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

32nd Meeting of the Advisory Council

Minutes of Virtual Meeting January 26, 2023

The National Center for Advancing Translational Sciences (NCATS) Advisory Council held a meeting in open session on January 26, 2023, from 1:02 p.m. to 4:47 p.m. EST via National Institutes of Health (NIH) VideoCast. 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 January 26, 2023, from 11:02 a.m. to 11:54 a.m. EST 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, NCATS

Council Members

Sergio A. Aguilar-Gaxiola, M.D., Ph.D.
Paul A. Harris, Ph.D.
Theodore R. Holman, Ph.D.
Annie M. Kennedy, B.S.
Matthias Kretzler, M.D.
Robin J. Mermelstein, Ph.D.
Keith J. Mueller, Ph.D.
Marshall L. Summar, M.D.
Annica M. Wayman, Ph.D.

Ad Hoc Council Members

None present

Representative Members

None present

Ex Officio Members

None present

Others Present

Michael S. Lauer, M.D., Deputy Director for Extramural Research and Director, Office of Extramural Research (OER), Office of the Director, NIH
NCATS leadership and staff

I. CLOSED SESSION OF THE NCATS ADVISORY COUNCIL

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

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

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

Dr. Rutter adjourned the closed session of the NCATS Advisory Council meeting on January 26, 2023, at 11:54 a.m. EST.

III. CALL TO ORDER, OPEN SESSION

Dr. Rutter called the meeting to order and welcomed members and guests to the 32nd 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 videocast.

IV. APPROVAL OF MINUTES: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council and Cures Acceleration Network (CAN) Review Board

Members approved the minutes from the September 2022 Council meeting with eight ayes, zero nays, and one abstention.

V. APPROVAL OF 2023 NCATS ADVISORY COUNCIL OPERATING PROCEDURES: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council and CAN Review Board

Members unanimously approved the 2023 NCATS Advisory Council Operating Procedures.

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

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

- May 25, 2023
- September 28, 2023
- January 18–19, 2024 (virtual meeting)
- May 23, 2024
- September 26, 2024

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

Dr. Rutter began by noting that she became the NCATS director on November 10, 2022, and is honored to be serving in this capacity. As acting director, she has had the privilege and distinction of working with the Council members and NCATS staff and looks forward to continuing.

She welcomed new Council members Sergio A. Aguilar-Gaxiola, M.D., Ph.D.; Robin J. Mermelstein, Ph.D.; and Annica M. Wayman, Ph.D. Dr. Rutter next said farewell to Advisory Council and Cures Acceleration

Network (CAN) Review Board members Theodore R. Holman, Ph.D., and Andrew W. Lo, Ph.D., who have completed their tenures. In addition, CAN Review Board members Kiran Reddy, M.D., and Elizabeth Stoner, M.D., have completed their tenures. She explained that NCATS is also starting to build capacity and is close to having a quorum for the CAN Review Board. She announced that Simon Frost, M.A., was recently appointed as a CAN Review Board member.

Dr. Rutter presented updates on NCATS, 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. She explained that QR codes were embedded throughout the PowerPoint presentations, which, when scanned, will direct viewers to NCATS web pages to provide more in-depth information about the programs and initiatives.

NCATS Staff Changes, Recruitments, and Memorials

- **Staff Changes.** Dr. Rutter reported that Lili M. Portilla, M.P.A., former director of the Office of Strategic Alliances (OSA) has left federal service and has taken a position as senior director of government programs at Novavax Inc. Ms. Portilla had been with NCATS since its beginning and played a major role in establishing and building OSA, which manages NCATS' Small Business Innovation Research/Small Business Technology Transfer programs. Krishna (Balki) Balakrishnan, Ph.D., M.B.A., will serve as acting director, OSA.

- **Leadership Recruitments.** Dr. Rutter reminded the Council that NCATS has several active leadership positions to fill, which she now can act on as director. The deputy director position will be open. The searches for directors of OSA and the Division of Rare Diseases Research Innovation (DRDRI) and scientific director of the Division of Preclinical Innovation (DPI) are in progress. NCATS is establishing a chief diversity officer position. Once these positions are filled, NCATS will be at full capacity, standing on a more solid foundation and able to charge into its future work.

- **In Memoria.** Dr. Rutter reflected on the lives and careers of two NCATS colleagues who recently passed away and recognized their contributions. Paul Shinn, B.S., group leader, Compound Management Group, DPI, played a significant role in working with people around the world to distribute compounds and/or compound libraries for drug screening. Mr. Shinn enabled a variety of work related to combination compound screening, which has informed cancer clinical trials. Jacob G. Mensah, M.S., contract cloud developer and senior advisor, Information Technology Resources Branch, had worked to establish the Infrastructure Operations Team and can be credited for building the necessary NCATS infrastructure for facilitating operations. The great work and contributions of these colleagues was recognized. Announcements and Events

Dr. Rutter highlighted recent NIH-wide announcements and events. She explained that during its December 8–9, 2022, meeting, the NIH Advisory Committee to the Director (ACD) discussed and highlighted several proposals of interest to NCATS, which she further described.

- **NIH Peer Review Criteria.** The Center for Scientific Review presented a proposed new framework for the NIH peer review criteria. A request for information (RFI) was issued in December 2022 and will remain open until March 2023. The goals are to refocus the first level of peer review to streamline the process and mitigate reputational bias in the peer review process. The aim is to reduce the administrative burden on reviewers and incentivize participation in

review, specifically refocusing the evaluation of both the investigator and the environment in the context of the proposed research.

- **Working Group on Re-envisioning NIH-Supported Postdoctoral Training.** The ACD established a working group to assess the postdoctoral state of affairs within the U.S. ecosystem. The charge is to evaluate evidence of the perceived shortage of Ph.D.'s seeking a U.S. position; assess and consider factors influencing the scope and persistence of the issue; review and compare other approaches to postdoctoral training; consider ways to support postdoctoral trainees' quality of life and work–life balance to increase retention; and engage key internal and external stakeholders. The draft recommendations are due in June 2023 and the final version in December 2023.

- **Working Group on Catalyzing the Development and Use of Novel Alternative Methods to Advance Biomedical Research.** This ACD working group has a scope that directly aligns with NCATS activities, including Tissue Chip for Drug Screening, the 3-D Tissue Bioprinting Program, as well as artificial intelligence approaches. The charge is to identify types of alternative methods and assess their strengths and weaknesses for studying human biology, circuit systems, and disease states; characterize the types of research, conditions, or diseases for which alternative methods are most applicable or beneficial; and articulate high-priority areas for NIH investment in the use and development of novel alternative methods. Preliminary findings are due in June 2023, stakeholder engagement will occur from June to November, and final recommendations will be made in December. Dr. Rutter highlighted that Danilo A. Tagle, Ph.D., M.S., director, Office of Special Initiatives, NCATS, serves as an e*x officio* member of this working group.

Dr. Rutter highlighted another NIH-wide effort:

- **Quantum Information Sciences (QIS) and Quantum Sensing.** Dr. Rutter co-chairs the QIS and Quantum Sensing in Biology Interest Group, along with Susan Gregurick, Ph.D., Associate Director for Data Science (ADDS) and Director, NIH Office of Data Science Strategy (ODSS), and Geetha Senthil, Ph.D., Program Officer, Office of Genomic Research Coordination, National Institute of Mental Health, on behalf of the broader NIH biomedical community. This interest group has participation from several other NIH institutes and centers (ICs), and collectively, they explore quantum sensing and other quantum work. This interest group helped organize a recent workshop titled "NIH Virtual Workshop: Near-Term Applications of Quantum Sensing Technologies in Biomedical Sciences." The video recording will be made available on the ODSS website soon.

NCATS 2024 Strategic Plan

Dr. Rutter reported that NCATS is in the process of developing its 2024 strategic plan, which will focus on the three audacious goals to provide (1) more treatments (2) to all people (3) more quickly. Other themes will include data science, training, and mentoring. Organizational efforts are underway and will be followed by initial stakeholder engagement to better understand the strengths in the broad

ecosystem of bringing more treatments to all people. Further updates will be provided at the May 2023 Council meeting.

Fiscal Year 2023 Budget

Dr. Rutter reported that the FY23 budget was signed into law on December 29, 2023, by President Joseph R. Biden. NCATS received an increase of 3.8 percent ($23 million) for the Clinical and Translational Science Awards (CTSA) Program and a 6.6 percent ($18 million) increase for non–CTSA Program activities. The overall increase to NIH was 5.5 percent ($2.5 billion), for a total appropriation of $47.7 billion. NCATS is looking forward to additional advances in translational science with this strong support from Congress.

Clinical Translational Science Awards (CTSA) Program Updates

Dr. Rutter highlighted some notable achievements in the CTSA Program since the last Council meeting, focusing on collaborations, and she provided examples of recent research.

- **Annual Meeting.** After a brief hiatus during the COVID-19 pandemic, NCATS convened the 2022 CTSA Program Annual Meeting on November 1 and 2 in Washington, D.C. The theme focused on diversity, equity, and inclusion, as well as access to health care. U.S. Food and Drug Administration (FDA) Commissioner Robert Califf, M.D., and Dr. Rutter were keynote speakers during the general session.

- **Advancing the Clinical Translational Science Enterprise: Virtual Roundtables.** NCATS had been discussing ways to enhance direct communication with the CTSA Program and convened the first series of roundtables in November 2022, largely starting with 60 principal investigators (PIs) and their executive leaders from across 25 institutions. The discussions focused on ways to promote communication across the consortium, provide feedback, and make requests for further opportunities to continue these discussions. When asked about the one word that describes the most important work of the CTSA Program, the roundtable participants responses most often included “collaboration,” “training,” “support,” “network,” “transforming,” “education,” and “informatics.” Dr. Rutter conveyed that she and Michael G. Kurilla, M.D., Ph.D., director, Division of Clinical Innovation, who oversees the CTSA Program, understand that this forum ensures that the CTSA Program and goals of the NCATS Strategic Plan are aligned.

- **Perceptions of Research Trustworthiness (PoRT) Scale.** CTSA PI Consuelo H. Wilkins, M.D., M.S.C.I., Vanderbilt University Medical Center, and her colleagues collaborated on a Recruitment Innovation Center–funded project. They developed a PoRT scale to better understand and address trust and distrust within minoritized racial and ethnic groups in the United States. These groups who are underrepresented in research also experience worse health outcomes. PoRT consists of scales that are well-validated in minority communities, which Dr. Rutter anticipates would begin to transform mistrust in biomedical research in these communities.

- **Study Sheds Light on Rare Genetic Disease in Children.** The University of Colorado Clinical and Translational Sciences Institute (CTSI) collaborated with the Rare Diseases Clinical Research Network (RDCRN) on a study to better understand the mechanisms of primary ciliary dyskinesia (PCD), a rare genetic disease. Children with PCD experience frequent lung, sinus, and ear infections and also have problems with reproduction as adults. The study results revealed

airway inflammation in children with PCD. These findings highlighted potential pathways for developing new therapeutics.

- **Updating the Diagnosis Paradigm for Lung Infections Caused by Soil Fungi.** The Washington University Institute of Clinical and Translational Sciences recently found more widespread issues associated with soil fungi in other areas of the United States. Soil fungi increase the risk of lung infections. Valley fever (Coccidioidomycosis) has been primarily linked to soil fungus heavily concentrated in the Southwest, including parts of California. Raising awareness of soil fungi infections linked to other regions across the country is leading to an update of the diagnosis. This update will help reduce the misdiagnoses of people within these areas by identifying the symptoms and those that overlap with other diagnoses, such as Valley fever.

- **FDA-Approved DuraFuse™ Dural Clips.** The Oregon Health & Science University Biomedical Innovation Program and the Oregon CTSI developed a device that enables closing sutures in a fraction of the time that it takes otherwise. Collaborating with NeuraMedica Inc. on commercialization, DuraFuse Dural Clips recently received FDA approval. Dr. Rutter highlighted that this is one example of advancing device development for enabling health care and potentially reducing concerns around the length of these surgeries.

- **Streamlined, Multisite, Accelerated Resources for Trials (SMART) Institutional Review Board (IRB) Platform.** NCATS has been involved with informing the national discussions on emergency preparedness, and the SMART IRB has been prominent in those discussions. The White House Office of Science and Technology Policy (OSTP) issued an RFI on clinical research infrastructure and emergency clinical trials. SMART IRB was specifically named as a model for facilitating adoption of a future Emergency Master Agreement framework. The SMART IRB significantly reduces the median number of days for IRB approval. Dr. Rutter commented that this is a model of how NCATS-supported programs collaborate to accelerate progress.

Clinical and Translational Science Awards Program Memoria

Dr. Rutter took a moment to remember CTSA Program colleagues who have recently passed away; all were leading scientists, scholars, physicians, and mentors in their respective fields. In addition to their academic appointments, Ralph Sacco, M.D., was director and PI at the University of Miami CTSI and also was a member of the CTSA Steering Committee; Susan Smyth, M.D., Ph.D., was senior associate director for the University of Kentucky Center for Clinical and Translation Science and also served on the CTSA Steering Committee; and Gerald Supinski, M.D., was an Institutional Mentored Career Development Award (KL2) program PI at the University of Kentucky Center for Clinical and Translation Science. Dr. Rutter reflected that the CTSA Program will continue to do great things because of the work that these scientists facilitated.

- **Rebecca Jackson Award for Outstanding Achievement in Education Innovation.** The Association for Clinical and Translational Science established an Outstanding Achievement Award in memory of founding director of The Ohio State University Center for Clinical and Translational Science and NCATS Council member Rebecca D. Jackson, Ph.D., who passed away in 2022. This award is one way to recognize Dr. Jackson's tremendous research contributions and leadership over the course of her career.

Division of Rare Diseases Research Innovation (DRDRI) Updates

Dr. Rutter reported updates across DRDRI programs and initiatives, touching on the background and context of the research.

- **Shortening the Diagnostic Odyssey.** People with rare diseases typically experience a prolonged diagnostic odyssey. For example, patients often have visits with many clinicians over several years and experience long waits before receiving an accurate diagnosis. NCATS has been seeking approaches to shorten the time to a diagnosis of a rare disease and released a funding opportunity announcement—Multidisciplinary, Machine-Assisted, Genomic Analysis and Clinical Approaches to Shortening the Rare Diseases Diagnostic Odyssey—using the biphasic UG3/UH3 mechanism. Alice Chen Grady, M.D., program officer, DRDRI, leads this program, and three projects were funded in FY22 and are in progress: 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; Machine-Assisted Interdisciplinary Approach for Early Clinical Evaluation of Neurodevelopmental Disorders; and Virtual Platforms for Genetics Evaluation in the Medically Underserved. These projects are examining electronic health records, 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.

- **Somatic Cell Genome Editing (SCGE) Program.** Translational science is not based on any one organ, disease, or discipline. NCATS has been supporting gene-targeted therapies and promoting many-diseases-at-a-time projects. The SCGE program is a Common Fund project managed by Philip J. (P.J.) Brooks, Ph.D., acting director, DRDRI, and supported by Deanna I. Portero, management analyst, DRDRI. Phase 1 (the first 5 years) has focused on technology development for gene-targeted therapies and has set the stage for clinical development for *in vivo* gene editing. Novel technologies were developed and examined in small- and large-animal models, evaluating safety and efficacy for many applications. An SCGE Toolkit has been established and contains the program's data (published and unpublished) and resources. All information is publicly available. Phase 2 of the program will transition into conducting preclinical and investigational new drug–enabling studies, improving assays and reagents, and initiating clinical trials in humans.

- **Accelerating Medicines Partnership® (AMP) and the AMP Bespoke Gene Therapy Consortium (BGTC).** The BGTC program celebrated its 1-year anniversary in November 2022. This program, which Dr. Brooks and his industry and the Food and Drug Administration (FDA) counterparts co-lead, is exploring adeno-associated virus (AAV) biology that aims to improve and optimize the dosages required during AAV gene therapies. The aim is to standardize and streamline regulatory requirements for approval of gene therapies for bespoke diseases. Several industry partnerships have been established in the BGTC. Disease nominations for the clinical workstream closed in February 2022; 61 nominations were received, and 14 leading candidates were selected. Final disease selections are anticipated in May 2023.

- **Rare Diseases Clinical Research Network (RDCRN).** More than 10,000 rare diseases exist, and leveraging the work being done across different networks and investigating similar symptomatology is essential. The RDCRN embodies the whole mantra of why NCATS' approach of addressing many diseases at a time is critical. Twenty teams are in the consortium, each

addressing at least three different related diseases. The RDCRN continues to engage other communities nationally and internationally.

- **A Rare Public Health Challenge Blog Post.** NCATS contributed a guest post to the *NIH Director's Blog* highlighting a rare diseases public health challenge. Dr. Rutter noted that the posted "Rare Diseases Are Not Rare Challenge" image she used illustrates that many rare diseases exist among us, both individually and in our communities.

- **Rare Disease Day (RDD) at NIH.** The RDD at NIH brings together all the voices, including scientists, clinicians, funders, patients, patient advocates, and leaders within the rare diseases community. This year's event will be held in person at the NIH Main Campus on February 28, 2023, and will be livestreamed via NIH VideoCast. Members interested in attending can register via the NCATS RDD 2023 website.

Tissue Chips in Space Program

Dr. Rutter reminded the Council that the Tissue Chips in Space Program has developed tissue chips, or microphysiological systems, that model human diseases and conditions, mimicking the pathology of major organs and tissues in the human body. The program is a partnership with the National Aeronautics and Space Administration (NASA), the Center for the Advancement of Science in Space (CASIS), and the International Space Station (ISS) National Laboratory. Tissue chips have supported gravity and microgravity experiments simultaneously and analyzed in parallel. Several launches of tissue chip projects to the ISS National Laboratory have occurred since inception of the program. The final launch is scheduled for March 2, 2023. Dr. Rutter remarked on this innovative, exciting program and congratulated Dr. Tagle and his team and the scientists for their incredible work. She expressed appreciation to NASA, the Center for the Advancement of Science in Space, the ISS National Laboratory, and the astronauts for their efforts.

NCATS COVID-19 Activities

Dr. Rutter provided an update on NCATS' COVID-19-related activities. She noted the spike in COVID-19 cases, which NCATS continues to monitor through the COVID-19 OpenData Portal.

- **National COVID Cohort Collaborative (N3C).** As of January 3, 2023, the N3C Data Enclave contains data from more than 17 million patients, 6.9 million of whom have received a COVID-19 diagnosis. More than 3,000 researchers are participating in this platform, which houses 21 billion rows of data. The N3C community continues to contribute to understanding long COVID-19 or post-acute sequelae of SARS-CoV-2 infection. Recent findings using N3C indicate that the severity of SARS-CoV-2 reinfections was similar to that of the initial infections, but the number of cases of long COVID-19 diagnosis also showed an increase after reinfections with re cent variants. RECOVER investigators have submitted or have in progress 13 manuscripts, are collaborating with the NIH *All of Us* program, and are promoting the initiative beyond journal publications to other NIH media outlets. The National Institute of Neurological Disorders and Stroke and the National Heart, Lung, and Blood Institute co-lead this effort.

- **Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Clinical Trials.** ACTIV is a public–private partnership managed by the Foundation for the NIH. NIH has activated six ACTIV trials investigating clinical targets across all stages of the disease, two of which Dr. Rutter highlighted. The ACTIV Master Protocol 1 of Immune Modulators (commonly called ACTIV-1 IM) trial focused on the inpatient population. Initial findings showed that abatacept and infliximab

failed to acceptably reach the primary endpoint (time to recovery at day 28), but the data on key secondary endpoints, day 28 mortality, and clinical outcomes were promising compared with placebo. NCATS is continuing to monitor this study, and findings will be published soon.

ACTIV-6 is an outpatient trial that used a decentralized approach and evaluated the reduction of COVID-19 symptoms in self-administered doses of medications delivered to patients who reported their responses in a series of questionnaires. Four study arms have been completed that examined the efficacy of repurposed drugs ivermectin, fluvoxamine, and fluticasone. Although no major differences were observed with ivermectin-400, ivermectin-600, or fluticasone-50, Dr. Rutter noted some important benefits from conducting these studies. The key findings and messages have informed the scientific community and provided insight to clinicians who are treating patients with COVID-19. The decentralized approach has been powerful in reducing the time to reach the study enrollment target. This approach also accelerated the time from study activation to release of the results in the public domain. The peer-reviewed articles are receiving positive attention.

Dr. Rutter summarized that NCATS mourns the loss of colleagues and friends. NCATS is standing on a firm foundation heading into the next decade, building on impactful advances. Excitement for engaging with stakeholders (e.g., CTSA roundtables) is building, and NCATS is looking forward to continuing these discussions to create the next iteration of the NCATS Strategic Plan.

Discussion

Annie M. Kennedy, B.S., inquired about plans to engage the broader rare diseases community in developing the 2024 NCATS Strategic Plan, prior engagement approaches, the milestones and timelines achieved, and ways to educate the community of such achievements, as well as the hurdles, to better inform the plan. Dr. Rutter explained that NCATS is in the process of developing its community engagement approaches, which will consist of internal and external engagements. She elaborated on three such approaches for external engagement: solicit input on the key goals of the strategic plan and highlight discussions around them; leverage existing community convenings among current stakeholders; and publish an RFI that would be publicly available for input from the community through the typical NIH channels. She noted the need to capitalize on the strengths and ongoing work and to complement rather than duplicate efforts.

Marshall L. Summar, M.D., expressed concern about the duplication of effort in convening the rare diseases research community, particularly with the interactions in Europe within the International Rare Diseases Research Consortium (IRDiRC) and others globally. Dr. Rutter recognized the concern and emphasized that NCATS' efforts are focused on rare diseases as a whole. Because translational science encompasses conducting translational research, increasing understanding of how to perform research on specific rare diseases and how to conduct that research on more than one disease at a time advances the field. Therefore, NCATS strategically engages with the community to discuss those areas, and some duplication has been beneficial for validation of efforts. For example, Dr. Brooks also serves on the IRDiRC, and these engagements help to ensure that NCATS is enabling rare diseases research.

Sergio A. Aguilar-Gaxiola, M.D., Ph.D., commented that engaging with and listening to the communities is complementary. He asked which communities (e.g., health equity) NCATS listens to, especially since community engagement is emphasized across the CTSA community. He also asked about specific outreach to communities that have and, in the future, could benefit from NCATS-supported research. Dr. Rutter explained that the CTSA Program has published reports on diversity, equity, inclusion, and accessibility, and they have focused on engaging and listening to diverse communities, as well as best

practices for engagement. The CTSA virtual roundtables are one way that NCATS is engaging the CTSA community, and these will be included in the strategic planning process.

Paul A. Harris, Ph.D., suggested convening a listening session with members from the CTSA Community Advisory Boards (CABs), which have extensive reach to the public. Dr. Rutter commented that NCATS had not convened such a session but could consider reaching out to these groups. She noted that a list of the CABs would be helpful.

Ms. Kennedy noted the process of drafting the 21st Century Cures Act legislation, which involved convening multiple stakeholder roundtables across the nation—composed of patients, patient advocates, clinicians, bench and translational scientists, and clinical trialists—to discuss opportunities for innovation and suggested revisiting those publications and transcripts to assist with the strategic planning.

Dr. Rutter will discuss with NCATS leadership a plan to convene the CTSA CABs as part of the strategic planning process and will solicit ideas from the CTSA community of specific groups to consider and some options for dates.

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

14:16:20 From Annie Kennedy to Everyone: One idea for the approach for the SP (if you haven't already considered this)… as you gather background an important source could be the many transcripts and publications from the Roundtables that were conducted by Congress in advance of the drafting of 21 CC. As you know, there were Roundtables convened throughout the nation that brought together a wide array of stakeholders. The yield was used to inform the content of the legislation. That said, so many of those themes brought forward would have direct applicability -- and might even help suggest a framework for your approach to stakeholder engagement? Just a thought.

14:20:20 From Joni Rutter to Everyone: Thanks @Annie -that's a fantastic idea to build from that set of activities for 21CC.

VIII. CLEARANCE OF CONCEPT

The Council received presentations on one new project that NCATS is considering for funding. At the end of the presentation, the members discussed the proposal and voted on whether to approve of NCATS' moving forward with the concept. Discussants for the concept were assigned prior to the meeting.

Introduction of the Office of Drug Development Partnership Programs (ODDPP) Concepts: Christine M. Colvis, Ph.D., Director, Office of Drug Development Partnerships Programs (ODDPP), NCATS

Christine M. Colvis, Ph.D., provided a brief review of ODDPP activities and introduced the Office's new concept. Dr. Colvis first welcomed new staff, Kihwa Kang, Ph.D., to the ODDPP. The overall goals of ODDPP are to develop partnerships that promote innovations, fill gaps in preclinical translational science from early discovery through early-stage clinical trials, and develop technologies and strategies to improve diversity, equity, inclusion, and accessibility in health care. Each ODDPP program corresponds to a different stage of the drug development pipeline. Two programs—the NIH Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®, and Illuminating the Druggable Genome—are NIH-wide efforts managed by NCATS. Four programs are NCATS-initiated: New Therapeutic Uses, LitCoin, Biomedical Data Translator, and Awards Supporting Cutting-Edge Technology for Translational Science (ASCETTS).

Preclinical Proof-of-Concept Studies for Rare Diseases Concept: Christine M. Colvis, Ph.D., Director, ODDPP, NCATS

Dr. Colvis presented a new concept on preclinical proof-of-concept studies for rare diseases, which are demonstrations of efficacy in a model system prior to conducting regulatory safety studies. A gap exists between early discovery/early preclinical development and investigational new drug (IND)–enabling development due to a lack of funding. The goal of this concept is to bridge the gap between novel compound development and initiation of IND-enabling studies, resulting in identification of meritorious compounds. The aim is to support efficacy testing for repurposing approved therapeutics to treat rare diseases.

NCATS proposes to provide funding to test the efficacy of meritorious compounds in an established rare disease preclinical model. This effort will require partnership with a rare diseases steering committee or oversight committee. NCATS anticipates that such a partnership would strengthen potential applications by bringing the patients' perspective into the translation process earlier than normal; encourage researchers who work adjacent to drug development to think more intentionally about the translational potential of their research; and increase use of existing rare disease models.

In terms of appropriateness for NCATS funding, this research puts patients first by requiring partnerships with rare diseases experts, patients, and patient advocates; increasing the use of existing rare disease models, on which meritorious compounds and repurposed therapeutics would be tested; and impelling basic scientists to think more intentionally about designing studies that withstand critical evaluation by industry and having more relevance to the patient population in question. The anticipated outcome will be strong preclinical efficacy data to attract subsequent investment in IND-enabling preclinical development within the rare diseases space. The potential impact is that several of the drug candidates will advance through development within other programs at NCATS or NIH and subsequently be used in clinical trials.

Reviewers are being asked to evaluate the number of compounds that transition into full IND-enabling preclinical development and to ensure that major obstacles are addressed (e.g., verifying that drug candidates are evaluated for merit during review, utilizing the best rare diseases models, increasing awareness in the rare diseases community of the partnership opportunities). The concept leverages other NCATS programs and initiatives, including the Division of Rare Diseases Research Innovation (DRDRI) Clinical Trial Readiness for Rare Diseases, Disorders and Syndromes program. In addition, the Division of Preclinical Innovation (DPI) has identified the transition from compound to full IND-enabling development as a "pain point" to be addressed. Strong efficacy data generated in this research would help alleviate this issue.

Discussion

Dr. Summar commended NCATS for developing this program. He noted a recent trend of family-based and patient-initiated organizations developing animal or biological models for rare diseases research and suggested connecting these groups with researchers who are conducting basic biology or therapeutic intervention trials. Dr. Summar also suggested broadly advertising this program to larger groups in the rare diseases community, including the National Organization for Rare Disorders.

Dr. Holman expressed his enthusiasm for the concept and shared his experience regarding developing small-molecule therapeutics and the challenge in receiving funding for the large disease targets. He explained that drugs with orphan disease designation attract investors, which enables the research to advance a drug to FDA approval; the larger disease targets can then be pursued. Dr. Holman noted that

success in using this approach requires determining the orphan indication that could potentially benefit from a specific discovery in development, partnering with orphan indication scientists to conduct the initial proof-of-concept studies, and identifying key stakeholders and venture capital investors. He encouraged the ODDPP to explore forums to engage stakeholders at symposia and to foster partnerships between scientists and stakeholders and investors in this space. Steven T. Pittenger, Ph.D., program officer, ODDPP, agreed with partnering and matching the groups with the rare diseases animal models with the venture capitalists and called attention to a workshop on pain research within the NIH HEAL Initiative℠ that convened investors and Small Business Innovation Research awardees to discuss their projects. A similar workshop could be hosted for rare diseases research; Dr. Pittenger will follow up with the Office of Strategic Alliance (OSA). Dr. Summar highlighted that the Blackstone Charitable Foundation sponsors a similar event and would be one group to connect with or model.

Matthias Kretzler, M.D., commented that connectivity maps and Library of Integrated Network-based Cellular Signatures have successfully examined mechanistic associations for known molecular pathways and would be an approach applicable to rare diseases research. Dr. Kretzler explained that the organ-on-a-chip will work with the appropriate induced pluripotent stem cells, which his laboratory recently demonstrated. A critical component is to map the disease molecularly beyond the genetic lesions to the activated pathways and those connections culminating in a model system map to the human disease. He noted that a genetically defined rare diseases network is becoming tractable and suggested that the request for applications for this concept include molecular phenotyping of model systems in the research scope, which he highlighted could be incentivized.

Ms. Kennedy agreed with engaging groups already active in this area of research—as well as with patients and patient advocacy groups—and establishing connections and engaging in specific matchmaking with organizations. She suggested contacting the Muscular Dystrophy Association Venture Philanthropy, which has been successful in identifying venture philanthropists to fund research.

Dr. Aguilar-Gaxiola underscored the need to better understand the translational aspect of the projects that will be supported and the measures of success. He suggested that applicants submit dissemination plans that involve working closely with the patients and their families on the translational component. Dr. Colvis noted that the aim also is to highlight the not-so-well-understood missed research opportunities in the field.

Dr. Pittenger and ODDPP leadership will solicit input from OSA on hosting a workshop with investors and rare diseases researchers and will leverage existing platforms (e.g., Blackstone Charitable Foundation).

Council members suggested that ODDPP connect or match family and patient rare diseases groups with researchers who are conducting rare diseases proof-of-concept studies.

Members unanimously approved the preclinical proof-of-concept studies for rare diseases concept.

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

14:27:22 From Annie Kennedy to Everyone: Or ask the PAGs what are best practices - what they'd do different next time.

14:28:56 From Joni Rutter to Everyone: yes @Annie -those are definitely the kinds of things we intend to ask.

14:37:23 From Annie Kennedy to Everyone: MDA has a program called MVP that does something very similar in the neuromuscular space.

14:43:43 From Steven Pittenger to Everyone: Thank you for sharing that information Annie! I will look into MVP.

14:48:57 From Marshall Summar to Everyone: I have never ceased to be amazed by the impact that bringing the basic researchers together with the patients has. Lasting impact on careers and efforts when they see that there is a real-world person that their work can possibly help.

14:53:35 From Ted Holman to Everyone: I completely agree. I still remember meeting stakeholders at a basic science conference. It was incredibly motivating

14:53:56 From Paul Harris to Everyone: +1 Marshall - agree with the transformational power of bringing researchers together with patients/participants.

IX. INVITED SPEAKER: Update on the NIH Data Management and Sharing Policy: Michael S. Lauer, M.D., Deputy Director for Extramural Research, NIH and Director, Office of Extramural Research (OER), Office of the Director, NIH

Michael S. Lauer, M.D., reported on implementation of the updated Data Management and Sharing (DMS) Policy and began with some background and history. Data sharing and the importance of data sharing for federally funded projects is an idea originating from the highest levels of government and is not a new topic. President Biden, who helped lead the development of the Cancer Moonshot^{SM} when he was vice president, emphasized the importance of data sharing as a core component of that program. In 2016, by overwhelming bipartisan majority, the 21st Century Cures Act was passed and signed by President Obama, and that law included a statute that the NIH director may require recipients of NIH awards to share scientific data generated from the awards to the extent feasible. Data sharing at NIH is required by law. The primary data sharing policy was implemented in 2003 and required submission of a data sharing and management plan for all awards greater than $500,000 in direct costs in any given year. Several other policies pertaining to specific programs and NIH institutes and centers (ICs) have been implemented, including the NIH Genomic Data Sharing Policy in 2014.

The development of the current DMS Policy has been an iterative process through consistent community engagement that began with the issuance of two requests for information—one in 2016 for strategies on data management, sharing, and citation and a second in 2018 on proposed provisions for a draft policy. In 2018, NIH published a request for comment, which included Tribal consultation and input from other federal agencies. The DMS Policy was released along with supplemental documents in October 2020, with the understanding that it would be implemented in January 2023.

Dr. Lauer explained that NIH wants data to be shared to advance rigorous and reproducible research and promote public trust in research. He described some studies and reports across these two key areas.

- **Rigorous and Reproducible Research.** The Center for Open Science conducted a study, subsequently published in the December 2021 issue of *eLife,* that examined the challenges in assessing replicability in preclinical cancer biology. The results showed that data could be obtained only for 68 percent of 193 experiments published in 53 high-impact peer-reviewed journals, even after contacting the authors of the original publications. Because effect sizes were found to be less than reported, some, but not all, experiments could be replicated. Dr. Lauer noted that these authors had not promised to share their data.

A 2022 European mixed-methods study reported in the *Journal of Clinical Epidemiology* evaluated 1,792 BioMed Central papers published in January 2019 that contained data availability statements. The results showed that only 7 percent provided the requested data.

Promising results of an assessment of clinical trial data usage of the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository established in 2000 showed that data from 88 of 100 available clinical trials were requested from external researchers at least once. The median time from when clinical trial data was made available in the repository to a first request was 235 days. A total of 277 articles were published on the basis of data from 47 trials, and citation rates mirrored those of NHLBI-funded investigators. As an external mid-career investigator at the time this data repository was operational, Dr. Lauer shared his experience of requesting and receiving timely data from the NHLBI data repository to support an epidemiology study, which he and his colleagues later published.

- **Public Trust in America's Research.** A 2019 Pew Research Center report on the trust and mistrust of scientific experts among Americans indicated that if data on a project are publicly available, the results are more likely to be trusted. Projects reviewed by an independent committee were even more trusted. Conversely, projects reviewed by the federal government were less trusted, and those by private industry were the least trusted.

Implementation of the 2023 NIH Data Management and Sharing (DMS) Policy

Dr. Lauer described the details of implementing the DMS Policy, which was effective January 25, 2023, and replaced the 2003 Data Sharing Policy. All research applications submitted to NIH must be accompanied by a DMS plan. Submitted plans are approved by the sponsoring institute, center, or office (ICO). Researchers must comply with the ICO-approved plan, and noncompliance may affect future funding.

Dr. Lauer noted that NIH defines scientific data as recorded factual material of sufficient quality to validate and replicate research findings, regardless of whether those data are used to support scholarly publications. Excluded are laboratory notebooks, preliminary analyses, case report forms, and objects. This Policy applies to research that generates data (e.g., research projects, career development awards, research centers), but does not apply to training (T awards), fellowship (F awards), construction (C06) and conference (R13/U13) awards.

Data are required to be shared no later than the release of a publication or at the end of an award cycle for unpublished data. Journal and repository policies will need to be considered. Additional expectations are that sharing be maximized; responsibly implemented in terms of protection, privacy rights, and confidentiality; and prospectively planned for at all stages of the research process. Potential limitations on data sharing consist of justifiable, ethical, and legal factors. These include informed consent; privacy or safety of research participants; explicit federal, state, local, or Tribal law regulation or policy; restrictions by existing or anticipated agreements with other parties; and data sets that cannot practically be digitized with reasonable efforts. The following reasons are not adequate justification for limiting sharing: the data set is small, the anticipated data will not be widely used, data are not thought to have a suitable repository. Additional considerations include Tribal sovereignty and the Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program policies.

To help the research community address these limitations, NIH established a Scientific Data Sharing website in April 2022 that serves as the central source for guidance. Aside from details on data management and sharing, this website contains information on genomics data sharing and model

organisms, and the content is updated on an ongoing basis. Comprehensive resources for understanding sharing policies also can be accessed from this website.

- **Plan Components.** Dr. Lauer discussed two major components of the DMS plan: elements and repositories. Applicants are requested to provide information on data type, related tools, software, and code; standards; data preservation, access, and timelines; access, distribution, and reuse considerations; and oversight of data management. A common theme of researchers was the need for examples of DMS plans, which many of the ICs have generated and posted to the data sharing website. NIH encourages the use of established repositories and can assist investigators in identifying those appropriate for their use. NIH ICs may designate specific data repositories in support of their funding opportunity announcements, which typically are managed by NIH. These are considered specialized, prioritizing data type and discipline-specific data, and can be found on the NIH-supported data repository list. Common examples include the National Library of Medicine's (NLM) database of Genotypes and Phenotypes and NHLBI's Biologic Specimen and Data Repository Information Coordinating Center. Other established repositories include institutional repositories, PubMed Central, and generalist data repositories (e.g., Dataverse, Dryad, Figshare) widely used in the scientific community.

- **Costs and Expenditures.** Dr. Lauer noted that NIH outlines the reasonable expenditures that can be considered as direct costs that occur during the award's performance period. These include costs for curating data, developing and supporting documentation, and preserving and sharing data through repositories, as well as local data management considerations. Costs for infrastructure, which typically are included as indirect costs, and those associated with the routine conduct of research are not considered data sharing costs. The NLM commissioned the National Academies of Sciences, Engineering, and Medicine to review what constitutes reasonable costs for various data management and sharing activities, and this information has informed the DMS Policy.

Data Management and Sharing (DMS) Plan Submission Process

Dr. Lauer explained that each plan or application should include a brief budget justification and description and a full budget proposal as a separate attachment. Peer reviewers will comment on the budget, and NIH program staff will assess the plans of fundable grants. Revisions to the plans following annual progress reports will be allowed but will require discussions with NIH program staff. Approved DMS plans become a term and condition of the research award, and progress is captured in the Research Performance Progress Report. NIH will perform compliance reviews annually. Failure to comply may result in an enforcement action, which the NIH will monitor and, to some extent, learn of noncompliance issues and resolutions from other groups in the research community. Dr. Lauer called attention to a recent report by Northwestern University library staff highlighting 10 simple rules for maximizing the recommendations of the NIH DMS Plan.

Outreach and Implementation

Dr. Lauer updated the Council on the DMS Policy implementation outreach efforts. He expressed appreciation to Cindy Danielson, Ph.D., associate director, Systems Integration, Office of Extramural Research (OER); Taunton Paine, M.A., director, Scientific Data Sharing Division, NIH Office of Science Policy (OSP); and Julia Slutsman, Ph.D., director, Genomic Data Sharing Policy Implementation, OER, for their tireless efforts over the past 3 years in preparing for the DMS Policy implementation. Dr. Lauer reviewed some outreach efforts across NIH and other federal agencies. To acquaint the broader

community with the updated DMS Policy, NIH hosted several webinars and seminars in 2022, and these will continue in 2023. In August 2022, the White House Office of Science and Technology Policy (OSTP) released a memorandum titled "Ensuring Free, Immediate, and Equitable Access to Federally Funded Research," indicating that articles that are published about work supported by the federal government should be publicly accessible, without embargo, at the time of or shortly after publication. This memorandum also emphasized having digital persistent identifiers connected to various aspects of research. Dr. Lauer noted that the NIH DMS Policy aligns with OSTP priorities on data sharing.

Discussion

Elaine Collier, M.D., senior advisor to the director, Office of Translational Medicine, NCATS, commented that NCATS has been working with OSP and OER on the implementation of the DMS Policy and has organized a group comprising representatives from each office, division, and program to share experiences and lessons learned. This group has developed educational programs on data sharing for the NCATS staff.

In response to a question from Marshall Summar, M.D., about addressing small sample sizes encountered in rare diseases research, Dr. Lauer explained that the Policy is not insisting that researchers share all data, but they must submit a DMS plan and describe their data, leading to a dialogue between the researchers and NIH program staff to discuss what is reasonable and feasible for their studies.

Paul Harris, Ph.D., asked about the responsibility of an institution to keep sharing data that have been deposited in a repository that is no longer active and the data sharing process after a grant closes. Dr. Lauer explained that data stored in an NIH repository will be available for the long term. Purchasing data sharing agreements during the active phase of a grant is one option for extending the grant beyond its closing. NIH is in the process of reviewing the uniform guidance on regulations pertaining to grant management across the federal government and will address questions about grant closeouts and cost principles.

Because some researchers, especially junior investigators, have limited resources at their respective institutions for supporting data sharing activities, Matthias Kretzler, M.D., strongly encouraged NCATS to continue the listening sessions in the scientific community to better understand the effect of the DMS Policy implementation in the long term. Dr. Lauer noted that one message that NIH is promoting is that sharing high-quality data early benefits junior investigators to help them start their own research programs.

Annie Kennedy commented on the lack of NIH-funded investigator data sharing with the patient communities and the significant barriers to establishing relationships with the researchers. She asked whether patients or patient advocacy groups (PAGs) had been involved in formulating the DMS Policy, ways of ensuring undue bias against some populations, and whether NIH has the ability to retrospectively determine data sharing noncompliance. Dr. Lauer explained that NIH did solicit input from patients and PAGs, and that OSP would have the specific details. He further explained that the new requirement for submission of DMS plans is one way NIH is ensuring issues (e.g., bias against certain populations) are addressed, and NIH is organizing an internal panel of data management experts as plan reviewers. Dr. Lauer added that NIH awards grants to institutions, not individual scientists, and can take the necessary actions on that level to address compliance concerns, including restrictions on funding.

Dr. Summar suggested touching base with the nationally recognized Black Women's Health Imperative to solicit its input on how the implementation of the DMS plans would affect enrolling patients in clinical trials, especially because of the existing trust issues. He asked about implementation of this policy

internally at NIH, and Dr. Lauer confirmed that the rules were the same for intramural and extramural researchers. Dr. Summar suggested that NIH develop a reporting mechanism to help inform the extramural community of internal implementation efforts.

Sergio Aguilar-Gaxiola, M.D., Ph.D., noted that the Clinical and Translational Science Awards Community Engagement Program is endeavoring to use its master database funded by NCATS to recruit diverse bench researchers at their respective institutions and asked about plans to consider this type of model as a potential data sharing repository. Dr. Lauer noted that the NIH *All of Us* program is one such model and will include updates of its use in this context in a future discussion on this topic.

Council members encouraged long-term follow-up on the DMS Policy implementation regarding impacts on rare diseases research and establishing a reporting mechanism to highlight the progress internally and externally.

PROGRAM UPDATE: Office of Special Initiatives (OSI): Danilo A. Tagle, Ph.D., M.S., Director, OSI, NCATS; Dobrila D. Rudnicki, Ph.D., Program Director, OSI, NCATS; and Samuel G. Michael, Chief, Information Technology Resources Branch, NCATS

Dr. Tagle provided a program update on OSI and focused his report on the A Specialized Platform for Innovative Research Exploration (ASPIRE) program. He recognized the OSI team, which includes program officers, administrative assistants, and program managers whose expertise spans several scientific disciplines. He welcomed two new staff members: program officer Dmitriy V. Krepkiy, Ph.D., who was previously National Institute of General Medical Sciences (NIGMS) SBIR/STTR coordinator, and program manager Kristifor Sunderic, Ph.D., who was previously an American Association for the Advancement of Science Fellow at the National Cancer Institute.

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. The programs and initiatives within OSI are intended to be catalytic and transformative, resulting in a paradigm shift in the field. ASPIRE is one such program, and it reflects NCATS' goals to provide more treatments to all people more quickly by employing automation and artificial intelligence to diversify chemical libraries and compounds being developed.

ASPIRE combines intramural and extramural programs of NCATS and seeks to explore the chemical space to identify biological drug targets. Dr. Tagle invited Dobrila D. Rudnicki, Ph.D., program director, OSI, and ASPIRE extramural initiative lead, to provide those updates and Samuel G. Michael, chief, Information Technology Resources Branch, ASPIRE intramural lead, to provide updates on the infrastructure and organization of the program.

A Specialized Platform for Innovative Research Exploration (ASPIRE): Extramural Programming

Dr. Rudnicki reminded the Council of the unmet need in the chemical and biological spaces that is central to the development of the ASPIRE program. The key translational challenge is that the vast uninterrogated chemical space (10^{63}) of potential pharmacologically active molecules exceeds the undrugged biological space (5×10^5). A reaction toolkit for accessing the relevant chemical space is limited in its capabilities and is outdated. Additionally, translational problems in drug development exist. The average time to develop a drug is 10 to 15 years, with an average cost of $2.6 billion from development to market. Shortening this cycle with elemental chemistry and biology will accelerate drug development. To address these issues, NCATS organized a brainstorming session as part of the process to develop the NCATS 2017 Strategic Plan to discuss areas of focus for translation. Participants identified leveraging automation to discover new drugs as one such area.

Government-funded and academic efforts in this research area at that time included the Defense Advanced Research Projects Agency program on automating small-molecule discovery and synthesis (commonly called Make-It) and the NIH Common Fund Glycoscience program led by NIGMS. Industry had several initiatives focusing on automation of chemical processes. Efforts to apply automation to discovery of new chemistries were limited. To address this gap, NCATS convened the Workshop on Automated Chemical Synthesis in October 2017 to identify the associated research opportunities, challenges, and roadblocks. Participants identified technical (e.g., data capturing, reporting, validating) and cultural challenges (e.g., lack of collaborations, lack of data sharing). High-quality data for automation and artificial intelligence need to be unbiased and standardized, with sufficient data points and compatible machine learning platforms.

Dr. Rudnicki described ways that automation would have an impact on chemistry, including liberating chemists from bench routines to spend time on more difficult synthetic challenges or intellectual pursuits. The desired users will be expert chemists, to allow them to focus on more complex tasks; nonexpert chemists, to allow them to increase productivity; and biologists, informatics scientists, and anyone able to formulate a molecular hypothesis. The optimal operational model should consist of a small number of capital-intensive robotic automation sites, with many innovative afferents, and should also support robust, affordable devices.

NCATS proposed the ASPIRE concept in September 2017, which the Council approved, culminating in an official program launch in 2018. The aims are to predict novel structures capable of modulating specific targets; to enable the small-scale synthesis of the suggested molecules; to test molecules in physiologically relevant biological assays; and to iteratively provide feedback to guide the design and synthesis of additional molecules. The overall goal is to address the translational roadblocks by combining automation, engineering, synthetic chemistry, biological screening, and artificial intelligence/machine learning.

The ASPIRE workflow is primarily designed to bring novel, safe, and effective treatments to all patients more quickly at lower cost. This workflow builds on the power of recent and emerging technological innovations, promotes multidisciplinary collaborations among a wide spectrum of stakeholders, and addresses health disparities and advances health equity. To this end, ASPIRE fits with NCATS' mission to demonstrate and disseminate innovative technologies that will bring diagnosis and treatments to all patients. It aims to deliver on NIH's efforts to increase reproducibility and scientific rigor.

- **Proof-of-Concept Study and Design Challenges.** In 2018, a pilot ASPIRE opportunity was funded by the NIH HEAL Initiative℠ through challenges and prize competitions. Challenges support the most innovative and cutting-edge ideas appropriate for addressing a health emergency and provide a flexible alternative to traditional funding mechanisms, such as contracts and grants. The ASPIRE Stage 1—Design Challenges for Translational Innovation in Pain, Opioid Use Disorder, and Overdose—encompassed five challenges: Challenge 1, Integrated Chemistry Database; Challenge 2, Electronic Synthetic Chemistry Portal; Challenge 3, Predictive Algorithms; Challenge 4, Biological Systems; and Challenge 5, Integrated Solution. The 17 winners were announced at the October 28, 2019, award ceremony, which also doubled as a team-building and networking event. In 2020, the ASPIRE Stage 2—Reduction-to-Practice Challenge—launched. The grand prize winner—Iterative Learning and Automated Modular Platform for Optimum Nonaddictive Analgesic Discovery—and runner-up—Closed Loop Bio-Assay-Chemputer for Next-Generation Analgesics (BioChemputer)—were announced in October 2022.

Dr. Rudnicki noted that NCATS intramural scientists have begun to establish the NCATS ASPIRE platform, which Mr. Michael further described. She highlighted that the next stage of ASPIRE, building

collaborations between the NCATS ASPIRE Laboratory and other research programs, is underway and described one recent initiative.

- **Collaborative Research Program.** This ASPIRE initiative has two goals: (1) Facilitate translational research between NCATS intramural scientists and the extramural community and (2) enhance the ability to discover and develop new chemistries toward previously undrugged biological targets across many human diseases and conditions. Two initiatives have been developed in this program, and requests for application (RFAs) have been released. One RFA is focusing on new chemistries for undrugged targets, and the second RFA is soliciting virtual approaches toward new chemistries for undrugged targets. Projects have been funded in each of these research areas, and details were provided later in the meeting.

A Specialized Platform for Innovative Research Exploration (ASPIRE) Intramural Infrastructure

Mr. Michael described the engineering component of ASPIRE, noting that this program is reimagining the research laboratory ecosystem as being composed of a modern laboratory bench and an integrated automated solution. Standardized, automation-assisted template development and template amplification both are essential for this new research laboratory design. Radical improvements to the existing structure will be necessary for a "smart" laboratory. These improvements include reagent handling, live feedback technologies, product isolation capabilities, optimized evaporative processes, and automated characterization.

NCATS has designed a fully integrated benchtop chemistry explorer encompassing serial processing of samples across a dashboard from the development of new chemistry to the production of testable hypotheses. The explorer works in concert with an enterprise-level reaction analytics platform, the ASPIRE Integrated Computational Platform (AICP). The ASPIRE framework, which includes the dashboard, serves to digitize and automate the bench, using the Internet of things (commonly called IoT) to automatically capture information from laboratory equipment housed in the proposed ASPIRE physical laboratory space and is being used by chemists and others in chemistry automation. The AICP is critical for linking both NCATS researchers and external researchers to the laboratory, thus providing them the ability to initiate experiments virtually.

ASPIRE is a five-step automated, closed-loop processing system. Steps in this Drug Discovery Design-Make-Test-Analyze (DMTA) cycle include *in silico* design, preparation, isolation, purification, and biological testing. Mr. Michael highlighted that NCATS has extensive experience in automating biological testing and that he looks forward to working with colleagues internally, as well as with external collaborators, on automating the processes in the DMTA cycle. He noted that after delays due to COVID-19, construction of the ASPIRE compound management space and physical modules has been completed, and some are operational. From a workflow perspective, ASPIRE's aim is autonomous assay execution and chemical synthesis that involves assay optimization across chemical libraries, followed by high-throughput and virtual screens, data analysis, chemistry route planning, and automated synthesis.

Mr. Michael explained that ASPIRE is a collaborative effort, the scope of which is too broad for NCATS alone. The extramural funding has allowed NCATS to augment internal development with world-class academic and commercial collaborators to build this innovative, robust platform, all with a team science approach. The ASPIRE Collaborative Research Program awardees are filing key roles, augmenting NCATS' capabilities, and enabling pilot studies. Key collaborators (and capabilities) include R. Graham Cooks, Ph.D., M.S., Purdue University (reaction screening); Gaurav Chopra, Ph.D., M.S., Purdue University (ledger for interactive query execution); Barry A. Bunin, Ph.D., Collaborative Drug Discovery Inc. (collaborative informatics); Connor W. Coley, Ph.D., M.S.CEP., Massachusetts Institute of Technology

(virtual informatics); and Lee Cronin, Ph.D., University of Glasgow (BioChemputer). Mr. Michael reported that this team of collaborators has approved signing a five-way NIH Research Collaborative Agreement to freely discuss future efforts.

Mr. Michael noted some continued growth of capabilities of the ASPIRE platform, including determining optimal reaction conditions through automation, using automated processes to produce molecules, exploring novel analytical techniques to determine which compounds were produced, and capturing data across instruments and processes.

Future Directions

Dr. Rudnicki noted future directions of the ASPIRE program. These include expanding collaboration with other NCATS initiatives and with other ICs and federal agencies, continuing collaboration with NIH HEAL Initiative℠ partners using Other Transactions, exploring additional chemical space by including natural product libraries and other biological targets and using synthetic biology, creating opportunities to support new chemistries that are amenable to automation, and developing new initiatives using SBIR grants and contracts to spur private-sector innovations. In closing, Dr. Rudnicki expressed appreciation to the ASPIRE team, NCATS leadership, OSI and other NCATS staff, and external collaborators for their support of ASPIRE.

Discussion

When asked about plans to partner with large biotechnology or pharmaceutical companies that already have significant investments is this research area, Mr. Michael explained that NCATS and ASPIRE have been working on collaborative projects with such companies in this space. For example, a Cooperative Research and Development Agreement was signed with Strateos, Inc. for development of an A-channel chemical synthesis device.

Dr. Wayman asked whether a specific disease to pilot ASPIRE had been considered and where ASPIRE aligns in the drug discovery process. Dr. Rudnicki explained that this phase of the program is examining undruggable targets, and she envisions that ASPIRE could provide insight for new treatments in support of rare diseases projects in the future. Mr. Michael added that ASPIRE fits with preclinical drug development from a screening perspective, and he noted that the technologies and techniques involved align downstream to clinical approaches.

X. PUBLIC COMMENTS

Comments from the public were accepted until February 10, 2023 (15 days after the meeting), and will be appended to the minutes.

XI. ADJOURNMENT OF THE OPEN MEETING

Dr. Rutter thanked the participants for their input. The next meeting is scheduled for May 25, 2023, and is planned as an in-person session. Dr. Rutter adjourned the meeting on January 26, 2023, at 4:47 p.m. EST.

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