Department of Health and Human Services
National Institutes of Health
National Center for Advancing Translational Sciences
36th Meeting of the
Advisory Council

Minutes of Hybrid Meeting
May 23, 2024

The National Center for Advancing Translational Sciences (NCATS) Advisory Council held a meeting in open session on May 23, 2024, from 10:37 a.m. to 4:37 p.m. ET, via National Institutes of Health (NIH) VideoCast and in Building 35A, Room 620/630, 9000 Rockville Pike, Bethesda, MD. Joni L. Rutter, Ph.D., NCATS Advisory Council Chair, led the meeting. In accordance with Public Law 92-463, the session was open to the public.

Prior to the meeting, the NCATS Advisory Council met in closed session on May 23, 2024, from 9:04 a.m. to 10:21 a.m. ET, for the review and consideration of grant applications.

NCATS ADVISORY COUNCIL MEMBERS PRESENT

Chair

Joni L. Rutter, Ph.D., Director, NCATS

Executive Secretary

Anna L. Ramsey-Ewing, Ph.D., Director, Division of Extramural Activities (DEA), NCATS

Council Members

Sergio A. Aguilar-Gaxiola, M.D., Ph.D.
Paul A. Harris, Ph.D.
Annie M. Kennedy, B.S.
Kelly Marie McVearry, Ph.D., Ed.M.
Robin J. Mermelstein, Ph.D.
Keith J. Mueller, Ph.D.

***Ad Hoc* Council Members**

None present

Representative Members

None present

***Ex Officio* Members**

None present

Others Present

Catharine E. Krebs, Ph.D., Medical Research Program Manager, Physicians Committee for Responsible Medicine (PCRM)
Peter Marks, M.D., Ph.D., Director, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA)
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 provisions of Public Law 117-286.

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.

Review of Grant Applications

The Council reviewed 76 research, research-related, and training grant applications with primary assignment to NCATS for a requested amount of $43,890,170 in first-year direct costs. The Council concurred with the recommendations of the initial review groups. For the record, it is noted that applications with secondary assignment to NCATS were also considered.

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

Joni L. Rutter, Ph.D. adjourned the closed session of the NCATS Advisory Council meeting on May 23, 2024, at 10:21 a.m. ET.

III. CALL TO ORDER, OPEN SESSION

Joni L. Rutter, Ph.D. called the meeting to order and welcomed members and guests to the 36th meeting of the NCATS Advisory Council. Anna L. Ramsey-Ewing, Ph.D., conducted the roll call and reviewed the meeting agenda. She noted the meeting logistics and reminded attendees that the open session was being livestreamed on NIH VideoCast.

IV. CONFIRMATION OF DATES FOR FUTURE NCATS ADVISORY COUNCIL MEETINGS: Anna L. Ramsey-Ewing, Ph.D., Director, Division of Extramural Activities, NCATS; Executive Secretary, NCATS Advisory Council

Anna L. Ramsey-Ewing, Ph.D. confirmed the schedule for the meetings of the NCATS Advisory Council for 2024, 2025, and 2026:

- September 19–20, 2024
- January 30–31, 2025 (virtual meeting)
- May 22–23, 2025
- September 18–19, 2025
- January 29–30, 2026 (virtual meeting)
- May 21–22, 2026
- September 17–18, 2026

V. DIRECTOR'S REPORT: Joni L. Rutter, Ph.D., Director, NCATS, Chair, NCATS Advisory Council

Joni L. Rutter, Ph. D. began by providing a recap of the January 2024 meeting. During that meeting, she conveyed that NCATS is operating under a continuing resolution until the 2024 federal budget is approved. NIH leadership is in place, and NCATS leadership continues to grow. NCATS has had several impactful advances, especially in the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)- 6 trial and in data science and large language models (e.g., LitCoin program) and somatic cell genome editing. The Division of Preclinical Innovation (DPI) has been advancing therapeutic development through nondisclosure agreements and Food and Drug Administration (FDA) Investigational New Drug (IND) submissions. NCATS has been promoting use of novel alternative methods (NAMs) to advance biomedical research and has been solidifying and deepening interactions

with the FDA. The 2024–2029 strategic plan is being drafted and is on schedule. NIH Director Monica Bertagnolli, M.D., shared her vision for NIH. Other program updates included information about NCATS' Office of Special Initiatives (OSI) and Office of Strategic Alliances (OSA).

After this review of the previous meeting, Dr. Rutter reported on the fiscal year 2024 (FY24) budget, announced NCATS and NIH staff changes, and highlighted progress in some of the NCATS offices, divisions, and programs. She provided a brief update on NCATS 2024–2029 strategic planning, noting that a detailed discussion will occur later during the meeting.

NCATS Fiscal Year 2024 Budget Recap

Dr. Rutter reported that NCATS received a $5 million increase in its FY24 appropriations above the FY23 enacted budget. Support for the Clinical and Translational Science Awards (CTSA) Program remained unchanged at $629.5 million. The budget for the Cures Acceleration Network (CAN) increased to $75 million and, for the first time, the CAN bill language changed from "up to" (i.e., a ceiling) to "shall be available." NIH received a $300-million increase in discretionary funding above the FY23 enacted budget, but funding decreased by $378 million because of the ending of the 21st Century Cures Act 7-year appropriations.

With this increase in the CAN budget, NCATS is planning to support two areas of research — (1) additional areas of rare diseases and tissue chips and (2) methylmalonic acidemia (MMA) — but is flexible to adjust to other scenarios as needed. MMA is a rare disease that involves the body's inability to break down proteins and fats properly, resulting in abnormally high levels of acid in the blood and body tissues (i.e., acidemia). NCATS is collaborating with the NIH Clinical Center *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and National Institute of Neurological Disorders and Stroke to conduct the first-in-human gene therapy clinical trial for MMA. This research complements NCATS' existing gene therapy programs, including the Platform Vector Gene Therapy (PaVe-GT) and the Bespoke Gene Therapy Consortium (BGTC), and is anticipated to move more quickly as a CAN-specific activity.

President Joseph R. Biden released the FY25 budget proposal on March 11, 2024. NIH will present its FY25 budget request during the Labor, Health and Human Services, Education, and Related Agencies Appropriations Subcommittee hearing being held May 23, 2024.

NCATS Staff Changes, Recruitments and Retirements

Dr. Rutter announced that NCATS has filled several leadership positions across center divisions and offices since the last Council meeting. Annica Wayman, Ph.D., has been named NCATS' deputy director. Dr. Wayman, former Council member and associate dean for Shady Grove Affairs, College of Natural and Mathematical Sciences, University of Maryland, Baltimore County (UMBC), is a research scientist, a scientist administrator, an educator, and a champion for advancing translational sciences. She helped launch UMBC's Bachelor of Science in Translational Life Science Technology program at Shady Grove. Although Dr. Wayman and Dr. Rutter will share some responsibilities, Dr. Wayman will be active in guiding NCATS' strategic direction and setting activities over the coming years.

Matthew D. Hall, Ph.D., is now scientific director and director, DPI, NCATS and previously was director, Early Translation Branch, DPI. Anton Simeonov, Ph.D., who was former and then acting scientific director, will be transitioning to chief, Chemical Genomics Branch, NCATS Laboratories.

Ashley S. Parker, Ph.D., is the new chief of staff, NCATS Office of the Director (OD), and has served in several capacities at NIH. These include as researcher at the National Cancer Institute (NCI) focusing on

the role of bacterial small ribonucleic acid (RNA) in posttranscriptional gene regulation and as a senior advisor at the U.S. Department of Health and Human Services Administration for Strategic Preparedness and Response. Dr. Parker, a trained chemist and microbiologist, was involved in developing therapeutic strategies for the response to the Mpox outbreak, Ebola virus preparedness, and COVID-19 therapeutics commercialization.

Josh Fessel, M.D., Ph.D., was named director, Office of Translational Medicine (OTM), and has previously served as senior advisor, Division of Clinical Innovation (DCI). Dr. Fessel will be able to work across NCATS to foster integrating programs and also will work closely with the clinical activities within NCATS intramural and extramural programs and strengthening interactions with the clinical counterparts of other NIH institutes and centers (ICs). Other topics under the purview of the OTM include human subjects research; diversity, equity, inclusion, and accessibility; regulatory activities and growth development; and clinical trials and ethics.

Sury Vepa, Ph.D., J.D., is deputy director, OSA, and has worked with NIH since 2005 in several positions. During a brief hiatus from NIH, Dr. Vepa taught and supervised attorneys enrolled in the Maryland Intellectual Property and Legal Resource Center, University of Maryland School of Law. In 2008, he returned to NIH, and in 2015, he joined OSA and served as senior licensing and patenting manager.

Dr. Rutter congratulated Keith R. Lamirande, M.B.A., associate director for administration, Executive Officer, on being a recipient of the Presidential Rank Awards for FY23 Senior Executive Service (SES) Meritorious Executive. These awards are conferred each year to select members of the SES and the Senior Foreign Service who have provided exceptional service to the American people over an extended period. Dr. Rutter also announced that Mr. Lamirande is retiring from NIH after 35 years of service to the federal government. She expressed appreciation to him for his work in growing NCATS, including the hiring of 150 staff in the previous year alone. Dr. Rutter primarily attributed this growth to the fluid administrative operations within the Office of Administrative Management. Bekah Geiger, M.S.W., has been named acting executive officer and has been deputy executive officer for the past 4 months. Ms. Geiger, a long-time champion of NIH, has served in a number of positions. A search for a new executive officer is underway.

NIH Staff Changes and Recruitments

Dr. Rutter highlighted NIH staff changes and recent recruitments. NIH is recruiting a director, National Library of Medicine (NLM). The application period opened on May 1, 2024, and closes on July 1, 2024. NIH remains successful in attracting talent from NCATS -supported activities, especially the CTSA Program. Joshua M. Levy, M.D., M.P.H., M.S., is clinical director and chief, Sinonasal and Olfaction Program, National Institute on Deafness and Other Communication Disorders.

Sean Mooney, Ph.D., director, Center for Information Technology (CIT), has been instrumental in implementing the NIH Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES) initiative. STRIDES is a cloud-based program that initially focused on intramural programs. Dr. Mooney has expanded the initiative to include extramural programs. Both intramural and extramural researchers are provided an opportunity to receive cloud-based experience at no cost for 90 days and $500 in credits for engaging and working in this cloud space.

News and Announcements

Dr. Rutter highlighted recent NIH-wide and NCATS -specific announcements and events.

- **White House Rare Disease Forum.** The White House Office of Science and Technology Policy hosted the first White House Rare Disease Forum. Dr. Rutter and Council member Annie M. Kennedy, B.S., participated in panel discussions.

- **Rare Disease Day (RDD) at NIH 2024.** RDD at NIH is planned and organized by the Division of Rare Diseases Research Innovation (DRDRI) and brings together all the voices within the rare diseases community, including scientists, clinicians, funders, patients, patient advocates, and other leaders. This year's event was held in person at the NIH Bethesda campus on February 29, 2024, and was livestreamed via NIH VideoCast. Further details can be accessed on the NCATS RDD 2024 website. During the event, the Cure JM (juvenile myositis) Foundation's Advocates Council, composed of patients and families, presented Dr. Rutter and NCATS with a proclamation of thanks accompanied by a plaque. Cure JM Advocates Council member and patient advocate James Best presented the proclamation, signed by more than 600 dignitaries from the Cure JM community. Dr. Rutter and NCATS were honored to receive this award.

- **Visits to NIH and NCATS.** On April 3, 2024, Jed Manocherian, founder and chairman of ACT for NIH: Advancing Cures Today, and Richard Turman, M.P.P, president, visited NIH and toured NCATS Laboratories. On April 26, 2024, the European Medicine Agency (EMA) chief medical officer and data scientists visited NCATS and heard about the efforts in drug repurposing, rare diseases and drug development, and NAMs. NCATS values these interactions and partnerships with the EMA, as well as those with the FDA.

- **Congressional Briefings and Activities.** NCATS has taken opportunities to visit with Congress during briefings on Capitol Hill to discuss and showcase ongoing programs and initiatives, including drug repurposing, quantum research, and the National COVID Cohort Collaborative. In May 2024, Dr. Rutter and other NCATS staff joined legislators at a showcase of artificial intelligence (AI) and the National Artificial Intelligence Research Resource (NAIRR) Pilot. They shared updates with Senator Martin Heinrich (D-New Mexico) and his staff and with Representatives Haley Stevens (D-Michigan), Anna Eshoo (D-California), and George William Foster (D-Illinois).

Dr. Rutter informed the Council that NCATS will be moving its offices to the NCI facility in Rockville, Maryland, in June 2024. Future in-person Council meetings will be held at this facility, which is close to NCATS laboratories.

NCATS Program Updates

Dr. Rutter provided an update on NCATS programs and highlighted genomic sequencing efforts in the CTSA Program.

- **Complement Animal Research in Experimentation (Complement-ARIE).** NCATS is working to implement the goals of Complement-ARIE, which is an NIH Common Fund program supported by 17 ICs, including NCATS. Dr. Rutter briefly reviewed the program goals, which include validating mature NAMs to support regulatory use and standardization. NCATS aims to move its Tissue Chips for Drug Screening and 3-D Tissue Bioprinting programs into a regulatory space. Complement-ARIE will focus on *in silico* approaches, *in chemico* methods, and cell-free assays.

- **Preclinical Proof-of-Concept Studies for Rare Diseases (R21s).** NCATS issued a request for applications (RFA) and notice of funding opportunity (NOFO) (RFA-TR-24-023) to provide funding to test efficacy of novel agents in an established rare disease preclinical model. This RFA, a reissuance of RFA-TR-23-016, will support efficacy testing for repurposing of approved therapeutics to treat rare diseases and requires a partnership plan with a rare disease steering/oversight committee composed of experts in the field, patients, and patient advocates. Steven T. Pittenger, Ph.D., program director, Office of Drug Development Partnership Programs (ODDPP), is leading this initiative. Applications are being accepted with three receipt dates: June 2024, June 2025, and June 2026.

- **Translational Science 2024.** In April 2024, the Association for Clinical and Translational Science hosted its annual meeting, Translational Science 2024 (TS24), in Las Vegas, Nevada. Dr. Rutter and NCATS staff attended and presented highlights of NCATS programs and initiatives.

Clinical and Translational Science Awards Program Collaborative Innovation Award (CCIA)

Dr. Rutter highlighted recent accomplishments in the CCIAs, focusing on genomics.

- **Genomic Medicine in Ill Infants and Newborns (GEMINI) Study.** During TS24, the GEMINI study received a Top Ten Clinical Research Achievement Award from the Clinical Research Forum. GEMINI was launched by the Tufts University CTSA under the leadership of Jonathan M. Davis, M.D. The GEMINI team compared targeted gene sequencing (TS) with whole-genome sequencing (WGS) to identify specific genes related to rare diseases. They found that TS did not report 164 variants identified by WGS, whereas WGS did not report 19 variants found by the TS neonatal gene-sequencing test. This research demonstrates the importance of WGS to the rare disease field.

- **Early Check: A Collaborative Innovation to Facilitate Pre-symptomatic Clinical Trials in Newborns.** Early Check is a large-scale free screening research program in North Carolina that is designed to identify children with rare health conditions before their symptoms appear. Early Check began in 2018 with testing for spinal muscular atrophy and fragile X syndrome. As of September 2020, the program had screened more than 10,000 newborns across North Carolina. All families were enrolled with virtual recruitment e-consent, which was in place prior to the COVID-19 pandemic. As a result of Early Check, spinal muscular atrophy and fragile-X syndrome have been added to the standard newborn screenings in North Carolina. This program is providing evidence for how powerful WGS can be for newborn screenings.

- **Blood Cancer with Genome Sequencing.** A new technology to detect blood cancers using WGS was developed in the Washington University School of Medicine in St. Louis CTSA. The researchers used a streamlined WGS approach to obtain the genetic profiles of 253 patients with myeloid cancers who also had full cytogenetic analysis, which is the standard practice. They successfully identified all 40 recurrent translocations and 91 copy number alterations that had been identified through cytogenetic analysis and with high confidence. WGS in this context is another promising tool to use in identifying specific genetic abnormalities associated with rare diseases and ultimately may lead to more accurate treatment for these diseases.

- **Collaborative CTSA Genomics Programs.** Robert C. Green, M.D., M.P.H., Brigham and Women's Hospital, and CTSA Program colleagues conducted a real-world, randomized controlled trial to study the impact of WGS in an ethnically and racially diverse population of healthy infants. The

team considered WGS in this population as one way to screen in underserved communities, with the goal of addressing how this approach can become more routine in pediatric care. They found WGS to be a straightforward, highly regarded approach for identifying diseases in these infants. Kenneth D. Mandl, M.D., M.P.H., Boston Children's Hospital, and CTSA Program colleagues developed a federated Genomics Information Commons (GIC), which is one of the few resources to house genomic, phenotypic, and biospecimen data at scale for the CTSA Program.

Establishing a Research Network in Primary Care Settings

Dr. Rutter informed the Council that Dr. Bertagnolli envisions establishing a research network in primary care settings supported by NIH and that NCATS anticipates playing a key role. The approach is fourfold: (1) expand enrollment efforts of existing NIH studies and pilot new studies as the infrastructure is established; (2) partner with existing clinical research networks and resources, expanding with new sites, capabilities, and collaborations as the network grows; (3) engage primary care sites and community network partners on prioritizing and planning research; and (4) implement study designs across the landscape of clinical trial innovations to minimize burden on patients and providers.

NIH released a Research Opportunity Announcement (ROA), "Integrating Clinical Research Into Primary Care Settings Through Network Research Hubs – A Pilot (OT2). This ROA will establish the Communities Advancing Research Equity for Health™ (CARE for Health™). NIH invites applications for organizations to serve as "Network Research Hubs" and establish infrastructure to conduct clinical research in primary care settings as a 2-year pilot. Eligible organizations include those located in states and jurisdictions with at least 25 percent of census tracts defined as rural (per the Rural-Urban Commuting Area Codes) and those that are part of or funded by NIH Institutional Development Award Clinical and Translational Research (IDeA CTR) awards, the CTSA Program, or the National Patient-Centered Clinical Research Network (commonly called PCORnet). The timeline is to obtain perspectives from external partners to inform planning for the network in spring 2024 and host listening sessions and a public workshop in June 2024. The next step will be a quick launch in FY24 to expand existing studies — to increase their engagement with underrepresented populations and enhance their accrual and collaboration — with an anticipated budget of $5 million in OD funds. The anticipation is to expand in 2025 and beyond to launch new studies across the network and further establish and solidify the network infrastructure.

NCATS Strategic Planning 2024–2029

Dr. Rutter briefly highlighted the status of the NCATS strategic planning process for developing the NCATS 2024–2029 Strategic Plan. The strategic planning committee has drafted the strategic plan and provided copies to the Council for review and comments for discussion later in the meeting.

Summary

Dr. Rutter summarized that NCATS leadership is in place and that NIH's search for director of NLM closes July 1, 2024. The FY24 budget was enacted, and discussions are underway on the FY25 budget. NCATS has had several impactful advances and received a thank you proclamation from the Cure JM community. NCATS activities have gained interest from Congress, and discussions with the FDA and EMA are ongoing. Increased CAN support bolsters gene therapy for MMA and increases research in other CAN-related activities. NCATS is primed for contributing to the NIH director's vision of a network in primary care settings supported by NIH. The NCATS 2024–2029 Strategic Plan draft is out for final comments. The Council will hear updates from the FDA and program updates from NCATS DRDRI and DPI.

Discussion

Ms. Kennedy commended NCATS for its tremendous efforts across programs and initiatives.

Dr. Rutter confirmed that the Council will have a separate discussion and time for comments on the draft NCATS 2024–2029 Strategic Plan later in the meeting.

VI. INVITED PRESENTATION AND DISCUSSION: Regulatory Considerations for Rare Disease Gene Therapy: Peter Marks, M.D., Ph.D., Director, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, (FDA)

Peter Marks, M.D., Ph.D., presented a regulatory perspective on current progress and challenges in the field of gene therapy. Gene therapy treatments can be delivered *ex vivo* (i.e., targeted nucleases delivered to cells extracted from the body that subsequently are reintroduced to the patient) or *in vivo* (i.e., direct delivery to the patient using a delivery vehicle). Genome editing with CRISPR-based editors is increasingly being used as a modality in gene therapy. The FDA has approved approximately 20 stem cell–based, T cell–based, and directly administered gene therapies. For example, Casgevy is a CRISPR-based gene therapy approved for treating sickle cell disease and beta thalassemia. Dr. Marks reviewed the benefits of gene therapy, which can address various diseases for long-term benefit and currently generally requires only a single dose. Depending on the design of the therapy, gene therapy often has a higher probability of success than small-molecule treatments. These advantages currently are offset by several challenges, including the complexity and cost of manufacturing gene therapy treatments, the potential for irreversible side effects, the special expertise required for administering treatment, and the challenge of developing a new business model.

The FDA's CBER is partnering with NCATS to address manufacturing, clinical development, and regulatory challenges associated with gene therapies. Through the Bespoke Gene Therapy Consortium (BGTC), the NCATS -led Platform Vector Gene Therapy (PaVe-GT) project, and other collaborations, the FDA supports efforts to harmonize and automate manufacturing processes for these treatments. The FDA is working to apply the platform technology provision outlined in the Omnibus Appropriations Act of 2023 (which noted that platform technology sponsors may reference or rely upon data from a previous application for a biological product that uses the same platform technology) and is exploring the possibility of concurrent submission and review to accelerate the approval process. The science inherent in developing many gene therapies facilitates the potential use of biomarkers (that are reasonably likely to predict clinical outcomes) as endpoints to accelerate gene therapy trials.

Global harmonization efforts related to the evaluation and regulation of gene therapy products can help facilitate more efficient clinical development of these products. Toward this end, the FDA is collaborating with global partners in the Collaboration on Gene Therapies Global (or CoGenT Global) pilot project to lower the barrier to entry into a regulatory environment, increase the efficiency of the regulatory process, and reduce time and costs for agencies and sponsors on a worldwide scale. The Support for clinical Trials Advancing Rare disease Therapeutics (START) pilot program will further accelerate the pace of development for products intended to address unmet medical needs by addressing development challenges through rapid *ad hoc* communication mechanisms rather than formal meetings. Three participants will be selected to join the START pilot program.

Discussion

In response to Dr. Rutter's question about whether platform-based technology approvals would help with commercialization efforts, Dr. Marks speculated that platform technologies might help with

economies of scale, enabling a robust portfolio of commercially viable products that might not be profitable on their own.

Paul A. Harris, Ph.D., asked for more information about the START pilot. Dr. Marks explained that an FDA-based project manager will be assigned to each participating company and will be available to help address development and regulatory issues as they arise. Minor questions will be answered immediately, and meetings will be convened (rapidly and without the need to submit a briefing) to address major issues. Dr. Marks noted that the START program might address additional issues. For example, companies, especially smaller ones, sometimes struggle to understand formal correspondence from the FDA, and more informal communication might be more easily comprehended.

Annie M. Kennedy, B.S., expressed appreciation to NCATS for helping to develop gene therapies that are benefiting patients with type 1 spinal muscular atrophy. For the first time, many of these patients are living beyond their second birthdays and graduating from preschool. She asked about efforts to help patients who have antibodies to adeno-associated vectors (AAVs) and are excluded from using approved therapies and participating in clinical trials. Dr. Marks described three relevant areas of research. Such methods as plasmapheresis are being investigated to clear or reduce AAV antibodies before gene therapy. Similar approaches already have been used by hematologists and oncologists for other purposes. Alternatively, new vectors are being developed to evade AAV immunity. The third approach involves completely forgoing the use of AAVs and delivering gene therapy via lipid nanoparticles.

Joni L. Rutter, Ph.D., asked about ways to leverage small business programs to support research leading to the manufacture of new gene therapies. Dr. Marks emphasized that research should focus on ways to manufacture gene therapies more efficiently and effectively. Companies that manufacture the equipment needed to produce such treatments will be just as critical as those developing gene therapies.

In response to Ms. Kennedy's request to speak about patients eligible for new treatments who are not being diagnosed during the optimal therapeutic window, Dr. Marks noted that this issue involved several challenges. He commented that newborn screening — as well as diagnostic tests for rare diseases in general — must improve. He added that potential treatments for those who are diagnosed late also should be investigated.

Michael G. Kurilla, M.D., Ph.D., director, Division of Clinical Innovation, agreed that global demand for rare disease gene therapies would make them more attractive from a business perspective. He asked for more information about efforts to harmonize regulatory requirements on the international level, because navigating such requirements is a major obstacle for small manufacturers. Dr. Marks referenced a recent World Health Organization (WHO) Implementation Workshop held in Muscat, Oman, on May 14–15, 2024, that he attended with industry and regulatory stakeholders from around the world. Such meetings are being convened to address global regulatory challenges by developing a system whereby WHO provides international authorization for treatments approved by major regulatory authorities.

VII. PROGRAM UPDATE PRESENTATION AND DISCUSSION: Division of Rare Diseases Research Innovation (DRDRI): Dominique C. Pichard, M.D., M.S., Director, DRDRI, NCATS

Dominique C. Pichard, M.D., M.S., provided an overview of and update on DRDRI activities. She highlighted the division's staff and their efforts to develop and administer critical DRDRI programs to address the unmet needs of millions of Americans with rare diseases. Dr. Pichard shared data from the EveryLife Foundation for Rare Diseases showing that the economic burden of rare diseases in the United States — including $418 billion in direct medical costs, $437 billion in productivity loss and other indirect

costs, and $111 billion in nonmedical and uncovered health care costs — totaled approximately $1 trillion in 2019.

To address the challenge of understanding and treating rare diseases, DRDRI directs programs in three areas: data and informatics, research, and collaboration. Dr. Pichard highlighted several activities across these areas.

Impact of Rare Diseases on Patients and Healthcare Systems (IDeaS)

Dr. Pichard reminded the Council that the IDeaS program is a collaborative effort among NCATS, industry, academic institutions, and international health care companies that aims to quantify the number of patients with a rare disease and measure the direct medical costs of 14 representative rare diseases within four different health care system databases. She noted that, despite using different methods, a preliminary analysis performed by the IDeaS team showed results that were similar to those published by the EveryLife Foundation for Rare Diseases. Dr. Pichard shared health care cost data from a patient with Batten disease (an inherited metabolic disorder), demonstrating costs before and after diagnosis. Even though the patient did not receive disease-modifying therapy, the diagnosis led to better treatment for the patient, which, in turn, led to reduced health care costs.

Shortening the Diagnostic Odyssey

Dr. Pichard explained that DRDRI has awarded funding to support three research projects for studying new tools and approaches to make it easier to correctly diagnose people with rare diseases. Each of the three projects explores a different approach for speeding up the timeline for a correct diagnosis, including machine learning, genetic analyses, and medical evaluation. Dr. Pichard reviewed one of the approaches, which were required to be easy to apply and used early in patient care by frontline health care providers.

- **Project GIVE (Genetic Inclusion by Virtual Evaluation) for the Rio Grande Valley.** Seema R. Lalani, M.D., a researcher at the Baylor College of Medicine, has been funded to work with a team from Baylor and The University of Texas Rio Grande Valley to address challenges faced by Hispanic populations in the Rio Grande Valley, including poverty and lack of insurance. The program aims to reduce the time to diagnosis by using a virtual platform to deliver state-of-the-art genetic evaluations to a medically underserved population, use whole-genome sequencing to provide genetic diagnoses to Hispanic children with rare diseases, and build genomic competency by educating frontline health care providers to expedite pediatric patient referrals in the case of suspected rare disease. Since February 2022, 221 children from 209 families have been referred to the program, and approximately 80 percent of the referred children (155 children from 148 families) have been accepted. With an enrollment of 115 patients, the target enrollment of 100 children has been achieved. More than 70 families have received whole-genome sequencing results that have led to full diagnoses in 25 families (35 percent solved), as well as partially solved diagnoses for two families and a medically actionable finding for a 2-year-old patient with Brugada syndrome. These efforts can easily be replicated in other medically underserved areas with limited resources.

Rare Diseases Clinical Research Network (RDCRN)

Dr. Pichard noted that the Rare Diseases Clinical Research Network (RDCRN) (or Network) was established through the 2002 Rare Diseases Act. NIH was directed to establish regional centers of excellence around rare disease therapeutic areas. The first centers were established in 2003, and the RDCRN has consistently grown through funding recompetitions. In its fourth cycle (2019–2024), the

Network comprised 20 research consortia, 170 patient advocacy groups (PAGs), 10 NIH ICs, and 295 clinical sites in 37 U.S. states and 10 other countries. Each consortium investigates three or more related diseases or conditions; consists of multiple clinical sites; conducts three to five clinical trials; and has a competitive pilot study program, a career development core, and a fully integrated PAG. More than 200 diseases are being studied, 80 clinical studies and 13 clinical trials are being supported, and RDCRN researchers have published 1,101 articles.

- **Translational Impact.** Since its inception, the RDCRN has conducted clinical trials (small Phase 1/2) directly funded by the U54 grant, and 18 trials currently are active. Several RDCRN-associated clinical trials (Phase 2/3) are ongoing. These trials are funded by industry, IC-specific grants, the Food and Drug Administration (FDA), and PAGs, and they have leveraged patient populations, clinical endpoints, biomarkers, and safety/efficacy data. The RDCRN has contributed to 12 FDA-approved treatments for 11 rare diseases.

- **Shared Data Environment.** The RDCRN has developed a shared data environment. In this process, the operational environment takes consented data from RDCRN studies and de-identifies them. The Data Management and Coordinating Center (DMCC) provides assurances about data quality and data-use limitations and ensures that metadata are available. These data are then passed from the DMCC to the shared data environment. This environment is governed by NIH, and data access is controlled through an NCATS Data Access Committee. The data are intended to be a public resource via controlled access.

- **Websites.** The main Network site serves as a gateway to 20 linked consortium sites. Visitors can find information about RDCRN diseases, learn about RDCRN research, connect with PAGs, read the latest RDCRN news, discover funding or training opportunities, and join the RDCRN contact registry or email list.

- **Notice of Funding Opportunity.** The Network currently has an available NOFO, Rare Diseases Clinical Research Consortia (RDCRC) for the RDCRN (PAR-24-206), to invite new and renewal applications for the RDCRC. Applications will be reviewed and awarded in 2025.

Program and Initiatives

Dr. Pichard provided further updates on DRDRI programs and initiatives.

- **Platform Vector Gene Therapy (PaVe-GT).** Using a platform design for rare diseases allows multiple therapies for the same disease to be tested in the same clinical trial. PaVe-GT is a project testing the hypothesis that a platform vector approach will increase efficiency in preclinical testing and clinical trial startup. Dr. Pichard emphasized that many different NCATS divisions and offices and other NIH institutes, centers, and offices are involved in PaVe-GT, bringing broad expertise to create transformative solutions for treating rare diseases.

- **Bespoke Gene Therapy Consortium (BGTC).** NCATS, Center for Biologics Evaluation and Research, and the Foundation for the NIH (FNIH) established the BGTC, a major component of the FNIH Gene Therapy Accelerating Medicines Partnership®. The mission is to streamline regulatory frameworks to accelerate gene therapies for rare diseases. BGTC goals include making AAV technology more accessible to a broader range of diseases, accelerating the potential to streamline preclinical and product testing, facilitating scientific and regulatory advances that will ultimately benefit the entire field, and shortening the time required to bring gene therapies to all individuals in need. The first version of the BGTC playbook — a simplified

roadmap to increase the likelihood of a product's success and accessibility to patients — was released in 2024. The roadmap will be piloted with eight BGTC assets and is designed to be continually iterative (as more information is gathered) and broadly applicable to other AAV gene therapies. Knowledge is shared within and between NCATS programs. For example, the orphan drug designation section in the playbook was developed based on results from the PaVe-GT project.

- **Somatic Cell Genome Editing (SCGE) Program.** NCATS, in partnership with National Institute of Neurological Disorders and Stroke, is leading the SCGE, a Common Fund program that began in 2017. The aim is to lower the barriers to new genome editing therapies. In SCGE Phase 1 (FY 2018–2023), the overarching goal was to improve the efficacy and specificity of genome editing approaches to reduce the burden of disease. During Phase 1, SCGE investigators developed quality tools to perform and assess effective genome editing tools in somatic cells of the body. SCGE Phase 2 (FY 2023–2027) focuses on accelerating the translation of *in vivo* genome editing therapies into the clinic.

- **Targeted Genome Editor Delivery (TARGETED) Challenge Prize**. **NCATS** is sponsoring the TARGETED Challenge to advance genome editing technology by sourcing innovative solutions for delivering genome editors to somatic cells. The aim is to improve the state of technology in two target areas: developing a programmable delivery system for gene editing and crossing the blood–brain barrier. Across both target areas, 30 Phase 1 prize winners already have been announced; Phase 2 of the competition is underway. Up to 10 Phase 2 prizes of $250,000 will be announced in 2025.

Conferences and Workshops

Dr. Pichard highlighted recent conferences and workshops.

- **Natural History Studies and Registries in the Development of Rare Disease Treatments Workshop.** On May 13, the DRDRI — in collaboration with the Reagan-Udall Foundation for the FDA; the Rare Diseases Team within the FDA Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine; the FDA Office of New Drugs; and the FDA Center for Drug Evaluation and Research — hosted this public workshop. The workshop brought together rare disease patient advocates, academic researchers, regulated industry, and other key personnel to discuss considerations for using natural history study and registry data in rare disease drug development programs. Approximately 230 people attended the workshop in person, along with 3,000 virtual registrants.

- **Rare Disease Day at NIH.** Dr. Pichard highlighted the enthusiasm and energy of the approximately 600 in-person attendees of Rare Disease Day. The hybrid event enabled more than 1,000 virtual participants to attend — many of whom might have difficulty traveling to the workshop. The event, which was the first Rare Disease Day attended by Dr. Bertagnolli in her capacity as NIH director, included more than 100 exhibitors and a display of art created by people living with rare diseases who wanted to share their stories.

Discussion

Annie M. Kennedy, B.S., commended the efforts and accomplishments of the DRDRI programs and noted that they should be publicized more widely. She recommended that measures beyond the

number of approved products be used to evaluate RDCRN consortia, especially those that have been continuously funded since the Network was established.

When asked whether the 12 FDA-approved products had anything in common that led to their success, Dr. Pichard remarked that this was something that could be investigated.

VIII. PROGRAM UPDATE PRESENTATION AND DISCUSSION: Division of Preclinical Innovation (DPI): Matthew D. Hall, Ph.D., Scientific Director and director DPI, NCATS

Matthew D. Hall, Ph.D., provided an update on DPI activities. Dr. Hall shared how his experience studying drug resistance led him to a successful collaboration — and ultimately a career — with NCATS. He highlighted team leads from his research group who oversee efforts in medicinal chemistry, data science and cheminformatics, and biology. Together, they develop high-throughput screens to identify molecules for a range of undrugged targets. Dr. Hall pointed out two NCATS efforts that were incorporated into an article published in *Science* about the NIH-led research response to COVID-19. The COVID-19 OpenData Portal enabled drug repurposing data relevant to SARS-CoV-2 to be shared with the research community, and the ACTIV Tracking Resistance and Coronavirus Evolution (or TRACE) initiative focused on identifying emerging variants of SARS-CoV-2. Dr. Hall also noted his personal connection to the work at NCATS — two of his nephews have rare diseases.

DPI programs aim to support research across the entire translational spectrum, from target development projects managed by DPI's Early Translation Branch, through assay development and lead optimization programs managed by the Therapeutic Development Branch and Chemical Genomics Branch, to preclinical development and clinical trials supported by core DPI functions and trans-DPI initiatives. DPI works across NCATS to develop programs with other programs and divisions; examples include the COVID-19 serosurvey with the CTSA Program; the COVID-19 rare disease serosurvey and PaVe-GT with Division of Rare Diseases Research Innovation; the 3-D Tissue Bioprinting Program and A Specialized Platform for Innovative Research Exploration (or ASPIRE) with Office of Special Initiatives; and the Preclinical Proof-of-Concept Studies for Rare Diseases RFAs with the Office of Drug Partnership Programs. DPI programs balance research and collaboration, sharing expertise in drug discovery and development with academic, private, and patient partners who are seeking advice about translational approaches, therapeutic ideas, or candidate products.

DPI efforts have a record of clinical success that includes more than 50 IND applications, as well as drug approvals for a gene therapy for aromatic l-amino acid decarboxylase deficiency (Upstaza), a small molecule to treat chronic yeast infections (Vivjoa), and another small molecule for treating Duchenne muscular dystrophy (Agamree). Dr. Hall highlighted several DPI activities.

- **Therapeutics for Rare and Neglected Diseases (TRND)**. The TRND program is designed to overcome challenges associated with drug development for more than 6,500 rare and neglected diseases by supporting scientific and technological innovations to improve success rates in the crucial preclinical stage of development. In FY24, 10 new TRND projects were accepted. These projects — which address one neglected disease and nine rare diseases — involve collaborations with academic institutions, advocacy organizations, biotechnology and pharmaceutical companies, government agencies, and a nonprofit organization to develop treatments for such indications as fibrotic/sclerotic conditions, mycobacterial infections, neurosensory disorders, neurodevelopmental conditions, preterm infantile disorder, and pulmonary disorders. Dr. Hall shared a preview of an online tracker that will list treatment candidates being developed by the

TRND program in an interactive infographic that shows their progress through the translational pipeline.

- **Platform Vector Gene Therapy (PaVe-GT)**. PaVe-GT is a project in partnership with DRDRI that aims to test the hypothesis that a platform approach will increase translational efficiency. PaVe-GT pairs DRDRI's research networks and resources with DPI's extensive preclinical and early clinical development expertise. The goal is to use common processes to develop treatments for four diseases (two forms of organic acidemias and two forms of congenital myasthenic syndromes) and make the resulting data publicly available. Four gene therapy treatments are being developed in parallel. DPI scientists are conducting all IND-enabling studies for these products, and interactions with the FDA already have begun. Dr. Hall emphasized the importance of sharing knowledge acquired during the project (via the PaVe-GT website, publications, and email updates) to accelerate the development of therapies by other groups.

- **CURE ID.** CURE ID is a web-based platform that enables health care providers, patients, and caregivers to share information about treating patients with repurposed drugs. Since its launch in 2019, CURE ID has accumulated 691 clinician reports, 42,922 reports extracted from electronic health records, and 2,056 registered users in 134 countries. CURE ID includes a data-gathering exercise focused on Long COVID that was developed in partnership with the FDA.

- **iPSC-Derived 3-D (i3D-RARE).** The goal of the i3D-RARE project is to develop validated rare disease (i.e., patient-derived and CRISPR-edited) induced pluripotent stem cells (iPSCs) and corresponding 3-D cellular models (e.g., spheroids, organoids, tissue chips) to accelerate the development of personalized therapeutics for rare diseases. These complex cellular models will be used to demonstrate the effectiveness of candidate therapeutics as part of the preclinical regulatory process (as authorized by the FDA Modernization Act 2.0). DPI teams involved in i3D-RARE include the Probe Discovery Program, 3-D Tissue Bioprinting Laboratory, Biology and Pharmacology team, TRND, Functional Genomics Laboratory, Stem Cell Translation Laboratory, and Informatics and Research Services Cores. Pilot studies on Alagille syndrome and Friedreich's ataxia have begun, and i3D-RARE models are being incorporated into PaVe-GT. In September 2023, NCATS hosted an i3D-RARE workshop that was attended by 472 U.S. and international registrants. The event's goal was to solicit feedback from the scientific community about the i3D-RARE approach. A report summarizing the sessions — including major needs and themes identified during the event — is being developed.

Discussion

Joni L. Rutter, Ph.D., clarified that the gene therapy she described earlier in the day is being developed to treat methylmalonic acidemia — a disease that is distinct from the acidemias associated with the PaVe-GT project described by Dr. Hall. She highlighted the value and effectiveness of DPI program managers who are helping to coordinate translational work within NCATS and across NIH.

Paul A. Harris, Ph.D, asked how input from patient advocates is incorporated into decisions about program directions. Dr. Hall noted that DPI guides and collaborates with rare disease foundations and parents of patients, often through connections within DRDRI. Later-stage projects (e.g., PaVe-GT, the TRND program) require not only a development pathway and an understanding of the landscape of other therapeutics but also awareness of the need for engagement with the rare diseases community. Dr. Hall noted plans to work with Dr. Rutter to develop scientific advisory groups composed of rare diseases community members.

IX. CLEARANCE OF CONCEPTS: Presentation and Discussion

The NCATS Advisory Council received presentations on four new projects that NCATS is considering funding. After each presentation, the members discussed the proposal and voted on whether to approve NCATS' moving forward with the concept. Discussants for the concept were assigned prior to the meeting.

Introduction of the Office of Special Initiatives (OSI) Concept: Danilo A. Tagle, Ph.D., M.S., Director, OSI, NCATS

Danilo A. Tagle, Ph.D., M.S., explained that the OSI mission is to address translational problems with innovative solutions through disruptive technologies and novel partnerships with patient advocacy groups and other government agencies. All the programs within OSI adhere to NCATS' operating principles of "the three D's": developing the technology, demonstrating its utility, and disseminating the technology for use by the community. This new concept focuses on OSI's newest program — quantum information sciences.

Prize Competition in Quantum-Enabled Technologies for Biomedical Applications Concept: Geetha Senthil, Ph.D., Deputy Director, OSI, NCATS

Geetha Senthil, Ph.D., presented a new concept for a prize competition in quantum-enabled technologies for biomedical applications. A major challenge in health care is the inability to detect diseases early. The current tools in the field are unable to detect many diseases in early stages and do not accurately diagnose diseases (e.g., cancer, cardiovascular disease, neurological conditions) for timely intervention. Limitations in early detection persist, such as high background noise and low signal capability. Computational limitations include high resource needs, high costs, and the inability to use small data sets. Next-generation quantum technologies are one approach to resolving these problems. NCATS proposes this concept to catalyze the application of innovative quantum-enabled approaches to improve early detection, diagnostics, and therapeutics development.

Quantum-enabled technologies for biomedical applications harness laws of quantum mechanics to engineer and read out quantum states at the subatomic level. This comprises two components. Quantum computing, moving from the classical binary bit to the two-state quantum bit (i.e., qubit), allows for improved speed, molecular dynamic simulations, and AI and machine learning predictions. Quantum sensing provides improved resolution, sensitivity, accuracy, and precision, thus moving from a detection of more than 10,000 cells at once to atomic-scale measurements of a single cell. Next-generation quantum technologies, specifically advanced computing and disease detection, bridge the gap between these two components.

Mature quantum-specific technologies with demonstrated applications in biomedical sciences include optically pumped magnetometers for brain imaging, magnetic encephalography for pediatric epilepsy, and magnetocardiography for fetal cardiac arrythmia. Studies of these technologies are being done through Superconducting Quantum Interference Device (SQUID) systems in adults and children. SQUIDs are cryogenic, bulky, expensive, not scalable, and not easy to use in children, especially in those who have rare diseases. The quantum-enabled devices are wearable, portable, and noncryogenic; have improved signal quality; have ease of use in pediatrics; can be deployed in low-resource areas; and are scalable and less expensive.

Quantum computing-specific technology (or the end-type of technology) is in the early stages, is rapidly emerging, and can be useful in accelerating drug discovery. Current drug design tools have limited power and accuracy, require a lengthy process, and are expensive computational resources. With

quantum-enabled technologies, the field can accelerate drug discovery with increased accuracy and can simulate drug–target interactions to design safer and more effective drugs.

Several federal-wide activities in fundamental technology research are currently underway related to implementation of the National Quantum Initiative. NIH established the Quantum Information Science (QIS) Working Group that is composed of members from 12 ICs, as well as experts from the U.S. Departments of Energy (DOE) and Defense, National Science Foundation, and National Institute of Standards and Technology. NIH has convened workshops to survey quantum-technology opportunities, including the NIH Virtual Workshop: Near-term Applications of Quantum Sensing Technologies in Biomedical Sciences and the Quantum Computing for Biomedical Computational and Data Sciences: A Joint DOE–NIH Roundtable. NCATS has the opportunity to de-risk the existing quantum technologies and apply them to solve translational problems in early detection and diagnosis by advancing prototypes for real-world applications.

This proposed initiative will consist of prize challenges to catalyze the application of quantum-enabled approaches through multidisciplinary efforts. The aim is to raise awareness and to recognize and reward quantum and biomedical teams that bring innovative quantum technology solutions to biomedical fields. The Quantum Sensing Challenge will solicit applications to develop sensing approaches to enhance preclinical drug discovery using novel scalable assays, enable early detection and accurate diagnosis using ultrasensitive and noninvasive approaches, and improve patient care and health monitoring using wearable and portable technologies. The Quantum Computing Challenge is designed to develop quantum algorithms to accelerate *in silico* drug discovery and simulations; improve diagnostics, specifically for rare diseases; and perform image and genomic sequence analysis for research and clinical applications. NCATS is partnering with several ICs and offices, including the Center for Information Technology , the National Eye Institute, the National Institute of Biomedical Imaging and Bioengineering, and the Office of Data Science Strategy.

In the ideation stage, the plan is to launch prize challenges to identify innovative solutions from a wide pool of innovators (e.g., industry, academia, public). In the implementation stage, NCATS will solicit applications for the Reduction-to-Practice Challenge or other funding mechanisms to implement best solutions to advance existing quantum technologies to useful and usable products for biomedical applications. NCATS expects novel quantum-enabled technologies and devices that are more sensitive and accurate than the current methods and novel quantum algorithms that perform better than currently available classical computing methods for drug discovery and diagnostics applications.

NCATS anticipates building multidisciplinary teams of biomedical and quantum experts. These technological improvements will result in better detection, diagnostics, drug discovery tools, and patient care, which would have a significant impact in the biomedical and public health fields. Also, they will have a positive impact on the national quantum economy ecosystem. The Council was asked for input on any additional areas that should be addressed through this initiative.

Discussion

Sergio A. Aguilar-Gaxiola, M.D., Ph.D., expressed his support for the concept and asked how NCATS intends to engage with those standing to benefit the most from this technology. Dr. Senthil noted the ongoing efforts over the past 2 years to increase awareness among biomedical scientists and experts in quantum sciences, bringing the communities together to build a multidisciplinary team. NCATS OSI has convened workshops and is building these communities and is now in touch with both communities. A 2024 workshop involving industry partners is planned. OSI has regularly communicated with the federal agencies that are supporting this technology. Since the last iteration of this technology, NIH has

established the QIS and Quantum Sensing in Biology Interest Group, which is a public-facing group that conducts monthly seminars so that biomedical scientists can continue this dialogue and educate both fields in exchanging knowledge and ideas. Joni L. Rutter, Ph.D., added that opportunities to use quantum computing potentially could help with developing an algorithm to identify ways to approach the diagnostic odyssey. Dr. Aguilar-Gaxiola suggested Community Engagement Studios as one approach to model. Dr. Rutter recommended including community engagement in the guidelines of the prize competition. Dr. Tagle highlighted that use of prize competitions crowdsources the potential solutions and broadens the input from technology experts and the people who will benefit from this technology.

Annie M. Kennedy, B.S., expressed her support for this concept, which is innovatively using prize challenges to address the barriers to diagnostics and therapeutics. She encouraged considering the end user (i.e., the patient) early in the process and having partner ICs and representatives of their respective advisory councils, patients, and PAGs serve as members of the prize competition selection committee, including reviewing the technologies. Ms. Kennedy underscored that all patient needs are not created equal.

Paul A. Harris, Ph.D., asked about the mechanics of the prize competition. Dr. Senthil clarified that this concept consists of two challenges — the Quantum Sensing Challenge and Quantum Computing Challenge — across two stages, ideation and implementation. In ideation, NCATS is soliciting teams who already have prototype technologies with technical feasibility applied in a biomedical context to evaluate its performance in the novel biomedical and translational context. The quantum technology experts are expected to collaborate with researchers in the biomedical or clinical sciences. The expectation is that they will optimize and further engineer the technology into a product. Proposals selected by the NIH QIS Working Group will advance to the implementation stage. The research will be milestone driven, and the applicants who deliver a working technology will be the prize winners.

Kelly Marie McVearry, Ph.D., Ed.M., observed that NCATS is collaborating and not intending to purchase a quantum computer. She asked whether this will be a concerted effort similar to the structure of the NAIRR to address differences in quantum computers and the associated algorithms developed.
Dr. Senthil noted that this prize competition is soliciting applications that address the problem and that developers can adapt their algorithms to the hardware.

Additional comments/questions posted in the chat to all participants:

14:55:20 From Kelly M McVearry to Everyone: yeshayesha@gmail.com Dr. Yelena Yesha leads a NSF-sponsored research center with some great graduate students working on quantum computing projects with DWAVE and Ames. Happy to make an introduction so these performers have awareness of the technology challenge and opportunity to collaborate with NCATS.

Members unanimously approved the prize competition in quantum-enabled technologies for biomedical applications concept.

Introduction of Office of Policy, Communications and Education (OPCE) Concept: Penny W. Burgoon, Ph.D., Director, OPCE, NCATS

Penny W. Burgoon, Ph.D., presented an overview of OPCE's Education Branch, which aims to build a large, highly skilled, and diverse translational science workforce equipped with the competencies needed to accelerate progress along the translational pipeline toward more health solutions for all people. This new concept addresses this vision. Dr. Burgoon acknowledged the four Education Branch staff members who manage NCATS' intramural training program, pilot and disseminate innovative educational resources in translational science and produce original scholarship.

Prize Competition in Translational Science Education and Training Concept: Amanda L. Vogel, Ph.D., M.P.H., Acting Chief, Education Branch, OPCE, NCATS

Amanda L. Vogel, Ph.D., M.P.H., presented a new concept to establish a prize competition in translational science education and training. A core goal of the Education Branch is to convene, collaborate, disseminate, and amplify community expertise. This concept aligns with this goal and aims to use the prize competition mechanism as an avenue to identify, amplify, and disseminate exceptional models of translational science education and training that have been generated by this new need.

Translational science is still in development. Trailblazers in translational science education and training across academia, industry, and professional societies are developing core content and methods to convey this content to varied audiences. A need exists to identify, amplify, and disseminate exemplary models of translational science education and training from the scientific community. NCATS' vision for the field of translational science education and training is to equip the workforce with the knowledge and skills needed to improve and accelerate translational research, which is reflected in NCATS Translational Science Principles. OPCE's recent publication, Advancing Translational Science Education, highlights this vision.

NCATS proposes this concept to (1) raise awareness of translational science education and training and the value it adds and (2) accelerate dissemination of exemplary models of core content, innovative teaching approaches, and ways of reaching diverse learners across training and career stages who have a variety of roles in the translational enterprise. This prize competition will recognize, reward, and disseminate translational science education and training programs that provide content that aligns with NCATS' understanding of the field of translational science; equip learners with knowledge and skills to overcome common bottlenecks and roadblocks; leverage innovative education and training modalities; reach broad and diverse audiences; and improve access to translational science education and training. The prize competition, unlike a grant, acknowledges that work has been done and aims to broaden the applicant pool to capture diverse approaches.

Regarding the prize competition's implementation and expected impact, NCATS anticipates that it will contribute to the existing work of developing translational science as a field of study. It is expected to complement existing activities and resources, including extramural funding for translational science training and education (e.g., NCATS' online courses in translational science and original scholarship). In addition, this prize competition is expected to stimulate interest in this field, promote NCATS' vision for content and accessibility, and identify and amplify exemplars that may not have been shared broadly and accelerate their dissemination.

The Council was asked to comment on (1) ways to most effectively conduct outreach to colleagues across sectors to solicit applications and (2) approaches for leveraging existing partnerships and stakeholders to solicit applications and disseminate winners' work.

Discussion

Sergio Aguilar-Gaxiola, M.D., Ph.D., observed that the Education Branch goal and the objective of the prize competition in translational science education and training concept suggest that training is unidirectional, in educating the communities. He emphasized that communities can educate the researchers and highlighted the Association of American Medical Colleges' principles of trustworthiness, which also speak to this point. Dr. Vogel clarified that community in the context of this concept includes anyone outside of government who has developed an education or training opportunity in translational science. Using a prize competition rather than a grant extends the opportunity beyond academia to engage community members and empower them as research partners. The intent is to engage a

broader set of partners in research with unique expertise not well known in the field. Dr. Aguilar-Gaxiola will share models of community engagement to consider when leveraging this concept.

Paul A. Harris, Ph.D., commented on informing proposal reviewers that this prize competition is filling a gap and emphasized the importance of the dissemination component of the competition. He suggested that the winners contribute to the dissemination of their own work rather than use NCATS investments. He also asked whether it was easier for faculty members to win a prize competition, such as this one, and spend the funds at their respective institutions as a grant or to receive the prize money directly as an individual or outside group. Dr. Ramsey-Ewing clarified that the faculty's institution would be best to address this question and noted that faculty members can donate funds as a traditional gift to the institution to be spent as they prescribe.

Robin J. Mermelstein, Ph.D., emphasized building demand for this education-related prize competition, especially because many CTSAs have built such programs and have limited participation. She suggested including approaches for increasing and motivating demand to ensure an audience exists for dissemination. Dr. Vogel noted a common theme in how to integrate new content into an existing curriculum and said it might be one area to highlight for this concept. Approaches with easy uptake and that are easy to implement and seamless to integrate with the curriculum, self-study, or professional development can be considered. She requested input on ways to stimulate sharing of models to overcome that challenge. Dr. Mermelstein emphasized thinking about who the translators are among media and reporters and how this translational science gets communicated to the public and informs policy. She noted that this group could be another audience for the prize competition.

Members unanimously approved the prize competition in translational science education and training concept.

Introduction of Division of Preclinical Innovation (DPI) Small Business Innovation Research (SBIR) Contract Concepts: Matthew D. Hall, Ph.D., Scientific Director, DPI, NCATS

Dr. Hall noted that the two new prize competition concepts will be managed under the SBIR program and will leverage the A Specialized Platform for Innovative Research Exploration (ASPIRE) and the iPSC-Derived 3-D (i3D) RARE programs.

Scalable Generation of Organoids Derived from Human iPS Cells SBIR Concept: Catherine Chen, Ph.D., Staff Scientist, Therapeutic Development Branch, DPI, NCATS

Catherine Chen, Ph.D., presented a new SBIR concept on scalable generation of liver and brain organoids derived from human-induced pluripotent stem (iPS) cells. Human iPS cell–derived organoids are widely used as a disease model system for drug development and in research and can be generated from easily obtainable patient samples, such as skin fibroblasts and blood cells. These cells have unlimited expansion capabilities and can be differentiated into various disease-relevant, two-dimensional (2-D) cell cultures and 3-D organoids to study the disease *in vitro* and to gain an understanding of the efficacy and toxicity of drug candidates. The demand for affordable, high-quality organoids has increased, but a bottleneck exists that can be attributed to labor-intensive production and lack of scalability and batch-to-batch reproducibility.

NCATS DPI proposes this concept to improve efficiency of the methods and reduce the costs in generating iPS cell–derived liver and brain organoids for disease modeling. The objectives of this SBIR contract are to produce liver and brain organoids from iPS cells at scale and with automation, reduce the cost for organoid production over available methods, and have reproducible generation of high-quality organoids with cryopreservation capability. The key areas include generating cryopreserveable liver and

brain organoids from human iPS cells and producing cell identity markers that can be confirmed in each type of organoid. The ability to integrate assay readouts (i.e., biosensors) in organoids is desired.

Disease modeling in human iPS cell–derived organoids is a fast-growing area, but a bottleneck to scalable production of high-quality organoids remains, which NCATS aims to alleviate. NCATS anticipates that this concept will enable a broad use of iPS cell–derived organoids for disease modeling and drug screening by facilitating commercial availability of these organoids as off-the-shelf catalog products. Integrating biosensors is expected to facilitate downstream functional assays in organoids. This SBIR effort is expected to benefit the pilot projects of NCATS' i3D-RARE program.

For this contract concept, reviewers are being asked to consider the scientific, technical, and programmatic significance of the goals of the proposed research and development activity; the availability of the technology and other resources necessary to achieve the required goals; the extent of identified practical, scientific, and clinical uses for the anticipated results; and the adequacy of inclusion of women, minorities, and individuals across the life span in clinical research, if applicable. The Council is being asked for advice on who the early adopters would be and which diseases would benefit most from this research.

Discussion

Robin J. Mermelstein, Ph.D., expressed her support and enthusiasm for the concept, which has broad application and is addressing an unmet need. She commented that reducing the bottlenecks will increase uptake and accelerate the use of these models and emphasized monitoring outreach to the research community to ensure distribution is not concentrated in any one region.

Kelly Marie McVearry, Ph.D., Ed.M., is impressed with the commercialization component and noted the role of PAGs and biotechnology companies as early adopters of this research. She emphasized expanding the scope to include kidney disease models and considering the lupus population. Dr. McVearry asked about selecting models to address and whether the SBIR Phase I/Phase II award limits applied to this concept, which she noted seems constrictive. Dr. Chen clarified that the rationale for the liver and brain models was based on ongoing research within DPI and on which organoid technology is sufficiently mature to be adopted in this manner. She pointed out that this concept, if successful, could expand to other organoid models. Krishna Balakrishnan, Ph.D., M.B.A., added that the usual Phase I/Phase II award amounts (Phase I up to $300,000 and Phase II up to $2 million) would be applicable and that the Phase I statement of work will be written to ensure that the aims of the concept are achievable. He explained that NCATS might focus on certain platform-building capabilities, such as reproducibility. Joni L. Rutter, Ph.D., called attention to the models that will be developed in the Complement-ARIE program in parallel to this SBIR concept. Dr. Balakrishnan commented on potential interest from private investors after companies have successfully solved the critical proof of concept or feasibility problem.

Members unanimously approved the scalable generation of organoids derived from human iPS cells SBIR concept.

Development of a Versatile Small Footprint Benchtop Device to Perform Batch Evaporation Concept: Samuel G. Michael, Chief, Information Technology Resources Branch (ITRB); Director, Research Services Core, NCATS

Samuel G. Michael presented a new SBIR concept to develop a versatile small footprint benchtop device to perform batch evaporation. In organic chemical synthesis, evaporation plays a crucial role in concentrating and purifying reaction mixtures, isolating products, and removing solvents or other volatile components. The challenge is in integrating an automated evaporation step into a broader

workflow for automated chemical synthesis (ACS). NCATS has focused on the automation of high-throughput screen automation of biology for two decades and — coupled with more than 20 years and billions of dollars of investment by industry — has worked to overcome this and other challenges and bottlenecks. Similar investment has not been made in the automation of chemistry.

NCATS proposes this concept to develop a batch evaporation device capable of evaporating multiple high-recovery vials simultaneously for an organic chemical synthesis process. The objective is to develop a batch evaporator that can be used as part of an ACS workflow that can reach 90 percent total evaporation in less than 10 minutes for common solvents used in ACS. The batch evaporator must be able to use high-recovery vials as specified by NCATS, be suitable for use within ACS workflows, be automation friendly and have an application programming interface.

Regarding implementation and impact, NCATS has patented a batch evaporation prototype device, developed using intramural resources in the ASPIRE program, and interest from other laboratories engaged in similar work remains high. NCATS' support of a commercial device with improvements will help overcome a key bottleneck in ACS workflows. NCATS anticipates that providing this device to the broader research community would also help overcome the key rate-limiting step in ACS workflows. A successful program would result in the availability of an off-the-shelf device that could be integrated into the ASPIRE Laboratory. NCATS intends to provide nonexclusive licensure to applicants producing a device meeting the criteria previously described.

For this contract concept, reviewers are being asked to consider the scientific, technical, and programmatic significance of the goals of the proposed research and development activity; the availability of the technology and other resources necessary to achieve the required goals; the extent of identified practical, scientific, and clinical uses for the anticipated results; and the adequacy of inclusion of women, minorities, and individuals across the life span in clinical research, if applicable.

Discussion

In response to a question from Kelly Marie McVearry, Ph.D., Ed.M., about use cases beyond biomedical research, Mr. Michael noted cooking applications, chemical fume hoods, and food processing or food technologies as other potential applications.

Dr. McVearry asked whether offering successful SBIR recipients exclusive licenses poses a concern for NCATS, especially if a small business thinks that it cannot commercialize its product after making a multiyear investment to develop a prototype and manufacture and scale production. Mr. Michael explained that NCATS would be open to offering exclusive licenses to applicants who have successful products and noted the time to execute those agreements, which could extend beyond the SBIR award period. Dr. Balakrishnan added that during product development cycles, companies can file for follow-on patents and would automatically start accruing protection for their products. He noted that an exclusive license would not be an advantage.

Keith J. Mueller, Ph.D., asked whether success would be measured by the utilization of the product or based on widespread adoption, and whether the concept would apply to non-chemists who are doing chemical research. Mr. Michael explained that market research on approaches to overcome bottlenecks in the ACS workflow is being conducted under the ASPIRE program; he highlighted purification as a major bottleneck, as well.

Members unanimously approved the development of the versatile small footprint benchtop device to perform batch evaporation SBIR concept.

X. SPECIAL TOPIC PRESENTATION AND DISCUSSION: NCATS 2024–2029 Strategic Plan: Meredith D. Temple-O'Connor, Ph.D., M.S., Chief, Policy Branch, Office of Policy, Communications and Education (OPCE), NCATS

Meredith D. Temple-O'Connor, Ph.D., M.S., explained that the day's discussion would focus on input from the Council about the draft NCATS Strategic Plan for 2024–2029. She reviewed the planning timeline from 2022 to the present. Following this discussion, the next step will be to finalize the strategic plan and disseminate it to the public in July 2024. The key theme throughout the planning process has been engagement with all NCATS' constituents, both internal and external. Dr. Temple-O'Connor reminded the Council of the in-depth conversations across the constituent communities, a request for information (RFI) (NOT-TR-23-027) to gather comments on the draft framework, the town halls, and meetings with the NCATS leadership team. NCATS received more than 1,700 comments, which the planning team synthesized using an NIH tool. Several key topics emerged among the communities, with common themes that informed the strategic plan.

The strategic plan framework encompasses the RFI comments and NCATS' vision (more treatments for all people more quickly) and resulted in five goals:

- Goal 1: Apply approaches to foster the identification of, development of, and access to more treatments.
- Goal 2: Enable all people to contribute to and benefit from translational science.
- Goal 3: Accelerate translation by addressing both scientific and operational challenges.
- Goal 4: Broadly utilize research and operations that cut across translational science efforts.
- Goal 5: Work together as stewards for advancing translational science to promote transparency, integrity, accountability, and social responsibility.

Dr. Temple-O'Connor acknowledged the planning committee for its team effort and expressed appreciation to OPCE Policy Branch staff, Jessica C. Walrath, Ph.D. and Jennifer M. Beierlein, Ph.D., for their tremendous effort in organizing and coordinating this process. She also acknowledged NCATS constituents (internal and external), who have been engaged from the beginning, and NCATS staff for their support and engagement. She noted that that the draft strategic plan, posted on the NCATS Strategic Plan website, will be out for public comment until June 14, 2024. Input is being collected via NCATS2024StrategicPlan@mail.nih.gov.

Discussion

Joni L. Rutter, Ph.D., explained that NCATS would like feedback from the Council members on their favorite goal or objective, whether these goals and objectives align with NCATS' vision and mission, and whether any areas are missing the mark.

Sergio Aguilar-Gaxiola, M.D., Ph.D., commended NCATS on the strategic plan and remarked that the process included engagement. He expressed that Goals 2 and 5 are his favorites, and he highlighted that the Goal 2 objective related to establishing and building trust is critical. He commented on the importance of trustworthiness conveyed by organizations, including NCATS, and in academic health and noted that this term is missing in the plan.

Keith J. Mueller, Ph.D., noted that Goal 2 is his favorite because it is inclusive of the rural population, whose needs are not always considered. He also noted that the Patient-Centered Outcomes Research Institute (PCORI) begins with asking research questions before the study designs and the goals are written. This strategic plan can consider PCORI's model.

Paul A. Harris, Ph.D., favors Goal 3 and the objectives that fit with NCATS' approach to address generalizable problems. His next favorite is Goal 2.

Kelly Marie McVearry, Ph.D., Ed.M., commented on how Goals 1–3 focus on engaging communities and aligning with NCATS' core mission and that they amplify a future message of inclusivity in translational science.

Dr. Rutter noted that Goal 4 is seemingly less tangible because of its crosscutting nature. She pointed out that the majority of NIH IC directors favor Goal 5 and advancing translational science. She commented that the goals are lofty and that all may not be achieved to the same extent. Some may fail, but the aim is to continue moving forward (or "failing forward") and making progress. Dr. Temple-O'Connor added that Goal 4 is the most challenging to address and that NCATS heard from its constituents that they appreciate not being siloed and having a strategic plan that maps perfectly to an organization. NCATS is venturing to do both, using teams to solve problems. This plan is a living document, where the goals, especially the Goal 4 objectives, will crosscut Goal 3. Dr. Temple-O'Connor reiterated that the strategic plan will not be a document that sits on a shelf permanently but one that will be subject to evaluations of progress.

In terms of what is missing, Dr. Aguilar-Gaxiola noted the limited emphasis in local communities (e.g., in neighborhoods) and on the factors that contribute to disease and noted an opportunity to assess and intervene in the many factors that impact health and lead to disparities. He also noted that NIH Director Monica M. Bertagnolli, M.D., in her remarks to the Council, highlighted her lived experience with community engagement and spoke about the United States investing 19 percent of its gross domestic product in health but still having higher mortality rates than other nations. FDA Commissioner Robert M. Califf, M.D., who was a principal investigator in the Duke University CTSA, presented similar statistics. These big picture aspects of health should be reflected in the plan. Dr. Rutter agreed and emphasized the opportunity to work closely with primary care networks, Federally Qualified Health Centers, community health centers, community advisory boards, and CTSA program communities. She also emphasized expanding Goal 2.

Dr. Mueller noted that Goal 2 objectives are exciting but challenging. One approach to engaging constituents in hard-to-reach communities is using digital health technologies to support decentralized trials. For objective 2.3, he noted that work is ongoing with the Health Resources and Services Administration's National Advisory Committee on Rural Health and Human Services to use technology to overcome barriers to access in rural and underserved communities. Dr. Aguilar-Gaxiola mentioned using the term "hardly reached" population to place the onus on researchers and the health care system rather than the population. Dr. Rutter summarized the discussion and reminded the Council that their comments can be submitted until June 14, 2024.

XI. PUBLIC COMMENTS

Joni L. Rutter, Ph.D., invited Catharine E. Krebs, Ph.D., medical research specialist, Physicians Committee for Responsible Medicine (PCRM), to provide her comments.

Dr. Krebs thanked NCATS for the opportunity to participate in the public comment period of the meeting. She conveyed that PCRM commends the great progress in advancing human-specific non-animal research at NIH, including ongoing programs, such as the Advisory Committee to the Director Working Group on Catalyzing the Development and Use of Novel Alternative Methods to Advance Biomedical Research and the newly approved Complement-ARIE program. Dr. Krebs highlighted the important role that scientific review and the NIH Center for Scientific Review (CSR) play in the successful

use and deployment of NAMs, as well as a few measures that can help ensure NAMs are evaluated in a constructive and equitable manner.

PCRM encouraged NCATS to play a key role in including specific review criteria in NOFOs; broadening the pool of NAM expertise available for scientific review groups; creating NAM-specific funding streams; and training reviewers to identify, address, and report incidences of animal method bias. CSR is already working to implement this last measure by expanding its bias awareness and mitigation training to include information and vignettes about scientific bias — the preference for one's own science or approach. Broader efforts to communicate the value of translational science are laid out in the draft strategic plan. PCRM supports this goal and encourages NCATS to clarify in the strategic plan the importance of scientific review in advancing NAMs and translational science, and to include specific measures previously described in this meeting to help reduce translational science roadblocks.

PCRM enthusiastically supports NCATS' exemplary strategic planning activities, which have included open and comprehensive gathering of stakeholder input through roundtable discussions, an RFI on the draft strategic plan framework, and an RFI on the draft strategic plan itself. PCRM encourages NCATS to share the success of these approaches with other ICs and offices and the NIH-wide strategic plan team to inspire similar efforts.

Dr. Rutter explained that PCRM sent NCATS a letter elaborating on this topic, which will be shared with the Council.

Other comments from the public were accepted until June 14, 2024 (15 days after the meeting) and will be appended to the minutes.

XII. ADJOURNMENT OF THE OPEN MEETING

Joni L. Rutter, Ph.D., thanked the participants for their input. The next meeting is scheduled for September 19–20, 2024, and is planned as an in-person session. Dr. Rutter adjourned the meeting on May 23, 2024, at 4:37 p.m. ET.

XIII. CERTIFICATIONS

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

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Joni L. Rutter. Ph.D. Date
Chair, NCATS Advisory Council
Director, National Center for Advancing Translational Sciences, NIH

_____ _____

Anna L. Ramsey-Ewing, Ph.D. Date
Executive Secretary, NCATS Advisory Council
Director, Division of Extramural Activities, NCATS