid crisis, which disproportionately affects these populations, has further increased this effort. CTSA investigators are engaged in a number of demonstration projects in rural U.S. states, including:

- **Indiana CTSA Community Health Coalition Development Program**: Expands health coalitions with non-traditional health care workers across Indiana. A rural health intervention was developed within the Indiana University’s Clinical Translational Sciences Institute–Moi University, Kenya, Africa partnership and has been implemented in Indianapolis, Indiana.

- **University of Arkansas for Medical Science CTSA Community Scientist Academy**: Trains community leaders in research methodology. Methodology and has resulted in the placement of research advocates in rural communities and the establishment of partnerships between researchers and community leaders.

- **Washington, Wyoming, Alaska, Montana, and Idaho (WWAMI) Network, University of Washington CTSA**: A clinical teaching network composed of an academic hub with six health professional schools and one medical school in the WWAMI region. The Community Outreach and Research Translations core leverages the WWAMI Network to develop community-practice based translational research networks. In addition, NCATS is beginning to work more closely with the NIH Institutional Development Award (IDeA) program on its rural health agenda.

- **Project Extension for Community Healthcare Outcomes (commonly called ECHO)** based at the **University of Mexico CTSA**: Distributes real-time virtual clinical and other telehealth methods for community-based providers and teams with specialists at university medical centers to assist primary care clinicians in rural and underserved communities.
Rare Diseases Registry Program (RaDaR) Reboot

NCATS envisioned a framework in which patient groups could deposit their registry data with controlled vocabularies and standards, thus promoting interoperability across registries. RaDaR (formerly the Global Rare Diseases Registry) is a web-based registry developed for and by patients to share tools and suggestions on a living (i.e., interactive) website platform. Its initial launch in 2017 focused on the patient’s contact and demographic data. Engaging patients as members of the research team is critical and encourages both groups to interact effectively. RaDaR allows patients to provide input on new drug development.

Division of Pre-Clinical Innovation (DPI)

Dr. Austin remarked on the advances in the DPI Therapeutic Development Branch, which consists of the Therapeutics for Rare and Neglected Diseases (TRND) and Bridging Development Gaps (BrIDGs) programs. Five investigational new drug (IND) applications have been submitted to the FDA in the last five months, two from the TRND program and three from the BrIDGs program. Of the five INDs submitted, four have cleared and one is pending principal investigator responses to the FDA’s questions. A sixth IND just recently was given the approval to move to the next phase. Dr. Austin remarked that six INDs in 5 months is phenomenal success by all accounts and credited the NCATS multidisciplinary team approach for this remarkable achievement.

NCATS Programs and Initiatives

- **Biomedical Data Translator (Translator):** The idea to develop the Translator progressed rapidly following initial discussions with the CAN Review Board in September 2016. A funding opportunity announcement (FOA) to develop a problem-solving/reasoning tool was issued in November 2017, and the inaugural open meeting and hackathon was held. In a Translator proof-of-principle study, a patient experiencing disabling symptoms of refractory cyclic vomiting was able to resume a normal life after the Translator data search found an obscure case report on a treatment for nausea.

- **Helping to End Addiction Long-term (HEAL) Initiative:** HEAL is NIH’s effort to address the opioid crisis. Congress appropriates $500 million annually to HEAL across the NIH; 12 Institutes and Centers (ICs) are leading 26 HEAL research projects—from prevention, basic, and translational research to clinical trials and implementation. Thirty-six FOAs have been released for FY 2019. Pain management is a major focus of the Initiative, and HEAL’s programs for pain span the research spectrum and the pipeline from basic discovery to implementation. NCATS manages both the pre-clinical screening platform and novel drug development program as well as the HEAL Pain Management Effectiveness Research Network (Pain-ERN). The CTSA Trial Innovation Network (TIN) provides clinical and biostatistical coordination for Pain-ERN effectiveness clinical trials. Pain-ERN trial applications are being reviewed by the HEAL Executive Council, and trials are expected to be funded in September 2019. There are six open NCATS-supported HEAL projects.
NCATS Meetings and Outreach

- NCATS, NIDA, and the National Institute of Neurological Disorders and Stroke (NINDS) co-sponsored the February 7–8, 2019, 2-day workshop: Opioid Crisis and the Future of Addiction and Pain Therapeutics: Opportunities, Tools, and Technologies. Participants discussed the state-of-the-art research in addiction and pain, particularly emphasizing the importance of rigor and reproducibility (R+R) in the HEAL effort, and the role of the NCATS Assay Guidance Manual (AGM) in providing guidance on R+R protocols.
- The Rare Disease Day at NIH event was held on March 1, 2019. Attendance was record breaking, at 2000 participants; 700 attended in person and 1200 by videocast.

Tissue Chips in Space

NCATS is collaborating with NASA and the International Space Station (ISS) National Laboratory (formerly known as the Center for the Advancement of Science in Space) on applying tissue chip technology to disorders that are highly prevalent on Earth, and develop rapidly in astronauts aboard the ISS. Four tissue chips mimicking bone and cartilage, the kidney, lung and bone marrow, and the blood-brain barrier were sent to the ISS on May 4, 2019. The purpose of these experiments is to model aging in slowly progressing diseases in microgravity to provide insights that could improve health on Earth.

VI. CTSA PROGRAM UPDATE: Michael G. Kurilla, M.D., Ph.D., Director, DCI, NCATS

Michael G. Kurilla, M.D., Ph.D., discussed highlights of the CTSA Program projects and activities. He announced that Robert S. Sherwin, M.D., founding director of the Yale Center for Clinical Investigation (YCCI) and principal investigator at the Yale CTSA, has retired. John H. Krystal, M.D., and Brian R. Smith, M.D., will serve as YCCI co-directors and Yale CTSA co–principal investigators.

NCATS awarded two new CTSA Program hubs in FY 2019:

- **Integrated Translational Health Research Institute of Virginia (iTHRIV):** Virginia’s second CTSA Program hub, iTHRIV University of Virginia CTSA, brings together a diverse array of partners, including Virginia Polytechnic Institute and State University.
- **New Jersey Alliance for Clinical and Translational Science (NJ ACTS):** Establishing the NJ ACTS partnership at Rutgers, The State University of New Jersey, reaches nearly seven of New Jersey’s nine million residents.

Apple Heart Study

The Apple Heart Study assessed wristwatch-based photoplethysmography to identify cardiac arrhythmias using the Apple Watch (Apple Inc., Cupertino, CA) and the Apple Heart Study mobile medical application (app). This population-based screening study for atrial fibrillation used an innovative recruitment strategy, with participants contacted through the Apple iPhone and Apple Heart Study app. More than 400,000 participants were enrolled in the study over a 2-year period. Irregular heartbeats identified by the app via the Apple Watch alerted participants to report to the medical facility for follow-up. The Stanford CTSA supported the Apple–Stanford School of Medicine agreement, and seven of its statisticians performed the analyses. The CTSA TIN liaison served as the lead.
University of Michigan Precision Health Study: Michigan Predictive Activity and Clinical Trajectories (MIPACT)

The University of Michigan MIPACT study, partially sponsored by Apple, aims to understand the relationship between wearable sensors, health information, and health outcomes. The study is being conducted in collaboration with the CTSA hub at the Michigan Institute for Clinical and Health Research. Patients within the Michigan Medicine system currently are being enrolled.

Fecal Microbiota Capsules Are Safe and Effective in Patients with Recurrent Hepatic Encephalopathy (HE): A Randomized, Blinded, Placebo-Controlled Trial

This CTSA Program Collaborative Innovation Award (CCIA)–funded clinical trial evaluated fecal microbiota transplants (FMT) in 20 cirrhotic outpatients with recurrent HE who were being treated with the standard of care (i.e., rifaximin/lactulose). The study suggests that modulating the microbiome affects the inflammatory conditions in the liver. Oral FMT administration was effective in patients and was associated with reduced hospitalizations.

MedStar Health Heart Disease Study

The Georgetown University–Howard University CTSA is supporting a study to evaluate Tara, an intelligent three-dimensional (3-D) Healthcare Assistant Avatar created using ObEN’s personal artificial intelligence technology to monitor heart failure patients in the home setting.

Rural Health Initiatives

- The CTSA Program hosted an “un-meeting” on rural health and health equity on April 8, 2019, in Gainesville, Florida. One meeting outcome was increased awareness of the U.S. Department of Agriculture National Institute of Food and Agriculture (NIFA) and its extension services and outreach into U.S. rural communities. NCATS will explore partnering with NIFA to align programs and initiatives.
- The 9th Annual Appalachian Translational Research Network Health Summit will be hosted by The Ohio State University on October 14–15, 2019.
- Three CTSA hubs—Oregon Health & Science University, University of Kentucky, and The Ohio State University—collaborate on the CCIA–funded Peer-Based Retention of People Who Use Drugs in Rural Research (PROUD-R2) study focusing on testing strategies to improve retention and foster facilitation of rural participants in clinical trials.
- CTSA KL2 Scholar Jessica Zegre-Hemsey, Ph.D., her team, and partners are conducting a feasibility study to assess automated defibrillators delivered by drones to rural communities in North Carolina.

Collaborations

- **Transforming Expanded Access to Maximize Support and Study (TEAMSS):** The goal of this CTSA collaboration among the University of Michigan, Duke University, the University of Texas Southwestern Medical Center, and the University of Rochester is to build a national framework for common access to experimental drugs, devices, and biologics. TEAMSS centers will engage small companies wanting to share their products, without a strain on their resources, through FDA’s expanded access program (i.e., compassionate use).
• **NCATS–Eli Lilly Externship Opportunity in Clinical and Translational Sciences**: CTSA Program scholars, trainees, and investigators are paired with an Eli Lilly project team for a 1-year externship program. NCATS’ point of contact is Joan Nagal, M.D., M.P.H. The target start date is July 9, 2019.

• **CTSA Training Linked (TL1) Team Approach to Osteosarcoma Cell Detection**: Two University of Florida TL1 scholars supported by the CTSA Program—Pablo Dopico, Ph.D. (engineering), and Henrietta Fasanya (biology)—are leading a transdisciplinary team of microfluidic engineers and cancer biologists in a collaboration to develop a circulating osteosarcoma cell detection device.

• **National Center for Data to Health (CD2H) Resource**: NCATS is piloting opportunities for a shared infrastructure to access CTSA tools made available in a secure computer cloud.

**Impact of the CTSA Program**

Dr. Kurilla highlighted two examples of projects affecting human health:

• Cornell Dots, or C Dots, was a 2007 pilot award to develop pre-clinical models using ultrasmall, tumor-targeting, core-shell silica nanoparticles, which advanced in 2014 to first-in-human trials, and then to commercialization in 2016 (Elucida Oncology™). Phase II trials are in progress.

• The Southern California Clinical and Translational Science Institute, University of Southern California CTSA is a supporter of Hollywood, Health & Society, a program that provides the entertainment industry with accurate and up-to-date information for storylines on health, safety, and national security. Consultations and storylines on television shows, such as Grey’s Anatomy, resulted in a patient’s following up on information from the television series and receiving the necessary treatment.

**Outreach**

Dr. Kurilla called attention to the Fall CTSA Program meeting being held on September 26–27, 2019, in Arlington, Virginia.

**Discussion**

Ronald J. Bartek, M.A., asked about the output of the expanded access program and whether the goal is to define, elucidate/educate, or develop new approaches. Dr. Kurilla explained that the aim is to create a framework to provide institutions with a common mechanism through which any company and any patient can participate. The FDA has recognized that as expanded access programs become more common, the value of these types of data increases. Also, these programs formalize how data are collected and standardize collections across clinical sites.

**VII. DIVISION OF PRE-CLINICAL INNOVATION UPDATE**

Christine M. Colvis, Ph.D., Director, Drug Development Partnership Programs, NCATS; Anton Simeonov, Ph.D., Scientific Director, DPI, NCATS

Dr. Austin stated that NCATS annually updates the Advisory Council and CAN Review Board on its Intramural Research Program (IRP). The NCATS IRP is different from those of the other NIH ICs in that investigators work in project teams and are not tenured or tenure-track principal investigators. This year’s NCATS IRP update will focus on the role of the IRP’s DPI in the HEAL Initiative.
Christine M. Colvis, Ph.D., explained that the NCATS IRP is the only NIH IRP receiving funding for the HEAL Initiative, partly based on DPI’s success in translating pre-clinical projects to clinical trials. DPI serves to establish research collaborations and productive partnerships. Dr. Colvis described the contributions that collaborators (IRP investigators) and NCATS (DPI) each make to a research partnership and noted that partnerships are milestone-driven, agile, dynamic, synergistic, and mission-specific. NCATS is accepting pre-proposal applications for collaborations on the HEAL project through Developing Drugs and Human Cell-Based Testing Platforms for Pain, Addition, and Overdose (NOT-TR-19-018). Proposals will be screened through an external evaluation process; no funding is attached to the proposals.

Anton Simeonov, Ph.D., pointed out that, aside from supporting HEAL across the translational pipeline, DPI has been asked to perform functions that are hard to access at other NIH ICs and require unique combinations of expertise, skills, and technologies. Problem areas being addressed include (1) improving platforms for testing new drug candidates; (2) discovery and development of novel pharmacological probes for testing novel biology in pain, addiction, and/or overdose; and (3) pre-clinical assays for late-stage drug candidates for IND applications. Dr. Simeonov elaborated on the enabling capabilities in the NCATS Stem Cell Translation and 3-D Biofabrication Laboratories and the available protocols and animal models to support HEAL.

Discussion
In response to a question from Andrew W. Lo, Ph.D., regarding whether DPI had considered working with industry partners on machine learning to identify pharmacological probes, Dr. Simeonov stated that the DPI works closely with industry partners in the area of predictive toxicology and pharmacokinetics and has had interactions with Atomwise, Inc. and Recursion Pharmaceuticals, for example. Lili Portilla, M.P.A., added that Recursion Pharmaceuticals is an NCATS Small Business Innovation Research awardee.

Rachel Ramoni, D.M.D., Sc.D., noted the robust pain research being conducted in the VA and a need for expertise in advancing products through the drug development pipeline.

Dr. Ling inquired about the potential for sponsoring a prize challenge opportunity. Dr. Colvis explained that prize challenges are not sponsored in the NCATS IRP. A Specialized Platform for Innovative Research Exploration (ASPIRE), an ongoing CAN program, sponsors prize challenges and supports the HEAL Initiative.

Brad Margus, M.B.A., emphasized the importance of communicating to the research community the mission of NCATS and its uniqueness in advancing translational science compared to a contract research organization (CRO). Dr. Simeonov explained that NCATS products are widely disseminated in the research community, including the protocols and knowledge for improving drug screening platforms and stem cell and pre-clinical development. He called attention to the Assay Guidance Manual, a National Center for Biotechnology Information e-book, whose content is managed by NCATS and is frequently accessed by users. This diverse experience and long list of publicly shared resources far exceed the offerings of any CRO. Theodore (Ted) Holman, Ph.D., added that researchers in academia often cannot afford the services of a CRO and that NCATS funding opportunities are making translational research possible in those instances.

Dr. Austin remarked on how NCATS performs projects as use cases to inform future efforts or initiatives. The HEAL projects, he added, are different in this respect because they are addressing an area that has had few successes in the private industry. The existing animal models for pain research are not translatable to humans. NCATS is enabling capabilities in testing therapeutics, new platforms and models, and IND support that are not being addressed elsewhere. Dr. Rosenblatt suggested considering
pain research across multiple targets. Dr. Stoner thinks that the intermediate knowledge transfer from pre-clinical studies on addiction to educate physicians on future clinical practices is a missing component. Dr. Austin said that this translational aspect is within the purview of NIDA and called attention to the Substance Abuse and Mental Health Services Administration’s Healing Communities Study.

Dr. Lo suggested exploring a new corporation (NewCo) business model as a platform for pharmaceutical companies to out-license their compounds, if facilitating this NewCo model would be within NCATS’ mandate.

VIII. CURES ACCELERATION NETWORK REVIEW BOARD UPDATE: G. Lynn Marks, M.D., Senior Advisor to the Office of the Director, BARDA, ASPR/HHS; and Chair, CAN Review Board

Dr. Marks described the step-by-step process of developing a CAN project—brainstorming ideas; developing a CAN Review Board proposal; deciding on the focus areas; and developing concepts, funding solicitations, and making awards—all culminating with solutions for NCATS. Workshops are convened throughout this process. The timeline from the concept vote to an award is approximately 1 year. The goal is to have a pool of ideas to advance as time and funding allow.

**Action Item:** At a future meeting, Drs. Austin and Marks will review with new members the language of the CAN Review Board’s charter regarding accountability and its proactive function relative to the reactive role of the Advisory Council.

**CAN Project Proposal 1: Gene Therapy**

Ronald J. Bartek, M.A., Co-Founder and Founding President, FARA, and Vice Chair, CAN Review Board, explained that at its December 2018 meeting, the CAN Review Board discussed and endorsed the gene therapy proposal, which was subsequently approved at the January 2019 Joint Advisory Council and CAN Review Board meeting. Mr. Bartek detailed the ongoing conferences and workshops:

- NCATS, NINDS, and United States Pharmacopeia co-sponsored a roundtable on standardization of adeno-associated virus (AAV) on March 8, 2019.
- NCATS is hosting a workshop on Central Nervous System Immunogenicity Considerations for AAV-mediated Gene Therapy on June 11, 2019.
- Mr. Bartek, Anne R. Pariser, M.D., and P.J. Brooks, Ph.D., from the ORDR are organizing a workshop on addressing the capacity for AAV vector manufacturing for clinical trials. The date is to be determined.

Mr. Bartek noted that two concepts related to the gene therapy proposal will be discussed later in the meeting.

**CAN Project Proposal 2: Drug Repurposing**

Dr. Colvis presented this proposal. Evidence has shown that drugs previously tested and/or approved for one indication may be useful for a second or even third indication. The problem remains that off-patent drugs offer little incentive for further investment. FDA has the ability to update generic drug labels with new safety information, but any updates on efficacy information for new indications require new data submissions by the drug sponsor. Because no mechanism exists to regain the investment or prevent off-
label prescribing of a generic drug without patent protection, studies to collect data for label updates for new indications are not likely.

Dr. Colvis indicated that overcoming barriers to generic drug repurposing will rely heavily on NCATS’ experiences with such programs as TRND and BrIDGs, the level of evidence and data sources, and sponsors willing to undertake the regulatory process. Efforts also would need to focus on encouraging private-sector engagement and identifying use cases. An off-patent drug repurposing workshop is being planned, with the date to be determined. The aim is to engage multiple stakeholders across the health care ecosystem to assess the landscape in a co-sponsored FDA and NCATS effort. The planning committee is composed of CAN Review Board members, NCATS staff, and external partners.

Dr. Colvis concluded that the CAN Review Board recommends this program of research to NCATS because the Center, in collaboration with the CAN Review Board, is uniquely equipped to advance the translational sciences needed to address many of the issues raised.

**Discussion**

Frank F. Weichold, M.D., Ph.D., agreed that, from a public health perspective, the potential medical care cost savings of drug repurposing is hard to measure. The business model would need to be addressed. Opportunities exist to form alliances with stakeholders across governmental agencies, leverage and understand the strength of real-world data, and make significant contributions at all stakeholder levels.

Dr. Rosenblatt asked about the frequency of requests for drug repurposing. Dr. Colvis pointed out that 80 percent of the calls received by the NCATS Drug Repurposing Program have been from persons wanting to repurpose a drug already on the market. Most of the research community is not aware of the proprietary compounds held by pharmaceutical companies.

Mr. Margus remarked on how conducting clinical trials with the risky drug delivery technologies may be the only way for a company to obtain intellectual property patent protection. These uncommon delivery methods open the potential for effective treatments that are beneficial to patients, which he has witnessed in his own immediate family. Dr. Reddy recommended engaging technology delivery companies as stakeholders in these discussions and experts in this area. Biosimilars also will have to be considered in the future.

A motion was made and seconded to advance the project proposal on drug repurposing.

**IX. CLEARANCE OF CONCEPTS**

The Council and Board received presentations on five 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.

**Order of Magnitude Increases in the Efficiency of Adeno-Associated Virus (AAV) Vector Production for Human Gene Therapy: P.J. Brooks, Ph.D., Program Director, ORDR, NCATS**

Dr. Brooks pointed out that multiple clinical successes in clinical trials using AAV vectors have been witnessed in recent years; however, challenges to manufacturing clinical-grade AAV vectors suitable for the clinic exist. AAV vector manufacturing is a focus and topic of interest to the CAN Review Board. The goal of this concept is to develop at least one technology that increases efficiency of production of clinical AAV by a factor of tenfold or higher to address the order-of-magnitude issues. The technology should be independently validated. The potential impact is twofold: a significant increase in the number of gene therapy clinical trials for many disease states and the existence of developed technology that could support NCATS DPI intramural projects.
Discussion

Mr. Bartek expressed his support for the concept and cited several reasons for the research. The wait time for a gene therapy trial is long, and the expense to patients can be high. The efficiency in AAV vector manufacturing has two components: time and cost. NCATS is exploring a platform of solutions that would be broadly applicable across many diseases, both rare and common.

Dr. Marks enthusiastically supports the concept and elaborated on this example of NCATS’ acting on the recommendations of the CAN Review Board. The opportunity exists for prize challenges to encourage diametrically opposing ideas that are far-reaching for a solution based on success.

Richard E. Kuntz, M.D., strongly supports the concept and wondered why the existing AAV vector manufacturers are not meeting the demands, given the simple risk model. Dr. Brooks replied that several large companies have become disillusioned with the current process and have developed in-house manufacturing capacity and are no longer in the market.

Dr. Austin spoke of the efforts of the NIH National Human Genome Research Institute (NHGRI) to fund DNA sequencing technology development, which was catalytic to commercial organization participation. He asked whether a tenfold order of magnitude improvement was sufficiently ambitious or suited to the scale of the problem. Kiran Reddy, M.D., sought clarity on the magnitude of the deficiency. Dr. Austin responded that calculations on the genome viral load (liters of viral supernatant) needed for one clinical trial of one disease (e.g., AveXis spinal muscular atrophy gene therapy trial) exceeds the capacity worldwide. This suggests that a 10,000-fold improvement in efficiency, similar to that of genome sequencing, might be feasible. The current cost of using the existing technologies is estimated at $3 million to $5 million per patient.

Mr. Bartek noted that AveXis built a gene therapy facility and that its vectors are proprietary. If NCATS broadly supports technology development for AAV vector manufacturing, it will reduce costs and provide vectors that would be commercially available.

Dr. Lo commented on the need for this concept. As of April 2019, 339 gene therapy trials were registered in ClinicalTrials.gov. Of the 339, 15 are Phase III trials. This trend is expected to increase in the coming years, demonstrating a need for increased and improved vector manufacturing. Because NCATS is mandated to avoid duplicating industry efforts, Dr. Lo questions whether this research would compete with, rather than complement, industry efforts. He suggested three ways to be ambitious: increase production capacity, address the immunogenicity problem, and increase the DNA payload from four kilobase pairs to roughly 20 kilobase pairs. Dr. Brooks explained that work in the area of the immune response is ongoing. Large companies are efficient in the manufacturing process and have the edge on marketing.

Members unanimously approved the Order of Magnitude Increases in the Efficiency of Adeno-Associated Virus (AAV) Vector Production for Human Gene Therapy concept.

Ethical, Legal, and Societal Implications in Translational Research: Elaine Collier, M.D., Senior Advisor to the Director, NCATS

Emerging discoveries and technologies raise potential ethical and legal issues that also may have societal implications. Evidence suggests that the familiarity and collaboration of translational researchers and bioethics and legal scholars can be beneficial. The pig brain revitalization studies are one such collaboration. To advance discoveries to impact health responsibly, engagement and collaboration of researchers, scholars, communities, and the public are needed. Elaine Collier, M.D., pointed out the major obstacles to be addressed and summarized the ongoing research and activities in this area, such
as the establishment of the Neuroethics Working Group within NIH’s Brain Research through the Advancing Innovative Neurotechnologies (BRAIN) Initiative and the NHGRI Ethical, Legal and Social Implications (ELSI) Research Program. The concept goals are to increase recognition of and research on these issues, encourage research on these challenging questions to collect data, foster collaboration between the two communities, and provide empirical data and frameworks for addressing these issues. The outcomes will be increases in projects, scholarship, research collaborations, and stakeholder engagement in these areas.

Discussion

Megan O’Boyle expressed concern that the patient voice was not included and cautioned against becoming too conservative regarding returning data to patients. In general, concepts that are funded should include an informed patient voice of the community. Dr. Collier explained that the patient’s voice was not intentionally left out of the concept and noted that patients are driving some of NCATS’ research. Approaches on how best to engage the patient’s voice are needed. Ms. O’Boyle suggested incorporating bioethics into medical training programs and training for junior investigators.

Mr. Bartek lauded the NCATS and NIH for addressing this important topic and taking a leading role in informing the public. Geoffrey Shiu Fei Ling, M.D., Ph.D., highlighted the importance of an ELSI program and of conducting this type of research.

Members unanimously approved the Ethical, Legal and Societal Implications in Translational Research concept.

Introduction of Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) Concepts: Lili Portilla, M.P.A., Director, Office of Strategic Alliances, NCATS

Ms. Portilla introduced two new SBIR/STTR concepts: one for a grant solicitation and one for a contract solicitation. She noted that SBIR funds support the research and that only U.S. businesses can apply. Ms. Portilla explained the differences between SBIR grant and contract mechanisms.

Non-viral Delivery Technologies for Somatic Genome Editing Therapeutics: P.J. Brooks, Ph.D., Program Director, ORDR, NCATS

Somatic genome editing has the potential to treat a large number of rare genetic disorders and has therapeutic implications for common diseases. Therapeutic benefit is maximized if the genome editing machinery has broad coverage in many somatic cell types. For many diseases, the ability to deliver genome editors to relevant cell types is limited. Research shows that non-viral delivery methods allow transient expression of genome editors and reduce toxicity. The concept outcome is the development of non-viral technologies to deliver genome editing machinery to a wide variety of cells and tissues, especially in cell types with no effective delivery technology currently available.

Discussion

Dr. Ling champions this concept, which could potentially be used in place of the AAV vector methodology in some cases. He remarked on how the concept makes good use of SBIR/STTR funds to conduct research not being performed elsewhere.

Dr. Marks asked why this research was not already captured in the Somatic Cell Genome Editing (SCGE) project. Dr. Brooks replied that the goals of the SCGE project are not quite aligned with this concept’s goals, which are more exploratory. Few small businesses were applying successfully to SCGE, likely because of the requirements and the manner in which the FOA was written. Dr. Austin added that the concept complements the NIH Common Fund programs, which do not have an SBIR/STTR component.
Members unanimously approved the Non-viral Delivery Technologies for Somatic Genome Editing Therapeutics concept.

**Alternatives to Commercially Available Cell Culture Insert Membranes and Manufacturing Techniques:**
*Sam Michael, Director, Automation and Compound Management, DPI, NCATS*

Despite the increased focus on the use of more complex cellular and tissue models (e.g., 3-D tissue printing) to provide physiologically relevant platforms for enhancing the development of therapeutics for patients, challenges exist. Biodegradable cell culture insert membranes that also provide structural support are needed, as commercially available alternatives are insufficient. Mr. Michael stated that NCATS thinks that a small business, via an SBIR contract mechanism, can provide a commercial solution to manufacture cell culture insert membranes in an automated and reproducible manner.

**Discussion**

Dr. Kuntz asked about partnering with nonprofit universities, such as the Fogarty Innovation Institute, to shepherd small businesses across the “valley of death” (i.e., the funding gap from an SBIR Phase II Award to commercialization). Dr. Portilla explained that the NCATS Office of Strategic Alliances does work and collaborate with these types of organizations and recognizes that SBIR/STTR funds alone cannot bring these technologies into commercialization.

Dr. Palkowitz wondered whether NCATS had considered expanding the cell culture insert membranes into an integrated package to broaden the commercial value. Mr. Michael replied that the scope is narrow in this initial phase, but over time this would be a component of a larger system.

Members unanimously approved the Alternatives to Commercially Available Membrane Inserts and Manufacturing Techniques concept.

**Action Item:** The Advisory Council and the CAN Review Board will discuss prioritizing an NCATS program focused on bridging the funding gap for devices, similar to the TRND and BrIDGs programs for therapeutics.

**Multi-disciplinary Approaches to Shortening the Diagnostic Odyssey for Rare Diseases: Anne R. Pariser, M.D., Director, ORDR, NCATS**

Many patients with a rare disease experience years-long delays in receiving a correct diagnosis (i.e., the “diagnostic odyssey”), lending to considerable anxiety and despair for patients and families. Current approaches to the rare disease diagnostic odyssey typically occur through idiosyncratic referrals to a small number of disease experts at tertiary care centers. The goal of this concept is to improve diagnostic accuracy and accelerate diagnosis for these patients through a multidisciplinary process that can be performed at the primary or secondary care levels by front-line providers. Approaches could be patient-centric, physician-centric, or disease-centric. Some current activity exists in each of these areas, but no comprehensive methods are using multiple approaches simultaneously. The outcome will be the development of a broadly adaptable, facile process with the potential impact of advancing the International Rare Diseases Research Consortium’s 2027 goals.

**Discussion**

Ms. O’Boyle pointed out that 30 percent of patients with a rare disease can be identified by genetic testing, which is 30 percent more than currently are being diagnosed; however, only a limited number of genetic counselors are available to provide timely results. Many parents of patients are self-diagnosing their children using online platforms, joining support groups, and providing samples to the associated registries, but these approaches may not be resulting in the correct diagnosis without genetic testing.
Any initiative that aligns with NIH’s Undiagnosed Diseases Program (UDP), such as this concept, is a strength.

Mr. Bartek elaborated on the importance of an early diagnosis to improve health outcomes for these patients. Although a valuable asset, the Undiagnosed Diseases Network is limited and is not applicable to most patients. He also suggested exploring information technology solutions, which could be embedded into existing NCATS programs and initiatives, such as the Biomedical Translator Program or RaDaR.

Dr. Reddy sees this concept as a rapid diagnostic odyssey tool to assist in evaluating complex cases, which can be widely distributed to physicians and clinicians worldwide.

Dr. Stoner pointed out the ethical issues that should be considered with regard to false positives; false negatives are of lesser concern. Dr. Pariser explained that false positives cannot be ruled out entirely, initially. It is anticipated that the concept’s multidisciplinary approach to rapidly diagnose patients will eliminate this issue.

Members unanimously approved the Multi-disciplinary Approaches to Shortening the Diagnostic Odyssey for Rare Diseases concept.

**Action Item:** Dr. Marks and the CAN Review Board will consider a discussion on the lack of medical coding for rare diseases and potential alternatives for tracking health care costs.

Dr. Austin made three points: (1) the UDP was initiated by the ORDR 10 years ago; (2) in light of the current technologies, most rare diseases are identifiable by syndrome or genotype-phenotype correlations, suggesting a systems problem, not a scientific problem; and (3) no ICD codes exist for more than 90 percent of rare diseases.

**X. 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 2:47 p.m. ET.

**XI. 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.

**XII. ADJOURNMENT OF CLOSED SESSION OF THE NCATS ADVISORY COUNCIL MEETING**

Dr. Austin adjourned the closed session of the NCATS Advisory Council meeting at 4:56 p.m. ET.

**CERTIFICATION**

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

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

G. Lynn Marks, M.D.
Chair, Cures Acceleration Network Review Board;
and
Senior Advisor to the Office of the Director, Biomedical Advanced Research and Development Authority, ASPR/HHS