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

33rd Meeting of the
Advisory Council

Minutes of Virtual Meeting
May 25, 2023

The National Center for Advancing Translational Sciences (NCATS) Advisory Council held a meeting in open session on May 25, 2023, from 1:03 p.m. to 5:31 p.m. EDT via National Institutes of Health (NIH) VideoCast and in Building B, Room 377, 9800 Medical Center Drive, Rockville, 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 25, 2023, from 11:01 a.m. to 12:06 p.m. EDT for the review and consideration of grant applications.

NCATS ADVISORY COUNCIL MEMBERS PRESENT

Chair

Joni L. Rutter, Ph.D., Director, NCATS (virtual)

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.
Matthias Kretzler, M.D. (virtual)
Kelly Marie McVearry, Ph.D., Ed.M.
Robin J. Mermelstein, Ph.D.
Keith J. Mueller, Ph.D.
Paula K. Shireman, M.D., M.B.A.
Annica M. Wayman, Ph.D.

***Ad Hoc* Council Members**

None present

Representative Members

None present

Ex Officio Members

None present

Others Present

Ron Bartek, M.A., Friedreich's Ataxia Research Alliance; NCATS Alliance
Catherine Krebs, Physicians Committee for Responsible Medicine
NCATS leadership and staff

I. CLOSED SESSION OF THE NCATS ADVISORY COUNCIL

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

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

Review of Grant Applications

The Council reviewed 87 research, research-related and training grant applications with primary assignment to NCATS for a requested amount of $42,727,333 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

Dr. Rutter adjourned the closed session of the NCATS Advisory Council meeting on May 25, 2023, at 12:06 p.m. EDT.

III. CALL TO ORDER, OPEN SESSION

Dr. Rutter called the meeting to order and welcomed members and guests to the 33rd meeting of the NCATS Advisory Council and the first with in-person attendance in three years. 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 videocast.

IV. APPROVAL OF MINUTES: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council

Members unanimously approved the minutes from the January 2023 Council meeting.

V. CONFIRMATION OF DATES FOR FUTURE MEETINGS: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council

Dr. Ramsey-Ewing confirmed the schedule for the meetings of the NCATS Advisory Council for 2023, 2024, and 2025:

- Sept. 28, 2023
- Jan. 18–19, 2024 (virtual meeting)
- May 23, 2024
- Sept. 26, 2024
- Jan. 30–31, 2025 (virtual meeting)
- May 22, 2025
- Sept. 25, 2025

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

Dr. Rutter began by providing a recap of the January 2023 meeting, which was her first meeting as director of NCATS. During that meeting, she conveyed that NCATS is standing on a firm foundation heading into the next decade, building on impactful advances. She remarked on the growing excitement

for engaging with stakeholders and added that NCATS is looking forward to continuing discussions on creating the next iteration of the NCATS Strategic Plan.

Dr. Rutter presented updates on NIH and NCATS staff changes, including staff and leadership transitions; made announcements; and reported on the fiscal year 2023 (FY23) budget. She highlighted progress in some of the NCATS offices, divisions, and programs and discussed COVID-19 activities. Dr. Rutter noted that Clare K. Schmitt, Ph.D., acting deputy director, NCATS, will moderate the discussions.

NIH and NCATS Staff Changes, Recruitments, and Retirements

Dr. Rutter reminded the Council that the NIH institutes and centers (ICs) and Office of the Director are conducting several leadership searches and have positions to fill. Various positions are open at the Center for Information Technology, Fogarty International Center, and National Institute of Allergy and Infectious Diseases. The search is ongoing for new directors of the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) and Office of Legislative Policy and Analysis. DPCPSI manages the NIH Common Fund Program, with which NCATS works closely.

President Joseph R. Biden has nominated Monica M. Bertagnolli, M.D., to become the new NIH director. Dr. Bertagnolli currently is National Cancer Institute (NCI) director, and her confirmation, which will be a lengthy process, will be conducted by the U.S. Senate. Lawrence A. Tabak, D.D.S., Ph.D., is continuing to serve as acting NIH director. As nominee, Dr. Bertagnolli will meet with individual members of Congress, a process that will be managed by the Department of Health and Human Services (HHS). Once confirmed, Dr. Bertagnolli can begin her role as NIH director. After the NIH director process concludes, the NCI director position will need to be filled, but that nominee does not require Senate confirmation.

Dr. Rutter noted that NCATS has several active leadership positions to fill across divisions and offices, which she, as director, has been able to address for the past six months. Searches are at various stages, and staff have been serving in acting positions in the interim. Updates will be provided at the September 2023 Council meeting.

Dr. Rutter welcomed Geetha Senthil, Ph.D., as the new deputy director, Office of Special Initiatives (OSI), who will be working with Danilo A. Tagle, Ph.D., M.S., director, OSI. Prior to coming to NCATS, Dr. Senthil held a variety of positions in the National Institute of Mental Health, including deputy director of the Office of Genomics Research Coordination and program director in the Division of Translational Research. Dr. Senthil also spent time as a policy analyst in the Office of Portfolio Analysis, DPCPSI. Prior to joining NIH, Dr. Senthil worked as regulatory project manager for clinical trials in the Office of Biostatistics and Epidemiology in the Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA). In addition, Dr. Rutter co-chairs the Quantum Information Sciences and Quantum Sensing in Biology Interest Group, along with Susan Gregurick, Ph.D., Office of Data Science Strategy, and Dr. Senthil served as programmatic lead of this group and has worked across HHS in this area.

Dr. Rutter informed the Council of two retirements from NCATS: Samuel Bozette, M.D., Ph.D., chief medical officer since 2019, and director, Office of Translational Medicine (OTM), and Antonette Neal, assistant for the Council and Committee Management and to the Office of the Director, DEA. Dr. Bozette retired in April 2023 and was an expert in infectious diseases, was involved with clinical trials, and had a career that influenced HIV policy and other types of infectious disease policies and economics. Dr. Bozette helped establish OTM during the COVID-19 pandemic, and his infectious disease expertise was invaluable. He worked with the Accelerating COVID-19 Therapeutic Interventions and Vaccines

(ACTIV) program—particularly, the ACTIV Master Protocol 1 of Immune Modulators (commonly called ACTIV-1 IM) and the newer trial Strategies and Treatments for Respiratory Infections and Viral Emergencies (commonly called STRIVE). Lastly, Dr. Bozette played a critical role in the National COVID Cohort Collaborative (N3C) data access processes.

Ms. Neal retired after 30 years of government service and has been with NCATS since its inception, has been a critical member of the Council and Committee Management teams behind the scenes, and has worked with Dr. Ramsey-Ewing, director, DEA, NCATS.

Announcements and Events

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

- **NCATS Budget At-a-Glance.** The overall budget for NCATS encompasses the Clinical and Translational Science Awards (CTSA) Program (68 percent) and all other activities (32 percent). The CTSA Program funds a nationwide network of research institutions with consortium-wide resource centers and collaborative initiatives. Of the other activities, the budget supports intramural and extramural programs, including drug repurposing, tissue chips, diagnostics, ethics, training, and the Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) programs. Funding for other activities also includes the Cures Acceleration Network (CAN), which stimulates transformative efforts using a platform approach and enables patient-centric innovations for studying, treating, and diagnosing rare diseases. Dr. Rutter noted that the budget process begins with the release of the President's budget proposal, which typically occurs in February. The President released the fiscal year 2024 (FY24) budget proposal in March 2023 and projects a flat budget across the federal government. The conversations around the FY24 budget are just beginning, and further updates will be provided at future meetings.

- **Rare Disease Day (RDD) at NIH.** NCATS partners with the NIH Clinical Center (Clinical Center) to host the annual RDD at NIH, which brings together all the voices (e.g., scientists, clinicians, funders, patients, patient advocates) and leaders within the rare diseases community. This year's event was held in person at the NIH Main Campus on February 28, 2023, and was live streamed via NIH VideoCast. More than 550 attended in person, and more than 1,750 tuned in virtually. This highly coordinated effort was led by Alice Chen Grady, M.D., program officer, Division of Rare Diseases Research Innovation (DRDRI); Meera Shah, M.P.H., program administrator, DRDRI; and Ainslie Tisdale, program analyst, DRDRI. Special guest panelists included Brian Wallach, J.D., amyotrophic lateral sclerosis (ALS) patient and co-founder of I AM ALS, who shared his story about his ALS journey. Mr. Wallach was joined by his wife and caregiver, Sandra Abrevaya, J.D., co-founder, I AM ALS. Other stories were shared by people with other rare diseases, teachers who are training the next generation of rare disease researchers, scientists, and patient advocates. Many of the aforementioned speakers described collaborations with academia and industry. The RDD 2023 ended with the announcement that the Food and Drug Administration (FDA) had approved a drug to treat Freidrich's ataxia. The next RDD is being planned for February 2024.

- **Association for Clinical and Translational Science (ACTS) Meeting.** ACTS held its annual meeting (Translational Science 2023) in April 2023 in Washington, D.C., and it was well attended. The CTSA principal investigators (PIs) met in a town hall session hosted by Dr. Rutter; Michael G. Kurilla, M.D., Ph.D., director, Division of Clinical Innovation (DCI); and Erica K. Rosemond, Ph.D.,

acting deputy director and chief, CTSA Program Branch, DCI, NCATS. The aim was to exchange ideas and discuss current issues related to clinical trials, collaborations and data (clinical and real-world) and to consider ways to engage and capitalize on opportunities in the future.

- **Advanced Research Projects Agency for Health (ARPA-H).** Dr. Rutter explained that NCATS has been engaged with ARPA-H since its launch within HHS and noted that the agency is in the early stages of its mission. In February 2023, ARPA-H leadership toured NCATS Laboratories (NCATS Labs). Dr. Rutter noted that ARPA-H will not have an intramural program or laboratories. The ARPA-H leadership was provided an opportunity to understand NCATS' capabilities and translational science efforts. Dr. Tagle is NCATS' central point of contact. Dr. Rutter expects to provide updates as interactions progress.

- **Tissue Chips in Space Program.** The final launch of the Tissue Chips in Space Program occurred on March 14, 2023; the Office of Special Initiatives sent two cardiac organoids to study heart function and therapeutics under microgravity conditions. These chips have been returned to earth and are being evaluated. Drs. Rutter and Tagle were present at the launch and met scientists and researchers who have been working on this project.

- **NCATS Alliance.** The NCATS Alliance (Alliance) was launched in March 2023. The organizations comprising the Alliance work independently from NCATS to raise awareness about the center's efforts to advance translation and improve health. Rachel Sher, J.D., M.P.H., partner, Manatt, Phelps & Phillips, LLP, is lead counsel for the Alliance. Ms. Sher, who has vast policy and legislative experience in bioscience and regulatory processes, including with the FDA, and former CAN Review Board vice chair Ronald Bartek, M.S., president, Friedreich's Ataxia Research Alliance, have enlisted eight initial partners to help advance translational science activities. The overarching goal is to help bring treatments to people faster. Dr. Rutter highlighted that the Alliance also visited NCATS Labs to better understand the ongoing activities. Further details can be accessed on the Alliance website.

- **Children's Inn at NIH Visit.** In April 2023, NCATS hosted a dinner at the Children's Inn at NIH to serve the community of families lodging at the Inn while their children receive treatment at NIH. Audie A. Atienza, Ph.D., program officer, Digital & Mobile Technologies Section, DCI, organizes this volunteer effort twice per year. Jennie Lucca, CEO, Children's Inn at NIH, and her staff play an important role in bringing children and families to NIH for clinical trials and studies while providing all the comforts of home. Dr. Rutter considers the staff at the Children's Inn at NIH to be key translational scientists because of their long-standing tradition of managing this activity.

- **Translational Science Principles.** NCATS recently published eight translational science principles, which Dr. Rutter reviewed. She highlighted that NCATS is revamping the internal NCATS Director's award categories to match each of the eight principles. NCATS also is printing stickers and magnets to distribute at scientific meetings, training events, and recruiting events. Dr. Rutter and NCATS hope that these items will remind people of translational science approaches and help to keep these principles at the forefront of their work. Further details can be found on the NCATS Translational Science Education & Training webpage.

NCATS Strategic Planning 2024–2029

Dr. Rutter briefly highlighted the status and timeline of the NCATS strategic planning process for developing its 2024 strategic plan. She noted that a detailed report will be provided later in the meeting.

NCATS began initial stakeholder engagement in November 2022. Activities consist of convening virtual roundtables encompassing an overview of NCATS; highlights of the audacious goals (i.e., more treatments to all people more quickly), with icebreaker questions; and discussions guided by questions to help understand the various perspectives across interested parties. NCATS recognizes this process as an opportunity to co-design the strategic plan, with input from diverse stakeholders so that all can take ownership.

NCATS COVID-19 Response Updates

Dr. Rutter provided an update on NCATS COVID-19–related activities. She noted that May 11, 2023, marked the end of the federal COVID-19 public health emergency declaration. All authorizations to collect certain types of public health data have expired. NCATS has established its resources, databases, and programs, such that they do not rely on the public health emergency authorizations or declarations. Most of the COVID-19 clinical trials activated during this period will be closing.

- **Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Clinical Trials.** Most of the ACTIV trials have ended, with the exception of ACTIV-6. The metformin arm of the trial, which is the final of five drugs to be evaluated during the 5-year study, will open for enrollment in July 2023. Research (COVID-OUT study) has demonstrated that metformin treatment prevents Long COVID or post-acute sequelae of SARS-CoV-2 infection. This phase of the ACTIV-6 trial will evaluate a primary endpoint of time to recovery from acute symptoms, with a 6-month follow-up.

- **COVID-19 OpenData Portal.** A new feature will be added to the COVID-19 OpenData Portal to incorporate an N3C component for real-world data. This portal provides a high-level summary of all SARS-CoV-2 therapeutics that have been created, tested and curated over the course of the COVID-19 pandemic. Data will continue to be updated, and new features are planned for this resource.

- **National COVID Cohort Collaborative Paxlovid™ Use Characterization Report.** In March 2022, the White House COVID-19 Response Team requested that NCATS examine Paxlovid (nirmatrelvir/ritonavir) use in the N3C Data Enclave and prepare a report addressing urgent public health questions about this drug. Data analysis revealed that of the 2.5 million adults with a COVID-19 diagnosis in the N3C database after emergency use authorization of Paxlovid in December 2021, roughly 1.3 million met the eligibility criteria based on guidelines from NIH, the FDA, and the Centers for Disease Control and Prevention (CDC). A total of 1 million study-eligible participants met the strict criteria for the electronic health record–based Paxlovid target trial emulation study. Results revealed that Paxlovid adoption was initially low, increased rapidly after 3 months, and then stabilized with widespread utilization. On average, 9 to 15 percent of the presumed eligible adults received Paxlovid, with the highest being 40 to 50 percent in some regions. In addition, many leading demographic, social determinants of health, and behavioral-related predictors, as well as health systems–related variables, aligned with whether presumed eligible persons in N3C received Paxlovid or not. Furthermore, the data on real-world effectiveness of Paxlovid in N3C showed that N3C COVID-19 patients who were prescribed Paxlovid had significantly reduced hospitalizations and mortality, findings that were robust even when accounting for multiple sensitivity analyses. Actual calculations of deaths and hospitalizations that were prevented in the follow-up period were possible and then used to make projections. In fact, projections illustrated that if prescribed to 50% of presumed eligible patients, Paxlovid could have prevented an estimated 48,000 deaths and 135,000

hospitalizations. A preliminary report was submitted to COVID-19 response coordinator Ashish K. Jha, M.D., in mid-April 2023 and a final report in May 2023. These findings have been uploaded to *medRxiv* as of the date of this meeting. Dr. Rutter acknowledged and thanked the internal DCI team for leading this effort and the CTSA Program, Clinical Trial Readiness Program, collaborators and patients for their support.

Impact Stories Across NCATS

Dr. Rutter highlighted some ways that NCATS programs have been impactful across several areas, as well as notable achievements.

- **Advancement of Women in Biomedical Careers.** The Women Scientists Advisors (WSA) committee subgroup within the Division of Preclinical Innovation (DPI) launched a new initiative in 2022 that provides outreach and engagement to local communities (e.g., Bethesda, Maryland; Washington, D.C.) with students in grades K–12. Women scientists from DPI host panel discussions about science careers with students in grades 6–12 and conduct role-playing activities developed by the WSA with students in grades K–5. This initiative increases visibility of women scientists and encourages development of students' scientific literacy while showing that science and scientists are relatable and that everyone interested can have a job in science.

- **Rebecca Jackson Award for Outstanding Achievement in Education Innovation.** Cynthia D. Morris, Ph.D., M.P.H., professor and assistant dean, Oregon Health & Science University, is the inaugural recipient of the Rebecca Jackson Award for Outstanding Achievement in Education Innovation. ACTS established this award in 2023 in memory of Dr. Jackson, who was the founding director of The Ohio State University Center for Clinical and Translational Science and a former NCATS Council member.

- **Institutional Mentored Career Development Award (KL2) Scholars.** Dr. Rutter highlighted two recent KL2 scholars and their research. Caroline M. Hsu, M.D., M.S., nephrologist, Tufts Medical Center, is investigating the prevalence of unrecognized infection and duration of response of serial SARS-CoV-2 antibody titers in COVID-19–vaccinated dialysis patients. Dr. Hsu found a high rate of undiagnosed SARS-CoV-2 infections among patients receiving maintenance dialysis, supporting the need for ongoing precautions, such as wearing a mask in dialysis facilities. These data also revealed that serial vaccine re-dosing is likely needed in this vulnerable population. Jill Roberts, Ph.D., assistant professor of neurosurgery and neuroscience, University of Kentucky College of Medicine, is studying treatments for Moyamoya Syndrome, which is a rare condition that causes the internal carotid arteries in the brain to become narrow or blocked, requiring invasive surgery in these patients. Dr. Roberts generated a novel mouse model using micro-coils to decrease blood flow, thus alleviating this blockage. This model is promising to enable treatment development, particularly beneficial in Kentucky, which has a higher prevalence of Moyamoya than other regions in the United States.

- **Rare Disability: Complete Sensory Neuropathy.** Peggy Mason, Ph.D., neuroscientist, The University of Chicago CTSA (Institute for Translational Medicine), has been working with Kim Stenger, J.D., who is the only person in the world with a rare condition classified as "complete sensory neuropathy," to better understand the cause of this disability. With this condition, a person has no pain, no sense of touch, and no temperature sensation. Dr. Mason, Ms. Stenger and the Institute for Translational Medicine are developing a documentary to teach the public about this disability and to highlight the research. A 2-minute trailer of this documentary

currently is available on YouTube. In addition, CBS News Chicago did a feature story on Ms. Stenger's journey. Dr. Rutter noted that this is one example of how the CTSA Program's work can influence and support science because of the hope it can offer to, and effect it can have on, people living with similar kinds of conditions.

- **The Walkability Project.** Debbie Oto-Kent, M.P.H., executive director, Health Education Council (HEC), member of the University of California, Davis (UC Davis) Center for Reducing Health Disparities (CRHD), and community advisory board (CAB) member of UC Davis CTSA (Clinical and Translational Science Center), is leading the Walkability Project. This project, designed to improve the health of residents in a Northern California community, is included in the National Academy of Medicine (NAM) program on Assessing Meaningful Community Engagement.
  Dr. Oto-Kent and UC Davis CRHD colleagues recently released assessment instruments important for community engagement programs. Dr. Rutter thanked Council member Sergio A. Aguilar-Gaxiola, M.D., Ph.D., who co-chaired this NAM project and also is director, UC Davis CRHD. The HEC–UC Davis CRHD team developed a 4-minute video that discusses how living in this area, which is considered a food desert, was not linked to health outcomes as expected. It was more about a community's feeling safe and connected, with the ability to walk around on pavement that is well cared for as they navigate their community.

- **University of Arkansas for Medical Sciences (UAMS) Translational Research Institute (TRI) Trainee Startup Company.** Two postdoctoral fellows (Megan Reed, Ph.D., and Julia Tobacyk, Ph.D.), award recipients in the UAMS TRI's Health Sciences Innovation and Entrepreneurship (HSIE) Training Program, are studying neonatal opioid withdrawal syndrome. Efforts have focused on evaluating buprenorphine, a drug known to help with opioid addiction and withdrawal in pregnancy. An active metabolite, norbuprenorphine, is implicated in neonatal opioid withdrawal syndrome. Eliminating this metabolite would reduce these effects. The HSIE team (postdoctoral fellows and their advisors) working on this project developed and tested a deuterated buprenorphine that does not metabolize to norbuprenorphine in mouse models. The next steps will be to evaluate this agent in humans and move forward to commercialization by the new UAMS startup company, Pediatrica Therapeutics, LLC. The successful outcome would enable pregnant individuals to undergo withdrawal more safely and with less effect on their children.

- **NCATS Small Business Innovation Research Success Story.** From to 2018 to 2021, NCATS awarded about $2 million in SBIR grants to support Intabio, Inc., which is developing a prototype device (Blaze System™) for determining characteristics and molecular structures of biologics to streamline and accelerate the process of moving these products to the clinic. With a Phase 2 SBIR grant, the company further refined and equipped the device for commercialization. In 2021 Intabio was acquired by SCIEX for an estimated $40 million. An NCATS SBIR grant helped Intabio to obtain additional seed funding and technical partners, shape the strategic direction of the company, and move from a startup company to a fully owned subsidiary of an established leader in the field.

- **Developing and Streamlining Approaches.** NCATS has a significant presence in the gene therapy space, has led several efforts across NIH, and has three main programs that span the clinical trial readiness continuum of development to a clinical trial. These programs include Somatic Cell Gene Editing (SCGE), the Accelerating Medicines Partnership® (AMP) Bespoke Gene Therapy Consortium (BGTC), and Platform Vector Gene Therapy (PaVe-GT). Dr. Rutter further elaborated on the PaVe-GT project, which is on schedule to begin a clinical trial in 2024 and addresses

scientific and operational bottlenecks. NCATS initiated this collaboration with the National Human Genome Research Institute, National Institute of Neurological Disorders and Stroke (NINDS), and Clinical Center to develop gene therapies for four rare diseases, with a goal to publicly share the scientific and regulatory experience gained at different stages of implementing the platform. In 2023, the PaVe-GT team successfully obtained FDA orphan drug designation (ODD) and rare pediatric disease (RPD) designation for an adeno-associated virus (AAV) gene therapy to treat propionic acidemia—specifically, AAV serotype 9 human propionyl-CoA carboxylase, alpha subunit (AAV9-hPCCA). This project has provided an increase in the ODD and RPD designations for gene therapy, especially for small companies. Data, templates, and conversations with the FDA on this work have been published and are available to the public. Dr. Rutter congratulated and acknowledged NCATS Labs colleagues Richa Lomash, Ph.D., and Elizabeth Ottinger, Ph.D.—who have led this effort—as well as the NCATS collaborators, Office of Strategic Alliances, and DRDRI.

Summary

Dr. Rutter communicated that President Biden nominates the NIH director and that NCATS has had several launches of programs, with many positive advances. A report on Paxlovid use analysis was completed at the request of the White House. The ending of pandemic authorities was announced, and several efforts, including real-world data of COVID-19 therapeutics and ODD and RPD designation for AAV9-hPCCA, were highlighted. More than 30 strategic planning discussions have been organized, and NCATS is looking forward to these discussions framing the NCATS 2024 Strategic Plan.

Discussion

Paul A. Harris, Ph.D., asked about collaborative discussions with ARPA-H and the time frame of those interactions. Dr. Rutter noted that ARPA-H recently released two of its key programs—osteoarthritis and cancer—and will be focusing on these topics. NCATS is having ongoing, productive, and collaborative discussions with ARPA-H leadership about areas for contributions, including real-world data and gene therapy efforts. As ARPA-H hires more program managers to present their new research ideas, activities are expected to increase. She expressed confidence that future engagement will be productive.

Dr. Aguilar-Gaxiola commended Dr. Rutter and NCATS on the strategic planning approach in sponsoring listening sessions across the nation and convening the roundtable discussions. He emphasized the importance of this level of outreach to the various groups, including CABs, in receiving meaningful feedback. Dr. Rutter credited NCATS' Strategic Plan Team with implementing this all-stakeholder outreach approach and noted that roundtable discussions with CABs and patient advisory groups (PAGs) affiliated with NCATS' Rare Disease Clinical Research Network (RDCRN) are planned for June 2023.

Paula K. Shireman, M.D., M.B.A., commented that engaging students from rural areas and underserved populations in science, medicine, or health care should begin as early as the third grade, when they tend to start falling behind in math and science. She asked about the WSA K–5 role-playing exercises that could be shared that would fit well with efforts at her institution. Dr. Rutter noted that the DPI women scientists have been working in the local communities but have not broadly shared these exercises. She also noted that NCATS can consider encouraging this broad level of outreach and highlighted the CTSA Program's efforts in rural communities.

Dr. Rutter will follow up with the Council on sharing lessons learned and best practices of DPI's new outreach initiative on the advancement of women in biomedical careers.

VII. SPECIAL PRESENTATION: 2024 NCATS Strategic Plan: Penny W. Burgoon, Ph.D., Director, Office of Policy, Communications and Education (OPCE), NCATS; Meredith D. Temple-O'Connor, Ph.D., Branch Chief, Policy Branch, OPCE, NCATS

Dr. Burgoon explained that the NCATS 2016 Strategic Plan is being updated and that broad solicitation of community engagement is in progress to better understand gaps and opportunities. She invited Dr. Temple-O'Connor to provide a status on the planning process. Dr. Burgoon followed with an update on initial community engagement activities and outcomes.

Planning Timeline and Stakeholder Engagement

Dr. Temple-O'Connor detailed the progress in developing the NCATS 2024 Strategic Plan. NCATS is co-designing a strategic plan that will serve as a roadmap for the next decade, and the center values input from diverse stakeholders. The aim is to make an actionable roadmap to achieve NCATS three audacious goals to provide (1) More treatments (2) To all people (3) More quickly. Early strategic planning started in 2021 but was put on hold after then-director Christopher P. Austin, M.D., announced his departure from NCATS.

The strategic planning process and timeline officially began in November 2022 after Joni L. Rutter, Ph.D., was named permanent director. The target strategic plan rollout and implementation is scheduled for early 2024. Initial stakeholder engagement fully launched in March 2023, with roundtable discussions consisting of an overview of NCATS by Dr. Rutter focusing on the translational science principles and audacious goals, icebreaker questions, and discussions guided by questions to help understand perspectives from all stakeholders. The NCATS Strategic Plan Team will continue this roundtable discussion forum with the Council later in today's meeting. After the roundtables conclude, the team will begin to synthesize the stakeholder feedback. NCATS plans to publish a request for information (RFI) to solicit additional input from stakeholders and the public.

The NCATS 2024 Strategic Plan will align with the NCATS mission and vision, echo NCATS values, be audacious yet attainable, create a roadmap with milestones for achieving success, and provide a powerful tool for NCATS to succeed and fail forward. In terms of building for the years ahead, NCATS intends to approach development of this strategic plan in a forward-thinking manner and evaluate progress and implementation on a regular basis rather than only after 5 years. Key approaches to NCATS' vision are to understand similarities across diseases, develop models, enhance clinical trials, and leverage real-world data. NCATS' audacious goals (more treatments for all people more quickly) are being used to frame the strategic plan but are not the plan's specific goals, which will be informed by the stakeholder feedback. Dr. Temple-O'Connor touched on other areas of framing NCATS' strategic planning, some of which align with the NIH Strategic Plan's objectives and crosscutting themes, including stewardship and operations.

Engagement at NCATS Roundtables

Dr. Burgoon explained that NCATS has convened more than 30 roundtable sessions to gather input from a variety of stakeholders, both internally and externally, to inform the 2024 Strategic Plan. Dr. Rutter has engaged with the CTSA Program PIs and other staff, and the NCATS Strategic Plan Team has engaged with the broader rare diseases community and the RDCRN PAGs. NCATS hosted two public roundtables

and will engage the Council members for their input later in the meeting. Additional sessions are scheduled for June with the CTSA CABs and other stakeholder groups.

NCATS held two virtual public roundtables on May 9 and May 10, 2023; more than 300 people registered and more than 200 attended, representing academia, nonprofit organizations, industry, and government. Participants discussed four main questions: (1) What are the biggest opportunities should NCATS engage and invest in over the next 5 to 10 years? (2) What big gaps and opportunities should NCATS be thinking about? (3) What is missing from the vision? (4) What else NCATS should consider to advance translational science? Participants discussed these questions across four different translational science perspectives: research; diversity, equity, inclusion, and accessibility (DEIA); community and patient engagement; and training and education. Prior to assembling into small groups, participants shared responses to icebreaker questions. When asked what words come to mind when they think about NCATS, common themes were translation, innovation, and collaboration, all of which are part of how NCATS operates to address translational science efficiently and effectively.

Dr. Burgoon noted some messages from the small-group discussions that focused on responses to what unmet needs or gaps in translation should be addressed by NCATS. From a research perspective, participants highlighted the representation in clinical research needed to establish human biology–based research hubs at large institutions around the country. For community engagement, participants noted that trial readiness for many rare diseases, as well as clinical trial design, is lacking. From the training and education perspective, they emphasized focusing on choke points in the journey from discovery to health solutions, such as preclinical model optimization and first-in-human trials. In the DEIA space, participants noted the need to address access and dissemination of new treatments to underserved communities.

Dr. Burgoon highlighted and summarized key takeaways from each of the breakout discussions thus far:

- **Research.** Promote dissemination and implementation, prevention, and data sharing.
- **Diversity, Equity, Inclusion, and Accessibility.** Build trust. Understand what translational science is and what it does. Build bridges with new partners.
- **Community and Patient Engagement.** Engage patients as partners. Engage communities earlier and in the research design. Address issues of access and adoption.
- **Training and Education.** Focus on team science and translational science training and workforce diversity. Understand career transitions in the context of translational science.

Several crosscutting themes emerged, including the following examples:

- Prevention in translational science
- Better treatments, not just more treatments
- Dissemination and implementation
- Novel clinical trial approaches
- Bridges to regulatory decision-making

In closing, Dr. Burgoon acknowledged the NCATS Strategic Plan Team; communications, information technology and website teams; and roundtable teams. Further details can be accessed from the NCATS Strategic Plan website.

Council Roundtable Discussion

Dr. Rutter opened and noted that NCATS is seeking the Council's feedback on participation in the roundtable discussions; input on what is missing that NCATS should be thinking about; and ideas on how to set priorities.

Annica M. Wayman, Ph.D., remarked on how the public roundtables were well structured and innovative enough to obtain four different perspectives on the same question, resulting in crosscutting themes in a systems approach to achieve NCATS goals. She noted that expanding the translational science workforce will play a role in providing more treatments more quickly to all people. Because participation from industry in the recent public roundtable was not as robust as the other groups, Dr. Wayman suggested that input from an industry-specific roundtable would be key for the goal that NCATS is trying to achieve. Dr. Wayman also emphasized that health equity and access is a goal to achieve, especially in emerging areas, such as cell or gene therapy, where cost is a significant issue. Dr. Rutter commented on building a different workforce in the biomedical sciences to support the emerging research and approaches, such as gene therapy, AAV delivery, translational research, and drug development. NCATS can ensure that its workforce understands the possibilities of a career in science to advance these activities. NCATS can engage different disciplines and backgrounds to develop key preclinical models that are more human cell–based and fit-for-purpose for its existing drug development program. Dr. Rutter also emphasized the importance of transdisciplinary science in contributing to its workforce.

Anna Ramsey-Ewing, Ph.D. noted that it would be helpful for the strategic plan to have a graphic of the translational science process and to show where NCATS plans to contribute, as well as the linkages to the downstream or upstream components.

Robin J. Mermelstein, Ph.D., commented that she enjoyed attending the public roundtables and commented how well run they were. She noted that NCATS' communications on the goal of more treatments to all people more quickly does not capture the concept of prevention. Most people would rather never have a disease than be concerned about the treatment of that disease. Dr. Mermelstein suggested thinking about messaging to incorporate prevention concepts. In terms of what is missing, she noted gatekeepers, who are "out-in-the-world" (not academic) clinicians and major organizations that manage most U.S. hospitals and health care systems and can help with dissemination of treatments where they are needed most.

Dr. Burgoon noted that access has been a common theme in both internal and external roundtables, which she considers the "first mile–last mile" problem of translation. When treatments are developed and do not reach the people who need them, NCATS has failed. When treatments are developed and different ways prevent or minimize potential diseases, even with the appropriate technology and do not address those, then NCATS has failed. NCATS does hear this feedback.

Annie M. Kennedy, B.S., framed the roundtable as a listening tour and was impressed with the engagement and diversity of stakeholders who were in attendance, which she credits to effective

advertising. Ms. Kennedy emphasized that many of the ideas and suggestions from the breakout sessions provide an opportunity for NCATS to elevate, optimize, and highlight some existing resources. Strategic planning does not necessarily mean starting over or building new. Existing resources may be repurposed to reach a broader audience that might not be familiar with them by branding them through partnership. Some of the current work may captivate people early in their careers (e.g., K–12, medical or graduate school): they could address the roundtable questions as new stakeholders. NCATS can consider convening a roundtable with this group, which is yet to be funded but could become part of intramural or extramural communities. Ms. Kennedy also noted that payors (health care private insurers) are gatekeepers for what ends up in formularies, which is what health care providers discuss. NCATS could convene this distinct group. Dr. Rutter noted that NCATS can consider intersecting with payors around clinical data science and the N3C program, expanding the WSA K–12 local efforts to discuss more of what NIH does, and leveraging Take Your Child to Work Day at NIH. She also sees value in repurposing NCATS resources and providing those in a central location that would be publicly available.

Sergio Aguilar-Gaxiola, M.D., Ph.D., noted that he participated in the DEIA and community engagement roundtables and thought that the special presentation update summarized what transpired and the multiple comments made during the discussion, and he had further ideas to convey. Regarding the vision of more treatments to all people more quickly, he emphasized building trust and becoming a trustworthy organization in which all people, especially those who have been excluded—the underserved and those who live in rural areas—benefit from NCATS efforts. Dr. Aguilar-Gaxiola also emphasized moving beyond the "waiting mode" (people coming to access treatments) of thinking about treatments that ignore institutional, structural, and perceptual barriers, especially in historically underserved communities, to the "seeking mode" (delivering the treatment to patients), and he promoted the consideration of telehealth services. He encouraged focusing on mental health and youth engagement.

Matthias Kretzler, M.D., commented on using trust models for engagements, leveraging the lessons learned in building relationships within the RDCRN, between patient organizations and NCATS, and engaging the international community. Dr. Rutter noted engagement and outreach with the scientific attaché of some of the U.S. Embassies and ongoing interactions as well as NCATS connections with the International Rare Diseases Research Consortium (IRDiRC).

Paul Harris, Ph.D., noted having attended the roundtables and being enthusiastic about how the questions were handled, especially that the participants were provided an opportunity to be anonymous. He suggested communicating updates on how the information will be used and potentially having ongoing updates.

Keith J. Mueller, Ph.D., noted two examples of dissemination at the community level in trying to achieve the goal of treatments to all people: (1) Engage social scientists who understand the dynamic core (the CTSAs provide a platform for such engagement) and (2) Model the University of Minnesota Clinical and Translational Science Institute project Rural Experts Advancing Community Health, which is helping elderly populations in rural areas with broadband access.

Paula Shireman, M.D., M.B.A., pointed out that county and state extension agents, who generally are organized through land-grant colleges and universities, know their communities and can help build trust with those communities. NCATS can consider engaging this group.

Michael Kurilla, M.D., Ph.D., recalled a CTSA Un-Meeting (an event without the rules and structure of a traditional conference) on rural health that was held before the COVID-19 pandemic, and the topic of extension services was discussed; many CTSAs work with them, but others were not aware of that

resource. Follow-up discussions with the U. S. Department of Agriculture (USDA), which has an extension service for farmers, indicated that those services do focus on health. He agrees that this group has connections to the community and will plan to resume those discussions with the USDA.

Council members encouraged convening industry-specific, early career–focused, and payor-specific roundtables.

The NCATS Strategic Plan Team will consider developing a graphic of the translational science process, illustrating NCATS' contribution and linkages to downstream or upstream components in the strategy.

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

14:51:22 From Annie Kennedy to Everyone: Comments around access and DEI suggest that the wonderful mission of "more treatments for all patients more quickly" could be amplified with the addition of one word? "Delivering more treatments for all people more quickly? – Delivering would enable engagement with critical stakeholder who need to better understand what's happening upstream as it informs decision making and access downstream.

14:52:21 From Annica Wayman, UMBC to Everyone: Good idea.

14:54:18 From Robin Mermelstein to Everyone: also perhaps attention to the acceptability of treatments to more people

14:54:57 From Meredith Temple-O'Connor, NCATS to Everyone: Thank you @Robin Mermelstein. This has come up in input sessions as well.

14:55:06 From Meredith Temple-O'Connor, NCATS to Everyone: Thank you @Annie Kennedy!

VIII. PROGRAM UPDATE: Division of Preclinical Innovation (DPI): Ewy A. Mathé, Ph.D., Director, Informatics Core, DPI, NCATS

Anton Simeonov, Ph.D., scientific director, DPI, introduced Ewy A. Mathé, Ph.D., director, Informatics Core, who joined NCATS in 2020. Dr. Mathé came to NCATS from The Ohio State University, where she was an assistant professor in the Department of Biomedical Informatics. Despite the challenges of starting shortly after the COVID-19 pandemic restrictions were imposed, Dr. Mathé was able to organize her team to produce transformative research investigating SARS-CoV-2, as well as focus on informatics efforts.

Dr. Mathé provided a DPI program update, focusing on the Informatics (IFX) Core. Before the 1960s, data were primarily qualitative and later transitioned to quantitative. The data field experienced a technology revolution through the 1980s, expanding to different applications. Beginning in 2010, data automation increased, which is where NCATS plays a key role, especially in generating and automating robust data on a large scale. Dr. Mathé noted some challenges in data generation: data types and data complexity are increasing, conducting large studies is very resource intensive, and extracting meaning from data is difficult and impedes being able to derive actionable insights. She described how IFX is generating and publicly disseminating data and analyzing these data using tools generated in house, as well as in collaboration with other experts.

Dr. Mathé reminded the Council of the DPI mission to transform therapeutic discovery approaches and tools, advance team science, and catalyze the biomedical community to deliver more effective therapies

to treat human diseases. The mission of IFX is to derive actionable insights from integrating translational research data and to accelerate the translation of findings into the clinic. Conceptually, IFX develops methods and tools to integrate various types of data, including preclinical, clinical, and experimental measurements; data can be gathered from literature, social media, and grants, etc. This integration results in a data set that is difficult to interpret and navigate. Additional methods are then applied to simplify these data and to answer a specific research question, leading to actionable insights that are beneficial to patients.

Prior to 2021, NCATS informatics was housed largely within the Early Translation Branch. The focus was on building informatics tools for discovering small molecules, probes, and cheminformatics. Starting in 2021, IFX became an independent research group, with a broader scope covering other translational research areas, including molecular profiling in biology and epidemiology. This new scope complements the historical scope, and ongoing and future efforts include developing new assay types, assessing mechanisms and targets in populations, and identifying predictive biomarkers. The overall aim is to inform clinical trials and FDA approvals. IFX uniquely has used and continues to use a cross-disciplinary team-science approach consisting of experts in bioinformatics, clinical informatics, different types of -omics, machine learning, software development, and project management. IFX also collaborates with other experts (biologists, chemists, engineers, and information technologists) within NCATS. The various disciplines collaborate and find ways to communicate and be multilingual (scientifically) to better understand the data, thus resulting in actionable insights.

COVID-19: Pushing Boundaries of Data and Informatics

Dr. Mathé described some ways in which IFX has focused efforts in response to the COVID-19 pandemic.

- **National COVID Cohort Collaborative.** N3C—one of the largest collections of harmonized clinical health data in the United States—provides real-time tracking and data availability for researchers and the public. N3C consists of 76 clinical sites and contains electronic health record (EHR) data from more than 18 million people, 7 million of whom have received a COVID-19 diagnosis. Data are housed in the secure N3C Data Enclave at NCATS.

- **Autoimmunity and Severe COVID-19 Studies.** N3C data recently accepted for publication have been used to investigate preexisting autoimmunity as a risk factor for COVID-19. During the early phases of COVID-19, the only autoimmune-related disease the CDC listed as a risk factor for more severe COVID-19 was type 1 diabetes. NCATS collaborated with the National Institute of Diabetes and Digestive and Kidney Diseases to evaluate whether treatment with immunosuppressive drugs could have a strong effect on the response to SARS-CoV-2. The goal was to directly evaluate the effect of autoimmunity and immunosuppressive drugs on COVID-19 severity to help inform health care guidelines and raise awareness for patients at risk. This N3C cohort consisted of 2,453,799 million adults with COVID-19. Of the cohort**,** 191,151 had a preexisting autoimmune disease (AID), 278,095 had prior exposure to immunosuppressants (IS), and 56,813 had both preexisting AID and IS. The findings showed that adults with preexisting AID, IS exposure, or both are more likely to have more severe disease outcomes. Results were consistent when taking into account COVID-19 vaccination status and antiviral treatments.

- **Metabolism and Severe COVID-19 Research.** NCATS collaborated with Harvard Medical School investigators to evaluate whether individual characteristics of metabolism predispose patients to severe COVID-19 symptoms. Prior studies were limited in cohort size or evaluated a single time point and had no data on study participants prior to a COVID-19 diagnosis. The metabolome was assessed in the plasma of patients with and without COVID-19 in samples from

a Harvard Medical School biobank and included baseline data collected prior to diagnosis of COVID-19. Results showed that amino acids, nucleotides, phosphatidylcholines, and sphingolipids are associated with severe COVID-19 outcomes. This study lays a foundation for identifying putative biomarkers for assessing molecular functions that predispose individuals to COVID-19.

- **CURE ID. Real-World Data for Global Health**. NCATS DCI, the FDA, and the Critical Path Institute co-developed CURE ID, which exists as an online platform and mobile app, to capture real-world data on the novel uses of existing drugs from clinicians (and soon to come from patients) to identify drug repurposing candidates. CURE ID also provides evidence for expanding drug labels, informs the design of clinical trials, and was piloted in COVID-19 cases. Additional support from a grant via the HHS Office of the Assistant Secretary for Planning and Evaluation, Office of the Secretary Patient-Centered Outcomes Research Trust Fund has enabled investigating different ways of incorporating data into CURE ID, including from EHRs. Distinctive from N3C, CURE ID has international clinical sites, many of which do not use common data models and are smaller, less resourced institutions. Data are publicly available through CURE ID, which provides an infrastructure applicable beyond COVID-19.

Actionable Insights: Integrating Complex Data

Dr. Mathé provided examples of how IFX derives actionable insights from integrating complex data and began with the category of drug**s** and drug substances. Although data repositories provide access to data and relevant information, they have limitations. Compiling, integrating, and reusing existing data are time and resource intensive. Drawing information from multiple sources remains challenging. It is essential to build on prior knowledge to access and interpret results. These challenges can be addressed by working on standards of interoperability, connecting different data types, and developing algorithms using machine learning tools and methods.

- **Global Substance Registration System (G-SRS).** IFX informaticians collaborated with the FDA to co-develop the G-SRS, a registration and public access online platform comprising data on substances found in medicinal products, including small molecules, antibodies, gene and cell therapies, and antisense oligonucleotides. G-SRS is the first International Organization for Standardization 11238–compliant substance registration system and has been broadly adopted by the FDA, World Health Organization, European Medicines Agency, and U.S. Pharmacopeia, as well as Germany's Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte).

- **NCATS Inxight Drugs.** IFX informaticians developed the Inxight Drugs portal to complement the G-SRS. This portal contains public, curated data from the FDA, NCATS, and private companies on marketing and regulatory status, ingredient definitions, biological activity, and clinical use. These data can be browsed and used with other resources. Efforts are in progress to enhance interoperability, which will enable access to all data types.

Dr. Mathé highlighted other NCATS informatics data applications. Bioplanet and the Relational database of Metabolomic Pathways (commonly called RaMP) are used for work in metabolism and molecular phenotypes. For diseases, IFX collaborates with DRDRI on the Genetic and Rare Diseases (GARD) Information Center and manages the Rare Disease Alert System. In support of assays, IFX works with the OpenData Portal and PubChem. Pharos is another user interface and supports protein targeting.

Navigating Through Translational Research Data

Dr. Mathé discussed examples of how IFX is directing various translational research data.

- **Rare Disease Clustering.** IFX aims to cluster rare diseases by finding shared disease characteristics to identify common targets and interventions. Data from NCATS' resources GARD and Pharos and external resources, such as Pathway Commons**,** were used in an integrated network of characteristics. A natural**-**language processing algorithm was used to define the clusters. The results revealed that Charcot-Marie-Tooth disease type 2C, metatropic dysplasia, and Brachyolmia type 3 share key characteristics: muscle filament sliding, muscle organ development, sarcomere organization, and calcium ion transport. The next steps will be to determine appropriate ways of intervening and targeting these pathways.

- **Biomedical Data Translator.** NCATS DPI collaborates with numerous academic institutions to host the Biomedical Data Translator (Translator). This large-scale effort aggregates many different types of information spanning the translational research spectrum**,** from basic science to clinical research. Users can perform queries in Translator of different diseases and link to putative targets and treatments to build a knowledge graph for building research hypotheses. For example, one study investigating glioblastoma showed a relationship with epidermal growth factor receptor tyrosine kinase and identified clinical trials evaluating treatment with gefitinib. Dr. Mathé emphasized that trustworthiness is built into Translator's results through details on evidence levels.

NCATS New Technologies

Dr. Mathé highlighted new technologies at NCATS in support of informatics. Metabolomics and multi-omics involve profiling metabolites, genes, and proteins, which can enable biomarker discovery, leading to identification of mechanisms that underlie diseases and drug response. IFX is working on robust data generation, including study design**,** and is developing reproducible protocols at scale. The aim is to develop this capability in house and in parallel with producing robust data analytics, with novel methods for interpretation.

In addition, efforts are focused on housing all molecular data in one system to facilitate data reuse. This new system will address many challenges. Public multi-omic repositories with analytics do not exist. Reusing data requires extensive computational resources. As this system is being built, IFX has adopted some guiding principles**:** use standard data formats and preprocessing**,** provide direct access to analytics software, and address interoperability with other NCATS resources. The scientific goal is to bridge the gap between preclinical and clinical efforts. The interface is currently in development.

Discussion

Annie Kennedy, B.S. commented that the rare diseases community has been advocating for real-world data to inform the different areas of the ecosystem, especially label expansion, and she commended NCATS for co-developing CURE ID.

Dr. Mathé confirmed that no protocol is available for the scientific community to use the newer in-house software, but IFX can consider releasing different versions in the future.

Matthias Kretzler, M.D. asked about the process for identifying and prioritizing projects and maintaining those projects. Dr. Mathé explained that some of the projects are supported by extramural funds, the

development of which is ongoing. Projects with broad impact and international reach also are ongoing. New ideas received, identified, and evaluated by NCATS trainees drive the prioritization. When these cases are used less frequently, they are deprioritized. Maintenance is more challenging with older projects with regard to budget. NCATS has been discussing building user communities for broader adoption of projects beyond IFX. Dr. Kretzler encouraged identifying areas critical and unique to IFX that would be different from a large informatics group and highlighting those in the NCATS 2024 Strategic Plan.

In response to a question from Dr. Harris on the Harvard Medical School collaboration, Dr. Mathé noted that this project was not work assigned to the N3C project. Agreements can be complicated but can be explored to enable investigations of different phenotypes within the N3C Data Enclave. Dr. Mathé emphasized that similar work had been in progress in NCATS prior to her joining DPI. Dr. Rutter noted the many explicit streams of data science and informatics NCATS intends to incorporate in the next strategic plan.

Annica Wayman, Ph.D. underscored the significance of IFX's work in making various databases more user-friendly and increasing users of those databases. She is looking forward to applications beyond the informatics field and having these efforts inform policy and medical practice.

Dr. Rutter and DPI will consider outlining areas critical and unique to IFX in the NCATS 2024 Strategic Plan.

IX. PROGRAM UPDATE: Division of Rare Diseases Research Innovation (DRDRI): P.J. Brooks, Ph.D., Acting Director, DRDRI, NCATS; Tiina K. Urv, Ph.D., Program Director, DRDRI, NCATS

P.J. Brooks, Ph.D., briefly reviewed that the DRDRI directs programs in three areas: data and informatics, research, and collaboration. He noted that the program update will highlight some of the activities across these areas.

Rare Diseases Clinical Research Network (RDCRN)

Dr. Urv explained that the RDCRN (or Network) was established through the 2002 Rare Diseases Act. NIH was directed to establish regional centers of excellence around rare diseases therapeutic areas. The first centers were established in 2003, and the RDCRN has consistently grown through funding competitions every 5 years. The RDCRN comprises 20 consortia and 1 Data Management and Coordinating Center (DMCC). NCATS partners with 10 ICs on this program. The NIH U54 cooperative agreement funding mechanism supports the Network and encompasses significant programmatic involvement from NIH program officials. Partnerships and interactions among program and scientific officers, the grantees, and Patient Advocacy Groups (PAG) are an important part of the RDCRN.

The current focus of the RDCRN is on clinical trial readiness. Each consortium investigates three or more related diseases or conditions, consists of multiple clinical sites, conducts three to five clinical trials, has a competitive pilot study program, has a career development core, and has a fully integrated PAG. The DMCC provides (1) Administrative support (facilitates operation, governance, and communication); (2) Clinical Research support (coordinates best practices, standardization, and good data practice); (3) Data Management (in collaboration with NCATS Information Technology Research Branch); and (4) Engagement and Dissemination (promotes patient engagement and broad research dissemination).

The RDCRN currently has 358 active sites, of which 197 are at unique locations, partners with 11 countries and has numerous consortia sites that are co-located with the Clinical and Translational

Science Awards (CTSA) sites. The RDCRN leadership is composed of three branches: PI leadership team, Coalition of PAG or PAG leadership team, and executive leadership committee. The DMCC leadership manages the Network, and Dr. Urv is the NIH representative. The steering committee chairs are elected by their peers, have a regular schedule of rotation, and serve as a vetting body of activities within the RDCRN. The Network has a wide variety of working and interest groups, all focusing on improving research. All members of the RDCRN have the opportunity to join a working group.

Dr. Urv noted that during preparation for the fourth award cycle (RDCRN4) cohort, NCATS recognized that the RDCRN has been in operation for nearly 20 years (NCATS' largest and longest-standing program) and reviewed the science and assessed the needs of the rare diseases community. The program was evaluated and updated. NCATS adopted an economies-of-scale approach, providing all tools of the shared environment to the RDCRN at once. The operational environment (or working environment) was developed for the consortia researchers as an internal site where the available tools (e.g., RedCap, Ambra, NIH Box) are shared across the consortia. The cloud environment, developed through a close collaborative relationship with the NCATS technical team, "lives at NCATS" but is managed by the DMCC. To date, NCATS has funded all cloud-related costs and manages the security using multifactor authentication through Duo. Tools are made available to consortia at no cost. The Children's Hospital Medical Center that houses the DMCC has no onsite infrastructure. All assets run on Amazon Web Services, Inc., NCATS uses third-party contracts, and all licenses are held by NCATS.

- **Data Sharing.** NCATS is building a data-sharing requirement into the RDCRN4. In the process, the operational environment takes consented data from RDCRN studies and de-identifies these data. The DMCC will provide assurances about data quality and data-use limitations and make sure metadata are available. These data will then be passed to the NIH shared data environment. This environment is NIH governed, and data access will be controlled through an NCATS Data Access Committee. The intent is that data will be available to the public through controlled access.

- **Accomplishments.** From 2004 to 2020, RDCRN investigators published 2,763 papers, with an average of 9 per consortium, and some authors or organizations published 5 papers. The RDCRN has been expanding, and the number of organizations significantly increased over time, with the largest increase in international collaborations occurring in 2020; 50 percent were from the same institution. The co-authorships and publication collaborations also increased over time. Despite the increase in the size of the Network, the number of clusters (groups) was unchanged from 2004 to 2015 and, overall, from 2004 to 2020, demonstrating that the individual rare disease groups are growing.

- **Translational Impact.** Since its inception, the RDCRN has conducted 81 clinical trials (small Phase 1/2) directly funded by the U54 grant, and 18 trials are currently active. Of the 33 consortia, 22 have conducted at least one clinical trial. At least 13 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 eight FDA-approved treatments for rare diseases.

Dr. Urv noted that the RDCRN takes a translational science approach to the challenges and is not investigating only one disease at a time, but a group of diseases. The RDCRN addresses common challenges the rare diseases community experiences and seeks solutions. The RDCRN focuses on such

issues as clinical trial readiness, high-quality data, and a shared work environment and shared tools, thus addressing the bottlenecks from many angles.

Genetic and Rare Diseases Information Center

Dr. Brooks explained that the GARD Information Center, a congressionally mandated program, received a major overhaul and was upgraded to GARD 2.0 to address security concerns and in response to the rapid pace of technology. Eric Sid, Ph.D., program director, DRDRI, leads this program, and efforts have been focused on increasing the interoperability of GARD to link with other activities around the world. The expectation is that GARD will be a base for informatics and information from other NCATS programs and initiatives.

Shortening the Diagnostic Odyssey

Dr. Brooks reminded the Council that NCATS released a notice of funding opportunity (NOFO)—Multidisciplinary, Machine-Assisted, Genomic Analysis and Clinical Approaches to Shortening the Rare Diseases Diagnostic Odyssey—in 2022. Alice Chen Grady, M.D., program officer, DRDRI, leads this program, and three projects were funded in FY22 and are in progress: (1) Using Electronic Medical Record Data to Shorten Diagnostic Odysseys for Rare Genetic Disorders in Children and Adults in Two New York City Health Care Settings; (2) Machine-Assisted Interdisciplinary Approach for Early Clinical Evaluation of Neurodevelopmental Disorders; and (3) Virtual Platforms for Genetics Evaluation in the Medically Underserved. These projects are examining EHRs, developing and validating genetic and machine learning–based algorithms to identify rare diseases, and assessing the medical needs of underserved communities. The projects will help to inform the next steps of this program.

Shared Molecular Etiologies (SaME)

Dr. Brooks noted the common theme that many rare genetic diseases exist, but far fewer genetic etiologies (e.g., premature stop codons) have been described. Using SaME, patients with different diseases that are caused by the same underlying genetic abnormality can be treated with the same therapy in a basket clinical trial, a design successful in genomically driven oncology basket trials. In FY21, the DRDRI published NOFO Basket Clinical Trials of Drugs Targeting SaME in Multiple Rare Diseases (UG3/UH3), and two projects have been funded: (1) Emerging Therapeutic Candidates for Rare Maternally Inherited Mitochondrial Diseases with Shared Etiologies and (2) Safety and Efficacy of Itacitinib in Treatment of JAK/STAT Pathway Disorders with Activating Mutations, which is a model of creating a new disease based on the molecular target. A second NOFO, Basket Clinical Trials of Drugs Targeting SaME in Multiple Rare Diseases (U44 Clinical Trial Required), uses the SBIR mechanism and is open for submitting applications.

In addition, the DRDRI collaborated with the IRDiRC to establish a SaME Underlying Multiple Rare Diseases Working Group composed of local and international members, which Dr. Brooks chairs. A manuscript describing the organizational structure is being prepared.

Platform Vector Gene Therapy (PaVe-GT)

Dr. Brooks noted that by using a platform design and AAV gene therapy vector for rare diseases, multiple therapies for the same disease can be tested in the same clinical trial. PaVe-GT is testing the hypothesis that a platform vector approach will increase efficiency in preclinical testing and clinical trial startup. PaVe-GT is evaluating four rare diseases in studies at the Clinical Center: two congenital

myasthenic syndromes and two organic acidemias. PaVe-GT clinical development utilizes the same manufacturing facility and process, thus reducing the time to start a trial. All data, including FDA communications, will be made available to the public. In addition to the highlight from Dr. Rutter on the Orphan Drug Designation (ODD) and Rare Pediatric Disease (RPD) designations for AAV9-hPCCA, Dr. Brooks explained that NCATS and the FDA/Center for Biologics Evaluation and Research (FDA/CBER) held an INitial Targeted Engagement for Regulatory Advice on CBER producTs (commonly called INTERACT) meeting and that those documents will be made available to the public. The first FDA investigational new drug (IND) application meeting for AAV9-hPCCA is scheduled for July 2023.

Bespoke Gene Therapy Consortium (BGTC)

NCATS, FDA/CBER, and the Foundation for the NIH (FNIH) established the BGTC, a major component of the FNIH Gene Therapy the Accelerating Medicines Partnership® (AMP). The goal is to identify and streamline the process of starting an AAV gene therapy trial. Eleven ICs and several private-sector partners are members of AMP and contribute 50 percent of the funding. The BGTC consists of two components. The basic science component focuses on AAV basic biology and translational implications to enhance vector generation and therapeutic gene expression. The larger clinical component seeks to advance access to AAV technologies and vectors for bespoke clinical applications. The aim is to create and build capacity, harmonize best practices (preclinical), and streamline the regulatory pathway (clinical). The BGTC is in the process of providing input on a minimal package of animal toxicity studies that will be required to support AAV clinical studies.

FNIH and NCATS closed solicitations for disease nominations for the clinical workstream in February 2022; 62 nominations were received, 14 leading candidates were selected, and 8 diseases will advance to the first human trials.

Somatic Cell Genome Editing (SCGE)

NCATS, in partnership with NINDS, is leading the SCGE, a Common Fund program that began in 2017. The aim is to lower the barriers for new genome editing therapies. Dr. Brooks highlighted that the SCGE consortium has been productive. In SCGE Phase 1 (the first 5 years), investigators generated more than 300 publications and were granted 241 patents, with 89 of the publications cited in those patents. Several licensing deals related to SCGE-funded advances resulted in startup companies. An SCGE Toolkit has been established and contains the program's data (published and unpublished) and resources. Twenty projects were funded in Phase 1, which focused on technology development for gene-targeted therapies. SCGE Phase 1 implemented an independent validation for novel delivery systems. In a study of AAV delivery of CRISPR for genome editing in mouse lung, 20 percent of cells were edited in the investigator's laboratory and were independently validated by the same system using the same protocols in an external laboratory. Results were similar, and these data have been published.

SCGE Phase 2 focuses on accelerating the translation of *in vivo* genome editing therapies into the clinic and has four initiatives: technology development, preclinical IND-enabling studies, clinical trials, and dissemination.

Genome Editing: Clinical Trials and Technology

Dr. Brooks highlighted other efforts in support of the SCGE.

- **Platform Clinical Trials of Genome Editors in Multiple Diseases.** Genome editing is a therapeutic platform, not a treatment for one disease at a time. NCATS published a NOFO soliciting applications for Platform Clinical Trials of Genome Editors in Multiple Diseases (UG3/UH3, Clinical Trial Required). Dr. Brooks anticipates updates at a future meeting.

- **Targeted Genome Editor Delivery (TARGETED) Challenge.** NIH, in partnership with NCATS and other components of NIH, 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. Top competitors could win up to $1 million in prize money and have their solutions independently tested and validated.

In closing, Dr. Brooks called attention to the special issue on gene-targeted therapies published in the March 2023 edition of the *American Journal of Medical Genetics Seminars in Medical Genetics.* This article captures the 2021 workshop that NCATS and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development co-sponsored on this topic.

Discussion

Annie Kennedy, B.S. suggested showcasing the eight approved treatments for rare diseases developed in the RDCRN to increase awareness in the community.

Dr. Kretzler encouraged NCATS to make toolkits accessible to the community and to ensure that the necessary information technology infrastructure is available to support this sharing.

Kelly Marie McVearry, Ph.D., Ed.M., asked what needs to change to make a common pathway for FDA approval a reality. Dr. Brooks explained that NCATS has been working through some of the hurdles for small molecules for SaME, which are less of a regulatory challenge than the requirements for biologics and therapeutic platforms. He emphasized funding some of the activities for drug development and communicating with the FDA as two key areas where NCATS will continue to focus efforts.

Paul Harris, Ph.D. commented that the FDA is comfortable with advancing one drug that treats multiple indications through the approval process but may have reservations that adverse events might be unique to one indication and not the other. The key is to demonstrate that the manufacturing platform is reliably producing the desired result and that the individual product is effective in that particular disease.

Council members suggested that the DRDRI consider a forum to showcase the approved treatments developed in the RDCRN and share toolkits generated in DRDRI programs with the rare disease community.

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

16:50:56 From Shireman to Everyone: Exciting progress and innovative approaches using the shared pathways concept.

X. OPEN DISCUSSION: Joni L. Rutter, Ph.D., Director, NCATS, Chair, NCATS Advisory Council

Joni Rutter, Ph.D. opened the floor to continue discussing the strategic planning questions on prioritization regarding the process; the potential impact of incorporating the stakeholder feedback into

the framework; and feasibility, resources and risks. Dr. Burgoon encouraged sending any additional comments after the meeting to NCATS2024StrategicPlan@mail.nih.gov. She noted that a (request for information (RFI) will be posted in summer 2023 to collect additional feedback from stakeholders and the general public.

Robin Mermelstein, Ph.D. emphasized streamlining and facilitating processes, in general, to allow time-sensitive rapid responses to scientific interactions. Dr. Rutter highlighted the Other Transactions Authority, which is designed to accelerate processes and is used by the CAN Review Board. Anna L. Ramsey-Ewing, Ph.D., as director of DEA, remarked with confidence that NCATS can move quickly and streamline processes. Although flexibilities were established with COVID-19, the DEA can move expeditiously without them. The issue would be a surge beyond capacity.

Kelly Marie McVearry, Ph. D., Ed.M. observed that leading venture capital firms were missing from the stakeholder groups.

In response to the question about impact and risk, Ms. Kennedy noted taking risks and failing fast. NCATS is the one that de-risks for the external stakeholders. She highlighted some observations regarding impact and influence. The RDCRN has contributed eight treatments for nine rare diseases. CURE ID is the leading application for real-world data to extend labeling. NCATS can perform the science that the pharmaceutical industry has limited ability to complete. NCATS has been leading antiviral programs in preparation for future pandemics.

Sergio Aguilar-Gaxiola, M.D., Ph.D. asked what feedback on the draft strategic plan NCATS would be expecting and suggested establishing a group that could be dissemination agents when the plan is ready. Dr. Burgoon noted that the strategic plan is a co-design and an update, meaning that the stakeholders, including the Council, are one part and that it will come back to the Council for additional feedback, all in an iterative process. Dr. Temple-O'Connor echoed that the process to develop the strategic plan is iterative and bidirectional in terms of feedback. She emphasized having an open mind and less of a predetermined path when approaching the task.

Annica Wayman, Ph.D. credited the prior NCATS strategic plans with guiding the NCATS' efforts since the center's inception and expressed concern about the new plan's pivoting too far away from that alignment. She underscored building an NCATS strategic plan now that ARPA-H has been launched and explained how that factors in. Drs. Burgoon, Temple-O'Connor, and Rutter thanked the Council members for their input and noted that NCATS recognizes the foundation built from the previous plans and areas to expand on.

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

17:06:22 From Meredith Temple-O'Connor, NCATS to Everyone: NCATS2024StrategicPlan@mail.nih.gov

17:25:02 From Meredith Temple-O'Connor, NCATS to Everyone: We're definitely NOT throwing out that plan!!

17:29:13 From Shireman to Everyone: Thanks to everyone! It was a great meeting!

XI. PUBLIC COMMENTS

Comments from the public were accepted until June 16, 2023 (15 days after the meeting) and will be appended to the minutes.

XII. ADJOURNMENT OF THE OPEN MEETING

Joni Rutter, Ph.D. thanked the participants for their input. The next meeting is scheduled for Sept. 28, 2023, and is planned as an in-person session. Dr. Rutter adjourned the meeting on May 25, 2023, at 5:31 p.m. EDT.

XIII. CERTIFICATIONS

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

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