Department of Health and Human Services
National Institutes of Health
National Center for Advancing Translational Sciences
35th Meeting of the
Advisory Council

Minutes of Virtual Meeting
January 19, 2024

The National Center for Advancing Translational Sciences (NCATS) Advisory Council held a meeting in open session on January 19, 2024, from 12:30 p.m. to 4:22 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 19, 2024, from 11:02 a.m. to 12:08 p.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

Gregory P. Jarosik, Ph.D., on behalf of 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.
Matthias Kretzler, M.D.
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.
Marshall L. Summar, M.D.
Annica M. Wayman, Ph.D.

***Ad Hoc* Council Members**

None present

Representative Members

None present

***Ex Officio* Members**

Monica M. Bertagnolli, M.D., Director, NIH

Others Present

Monica M. Bertagnolli, M.D., 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.

Review of Grant Applications

The Council reviewed 88 research, research-related, and training grant applications with primary assignment to NCATS for a requested amount of $60,934,071 in first-year direct costs. The Council concurred with the recommendations of the initial review groups. For the record, it is noted that applications with secondary assignment to NCATS were also considered.

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

Joni L. Rutter, Ph.D. adjourned the closed session of the NCATS Advisory Council meeting on January 19, 2024, at 12:08 p.m. EST.

III. CALL TO ORDER, OPEN SESSION

Dr. Rutter called the meeting to order and welcomed members and guests to the 35th meeting of the NCATS Advisory Council. She noted that Gregory P. Jarosik, Ph.D., deputy director, DEA, would perform the duties of the executive secretary on behalf of Anna L. Ramsey-Ewing, Ph.D. Dr. Jarosik conducted the roll call and reviewed the meeting agenda. He noted the meeting logistics and reminded attendees that the open session was being VideoCast.

IV. APPROVAL OF 2024 NCATS ADVISORY COUNCIL OPERATING PROCEDURES: Gregory P. Jarosik, Ph.D., on behalf of Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council

Members unanimously approved the 2024 NCATS Advisory Council Operating Procedures.

V. CONFIRMATION OF DATES FOR FUTURE MEETINGS: Gregory P. Jarosik, Ph.D., on behalf of Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council

Dr. Jarosik confirmed the schedule for the meetings of the NCATS Advisory Council for 2024 and 2025:

- May 23, 2024
- September 19, 2024
- January 30–31, 2025 (virtual meeting)
- May 22, 2025
- September 18, 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 September 2023 meeting. During that meeting, she conveyed that President Joseph R. Biden had nominated Monica M. Bertagnolli, M.D., as the new NIH director; NCATS leadership is growing; and the center had made several impactful advances. Other program updates included information about NCATS' Division of Clinical Innovation (DCI) and Office of

Drug Development Partnership Programs (ODDPP) and the Advanced Research Projects Agency for Health. After this review of the previous meeting, Dr. Rutter presented updates on NIH and NCATS staff changes; made announcements; and reported on the fiscal year 2024 (FY24) budget and NCATS 2024–2029 strategic planning. She discussed COVID-19-related activities and highlighted progress in some of the NCATS offices, divisions, and programs.

News and Announcements

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

- **NIH Staff Changes and Recruitments**

Dr. Rutter noted that Dr. Bertagnolli assumed her role as NIH director on November 9, 2023, and has been conducting NIH-wide interviews. In an interview published in the November 24, 2023, issue of the *NIH Record*, Dr. Bertagnolli outlined the following as chief among her key priorities: ensuring that clinical trials yield the best results by increasing the diversity of participants, embracing the rapid expansion of new learning-based analytical tools and ensuring that their use improves care for all people, restoring trust in science by making it accessible to all communities and inspiring the next generation of doctors and scientists, and leveraging commonalities across all diseases. Dr. Rutter also noted that Dr. Bertagnolli would elaborate on her vision for NIH later in the meeting.

Dr. Rutter announced that W. Kimryn Rathmell, M.D., Ph.D., was named director, National Cancer Institute (NCI). She reminded the Council that several leadership positions are open within NIH institutes and centers (ICs) and the NIH Office of the Director and that searches are in progress. These include directors for the National Library of Medicine and the Fogarty International Center.

- **NCATS Council and Staff Changes, Memorials, Recruitments, and Retirements**

Dr. Rutter extended appreciation to two NCATS Advisory Council members who have completed their tenures and are retiring: Matthias Kretzler, M.D., and Marshall L. Summar, M.D. Dr. Summar also served on the Cures Acceleration Network Review Board.

Dr. Rutter next reflected on the life and career of Council member Rajesh Ranganathan, Ph.D., who passed away in 2023, and recognized his contributions. Dr. Ranganathan was a consultant with Sun Pharma Advanced Research and previously led the translational efforts at the National Institute of Neurological Disorders and Stroke. He helped launch the Blueprint Neurotherapeutics Network, played a pivotal role in the establishment of NCATS, and initiated the translational science training program at the NIH Office of Intramural Training & Education.

Several leadership positions are open across center divisions and offices, and NCATS is close to announcing the new scientific director of the Division of Preclinical Innovation (DPI), as well as new staff in various positions within the Office of Translational Medicine (OTM). The process is also underway to fill the positions of deputy director and chief of staff.

Dr. Rutter announced that Clare K. Schmitt, Ph.D., NCATS acting deputy director, is retiring on January 26, 2024, after 26 years of service to the federal government. Dr. Rutter expressed appreciation to Dr. Schmitt, who served in this capacity for 3 years, noting that her mastery of emotional intelligence has been a valuable guiding light for NCATS. Dr. Schmitt joined NIH in 2000 and has worked in microbiology, with a keen focus on microbial pathogenesis, foodborne and waterborne illnesses, and the translation of basic science into life-saving solutions. During the pandemic, she was instrumental in helping NCATS navigate its response in this area of research.

- **NCATS Appropriations: Fiscal Year 2024**

Dr. Rutter reported that NCATS is operating under a continuing resolution through March 8, 2024. The status of the House and the Senate Appropriations Committees bills—which propose a flat budget for NCATS—has not changed since the last Council update.

News and Announcements

Dr. Rutter highlighted recent NIH-wide and NCATS-specific announcements and events. She explained that during its December 14–15, 2023, meeting, the NIH Advisory Committee to the Director (ACD) discussed and highlighted several proposals of interest to NCATS, which she further described.

- **Working Group on Re-envisioning NIH-Supported Postdoctoral Training.** The Working Group's 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 Working Group proposed six recommendations: increase pay and benefits for NIH-supported postdoctoral scholars, create and expand mechanisms to support the full talent pool of postdoctoral scholars, facilitate transition of postdoctoral scholars into their next career stage, promote the training and professional development of postdoctoral scholars and their mentors, support safe and diverse perspectives and research environments within institutions, and improve the means to measure and share career progression for postdoctoral scholars. NIH is actively considering and developing plans for implementing these recommendations.

- **Working Group on Catalyzing the Development and Use of Novel Alternative Methods (NAMs) to Advance Biomedical Research.** The charge to this ACD working group is to identify types of alternative methods being developed 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 NAMs.
  Dr. Rutter acknowledged the working group members, who represent the U.S. Food and Drug Administration (FDA), U.S. Environmental Protection Agency (EPA), NIH/NCATS, and the extramural community. Three NAMs have been identified to consider for NIH investments: *in chemico* methods, which include cell-free methods and chemical genetics; *in vitro* methods, such as cultured cells, induced pluripotent stem cells (iPSCs), microphysiological systems or tissue chips, and 3-D tissue bioprinting; and *in silico* methods for computational approaches. NAMs are valuable for conducting basic research, uncovering human pathological and physiological mechanisms, and translating knowledge into products and practice. The ACD NAMs Working Group proposed the following recommendations to catalyze the development and use of NAMs: prioritize the development and use of NAMs, establish resources and infrastructure for high-quality data sets, promote dissemination of NAM technologies, invest in training to bolster the next cadre of scientists, facilitate interdisciplinary teams, promote social responsibility in both the creation and the deployment of NAMs across the research life cycle, and support and maintain coordinated infrastructure to develop and use NAMs effectively and responsibly.

- **Complement Animal Research in Experimentation (Complement-ARIE).** The ACD NAMs Working Group's recommendations on NAMs will be integrated into Complement-ARIE, which is an NIH Common Fund program supported by 17 ICs, including NCATS. Complement-ARIE strategic

planning activities began with three public listening sessions in October 2023 that convened representatives from multiple sectors to gain insight into current opportunities and roadblocks in NAM development. Other strategic planning activities to inform concept development include conducting a landscape analysis and sponsoring an ideation prize. Further details can be found on the Complement-ARIE Strategic Planning website.

- **NCATS Interactions with the U.S. Food and Drug Administration.** Dr. Rutter updated the Council on NCATS' recent interactions with the FDA. She explained that because of its place in the translational pipeline and spectrum of preclinical and clinical activities, NCATS has been strengthening its partnership with the FDA and is continuing to work with the agency on various topics, including gene therapy, NAMs, and natural history studies for rare diseases.

- **Center for Biologics Evaluation and Research (CBER)–NCATS Research Retreat.** An informal NCATS–CBER research retreat was held on November 13, 2023, at the FDA White Oak Campus. The overarching theme was gene therapy and gene editing and ways to include relevant areas of informatics.

- **NCATS–National Center for Toxicological Research (NCTR) Retreat.** This retreat was held on January 8, 2023, in Jefferson, Arkansas. The main goals were to identify gaps and opportunities for advancing human cell–based models for safety and efficacy and to discuss areas of need for validation and qualification of models for rare diseases. Dr. Rutter remarked that NCTR is a valuable partner because of its work with animal models, which will be critical to understanding and incorporating NAMs.

- **Natural History Studies and Registries in the Development of Rare Diseases Treatment Workshop.** NCATS and the FDA are planning a hybrid workshop to be held on May 11, 2024, at the FDA White Oak Campus and virtually. The aim is to address the role and design of registries and natural history studies to inform the development of treatments for rare diseases, including aspects of clinical trial design (e.g., clinical outcome assessments, endpoints, and biomarkers). Workshop registration will open soon.

NCATS Program Updates

Dr. Rutter provided an update on innovations at NCATS and their impact across programs.

- **IPSC-Derived 3-D (i3D-RARE) Workshop.** In September 2023, NCATS convened stakeholders from different areas of the biomedical research community to consider i3D-RARE, a precision medicine platform of cellular models for accelerating the development of therapeutics for rare diseases. The workshop participants discussed gaps and bottlenecks in the development process—as well as the challenges of using these models for rare diseases, which is critical because animal models for investigating rare diseases are limited. The workshop was recorded and can be accessed on NCATS' YouTube channel.

- **3-D Tissue Models for Gene Therapy Efficacy Testing: Platform Vector Gene Therapy (PaVe-GT) Program.** Dr. Rutter noted that Elizabeth A. Ottinger, Ph.D., senior program manager, Therapeutics for Rare and Neglected Diseases, DPI, and Marc Ferrer, Ph.D., director, 3-D Tissue Bioprinting Laboratory, Early Translation Branch, DPI, have developed 3-D tissue models for gene therapy through the PaVe-GT program. This program's pilot project, using a platform design and adeno-associated virus (AAV) gene therapy vector for rare diseases, is evaluating four rare diseases in studies at the NIH Clinical Center: two congenital myasthenic syndromes

involving the neuromuscular junction and two organic acidemias. Dr. Rutter highlighted two efficacy testing models being developed by the PaVe-GT team. In collaboration with University of Pittsburgh researchers, liver spheroids for the organic acidemias gene therapy were generated using a patient's iPSCs. The team has created the organoids and is evaluating ways to infuse the AAV vectors and observe the functional readouts to determine the value and usefulness of this approach. Additionally, biofabricated neuromuscular junction tissue models for congenital myasthenic syndromes were generated using CRISPR-edited iPSCs in collaboration with National Heart, Lung, and Blood Institute investigators. Functional readouts from this approach also are being evaluated.

- **NCATS Large Language Model (LLM) Colloquium.** On November 20, 2023, NCATS convened a hybrid meeting to discuss opportunities for using LLMs in translational science and invited Eric J. Topol, M.D., Scripps Research Institute, as the keynote speaker. Participants at the LLM colloquium identified evolving needs in multiple areas, including computational and data resources, trustworthiness, consensus best practices, regulations, and policy. The meeting was recorded and can be accessed via the NCI website.

- **LitCoin.** The Office of Drug Development Partnership Programs leads the LitCoin program, which has two main goals: (1) incentivize data and knowledge sharing and (2) build machine-readable, artificial intelligence (AI)–ready knowledge from free text of scientific literature. In terms of building machine-readable, AI-ready knowledge, Dr. Rutter emphasized that LLMs will automatically identify key findings in submitted materials and will allow quick, accurate, and consistent identification of scientific research findings at scale. Within this process, findings are stratified into subject, object, and relation and are assembled into machine-readable paper- and field-level knowledge graphs. Before being incorporated into LitCoin, the resulting knowledge graphs will be validated by the author and peer reviewed to ensure accuracy of the AI-ready knowledge. As reported during the September Council meeting, RTI International and its collaborators (Renaissance Computing Institute and CoVar, LLC) were awarded a contract to assist in developing the LitCoin algorithm and its underlying knowledge graph. Current efforts have focused on building a custom LLM prototype, HEALpaca, that leverages Llama 2—Meta Platforms, Inc.'s LLM—which has been helpful for translational science, rare diseases, and related fields. HEALpaca, which is part of the NIH Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®, is being iteratively improved through manual evaluation of results, reannotation, and retraining. Early evidence suggests that HEALpaca may outperform OpenAI's GPT4 in human comparison of model outputs.

- **Translational Science (TS) Education.** In 2023, NCATS published eight TS principles and printed stickers and magnets conveying these principles for distribution at scientific meetings, training events, and recruiting events. Dr. Rutter has been highlighting the TS principles in her Director's Messages, and these principles were a key theme during the annual Clinical and Translational Science Awards (CTSA) meeting. To help the scientific community identify models of education and training in this area, NCATS published a literature review on TS education and training aligned with the NCATS definition of TS. Further details can be found on the NCATS Translational Science Education and Training website. In 2024, NCATS will debut a suite of open-access online educational videos describing effective approaches in TS, case studies of NCATS successes, and education and training resources available to the scientific community.

Clinical and Translational Science Awards (CTSA) Program: Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) and National COVID Cohort Collaborative (N3C)

Dr. Rutter provided an update on NCATS' COVID-19–related activities, including ongoing efforts and new directions.

- **NCATS National COVID Cohort Collaborative Preprint Study on Paxlovid™ Effectiveness.** In response to a request from the White House COVID-19 Response Team, NCATS used the N3C Data Enclave to prepare a report on the use of Paxlovid (nirmatrelvir/ritonavir). The findings of the *National COVID Cohort Collaborative Paxlovid™ Use Characterization Report*, which addresses urgent public health questions about this drug, are still in preprint. Results revealed that Paxlovid adoption was initially low in 2021 and increased in 2022 and 2023 with widespread utilization, but it has not reached its maximum potential. This publication has received positive attention in the press and was recently reported in the *New York Times*, *Washington Post*, and *USA Today*. Dr. Rutter noted that Josh Fessel M.D., Ph.D., senior clinical advisor, DCI, who coordinated this effort, sought to address the question on whether receiving Paxlovid within the recommended time frame would reduce the likelihood of death or hospitalization. The data showed that approximately 48,000 deaths and 135,000 hospitalizations could potentially have been prevented if the eligible adults had received Paxlovid. NCATS remains interested in understanding the use of therapeutic tools for fighting and combating COVID-19 because the disease still affects public health.

- **Accelerating COVID-19 Therapeutic Interventions and Vaccines 6 (ACTIV-6) Trial**. ACTIV-6 is a fully virtual 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. The metformin arm of ACTIV-6 is evaluating the final of five drugs used during the 5-year study. The Early Outpatient Treatment for SARS-CoV-2 Infection (COVID-19) trial (COVID-OUT), which was completed prior to this study, suggested a benefit of using metformin to prevent long COVID. This phase of the ACTIV-6 trial is being managed for NCATS by Sarah E. Dunsmore, Ph.D., program director, OTM; it will evaluate a primary endpoint of time to recovery from acute symptoms, with a 6-month follow-up. ACTIV-6 has enrolled nearly 1,800 participants since the trial opened, and the goal is to perform these evaluations and follow-ups in 3,000 participants. Data from ACTIV-6, which is examining metformin in a randomized trial, combined with real-world metformin usage data collected under similar conditions through the N3C Public Health Answers to Speed Tractable Results (PHASTR), will form and test a use case for trial emulation methodology. NCATS launched PHASTR in 2023 with the aim of extracting from the N3C Data Enclave electronic health record (EHR) data of outpatients who started taking metformin after a positive COVID-19 test. Information about the Metformin Target Trial Emulation Using N3C Data Enclave and PHASTR, as well as validation of COVID-OUT results, can be accessed from the N3C Dashboard.

- **National Virtual Research Infrastructure.** N3C is overperforming and has been successful due to the efforts of the NCATS teams supporting this program and those of the extramural community. The CTSA Program has contributed to and shared the vision of N3C, and the Rare Diseases Clinical Research Network (RDCRN) laid the framework for integrating disparate data types into this virtual research infrastructure. NCATS already had the tools in place to build and prepare for such a health crisis as the COVID-19 pandemic. The CTSA Program further expanded this readiness. Dr. Rutter expressed appreciation to all who have worked to create this national

virtual research infrastructure with governance, interoperability, de-identification, and best practices, all of which are important for evaluating the various data types.

Dr. Rutter explained that NCATS started N3C when COVID-19 emerged and now is exploring ways to expand into non-COVID-19 applications. An effort being led by Kenneth R. Gersing, M.D., is comparing EHRs from two hospitals that are completely disparate and developing model-to-model conversions. The next step would be to use code map services with these models and map those onto Fast Healthcare Interoperability Resources, for example. This process entails collaboration, real-world data linkage, FDA submissions and pharmacovigilance, and controlled vocabulary transformation for these disparate EHR data sources. Additionally, NCATS is considering moving to a tenant model—a federated approach in which the data are housed at an academic medical center and computing resources are shared—and is testing this model for feasibility. Investigators interested in a research question can deliver their data to an enclave similar to N3C. Other users then have the opportunity to add their data, thus creating tenant models of a particular research question that researchers can use and evaluate.

NCATS Division Updates

Dr. Rutter provided brief updates on progress in DPI and the Division of Rare Diseases Research Innovation (DRDRI).

- **Rare Disease Day (RDD) at NIH 2024.** RDD at NIH is planned and organized by DRDRI and brings together all the voices within the rare disease community, including scientists, clinicians, funders, patients, patient advocates, and other leaders. This year's event will be held in person at the NIH Bethesda Campus on February 29, 2024, and will be livestreamed via NIH VideoCast. Featured sessions include discussions of AI and its role in rare diseases research, recent approvals and advancements in gene therapy, and rare disease stories from our community. Members interested in attending can register through the NCATS RDD 2024 website.

- **Shared Molecular Etiologies (SaME).** DRDRI funded two projects under the Basket Clinical Trials of Drugs Targeting SaME in Multiple Rare Diseases (UG3/UH3 Clinical Trial Required): (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. Both projects received "Safe to Proceed" letters from the FDA. The Basket Clinical Trials of Drugs Targeting SaME in Multiple Rare Diseases (U44 Clinical Trial Required) initiative uses the Small Business Innovation Research (SBIR) mechanism; applications are due by March 14, 2024.

- **Somatic Cell Genome Editing (SCGE) Program.** The SCGE program, a Common Fund project managed by Philip J. (P.J.) Brooks, Ph.D., deputy director, DRDRI, is transitioning to Phase 2, advancing the Phase 1 gene-editing activities toward clinical development. One challenge in transitioning SCGE from Phase 1 to Phase 2 was the lack of targeted delivery systems for delivering genome editors to somatic cells. To address this issue, NCATS launched the Targeted Genome Editor Delivery (TARGETED) Challenge in September 2023. The TARGETED Challenge is a multiphase competition funded through the NIH Common Fund. The goal is to deliver targeted therapies to hard-to-reach places in the body and understand how to innovate in this space to make gene editing a reality for a variety of diseases. Thirty winners were announced in the first phase of the TARGETED Challenge, and the second phase is underway. An informational webinar is scheduled for January 25, 2024.

- **Therapeutic Development Branch (TDB) Projects.** DPI's TDB achieved several regulatory milestones in 2023, including FDA drug approval to treat muscular dystrophy and Investigational New Drug (IND) Safe to Proceed treatments from the FDA. TDB also held pre-IND meetings with the FDA and received Orphan Drug and Rare Pediatric Disease Designations from the FDA for a variety of rare disease treatments.

- **Intramural Training Program.** DPI matured its Intramural Training Program with several accomplishments in 2023. Belen Hurle, Ph.D., the new director of Intramural Translational Training, and Marcus G. Hodges, Ph.D., lead, Intramural Trainee Development, launched a range of new opportunities. These include courses and workshops, grant writing retreats, and networking for career development. Drs. Hurle and Hodges also expanded engagement with two national professional societies dedicated to fostering a diverse scientific workforce: the Annual Biomedical Research Conference for Minoritized Scientists and the Society for Advancement of Chicanos/Hispanics and Native Americans in Science.

NCATS Strategic Planning 2024–2029

Dr. Rutter briefly highlighted the status of the NCATS strategic planning process for developing the center's 2024–2029 strategic plan. NCATS has evaluated the feedback received from stakeholder communities (i.e., CTSAs, NCATS staff, public roundtables, and the RDCRN), and is at the point of drafting the strategic plan. Further details will be provided during the May 2024 Council meeting.

Summary

Dr. Rutter summarized that NCATS is operating under a continuing resolution until the 2024 federal budget is approved. NCATS has had several impactful advances—especially in data science, gene therapy, and gene editing—and has been solidifying and deepening interactions with the FDA. The 2024–2029 strategic plan is being drafted and is on schedule. The NIH director, Dr. Bertagnolli, has been invited to share her vision for NIH. Today, program updates include information about NCATS' Office of Special Initiatives (OSI) and Office of Strategic Alliances (OSA).

Discussion

Sergio A. Aguilar-Gaxiola, M.D., Ph.D., encouraged requesting public comments on the draft strategic plan when it is made available, especially from the community stakeholders. Meredith D. Temple-O'Connor, Ph.D., branch chief, Policy Branch, Office of Policy, Communications and Education, explained that NCATS released a request for information (RFI), NOT-TR-23-027, for comments on the draft framework. The RFI closed on November 1, 2023, and more than 50 responses were received. Dr. Temple-O'Connor further explained that ICs typically post their draft strategic plans on their websites and provide all constituents the opportunity to review and provide feedback prior to the plans being finalized. The tentative timeline is that a first draft with substantial content will be prepared for discussion during the May 2024 Council meeting. The draft will then be posted to the NCATS website. In addition, the communications team is working on approaches for reaching the various groups, including specific outreach to the public roundtable participants. Dr. Rutter added that NCATS can consider another RFI but speculated that including information about the draft plan in the monthly Director's Message will be more effective outreach to the community.

Dr. Aguilar-Gaxiola noted the increased awareness in the community engagement field about the importance of trustworthiness and how critically important it is that institutions and agencies be trustworthy. He called attention to a pending update to the Centers for Disease Control and

Prevention's (CDC) *Principles of Community Engagement,* in which trustworthiness was added as a fundamental element for advancing health equity. Dr. Rutter remarked that she views trust and trustworthiness as different but intertwined terms. Both were clear themes in the community discussions about the NCATS strategic plan for 2024–2029.

Annica M. Wayman, Ph.D., commented on the linkages between programs and initiatives, such as preclinical research, LitCoin, gene-editing studies, and rare disease models. She noted that the TS principles and printed stickers and magnets can be distributed to the private sector to reach newly established translational science teams. Dr. Wayman also emphasized increasing awareness of the FDA IND submissions and including an impact section in the new strategic plan. Dr. Rutter noted that NCATS' new website includes an impact webpage to highlight the success of the programs and initiatives. A graphic is being considered for the strategic plan.

Dr. Summar suggested incorporating machine learning and chatbot systems into natural history studies to ask less formalistic questions. He also suggested including these types of tools for interacting with patients about their data, which potentially could allow for broader data collection.

VII. INVITED SPEAKER: NIH Director's Introduction: Monica M. Bertagnolli, M.D., Director, NIH

Joni L. Rutter, Ph.D. introduced Monica Bertagnolli, M.D., the 17th NIH director, who is the first surgeon and the second woman to hold this position. Dr. Bertagnolli previously served as the 16th National Cancer Institute (NCI) director. She has led translational science initiatives within the NCI-funded cooperative groups program, now known as the NCI National Clinical Trials Network (NCTN) and also was a chair of the Alliance for Clinical Trials in Oncology, which is an NCTN member organization.

Dr. Bertagnolli began her remarks by noting that she had the opportunity to serve as first assistant to a former postdoctoral fellow in her laboratory and surgical oncology trainee Stephanie L. Goff, M.D., who is a senior surgeon at the NIH Clinical Center in the Surgery Branch. Dr. Bertagnolli discussed NIH as a galvanizing force, as well as the budget climate, and shared guiding principles and her vision for NIH.

NIH's Galvanizing Force: The Desire for Long, Healthy Lives

Dr. Bertagnolli stated that the health of the U.S. population is declining, which is a trend that must be reversed. The desire for long, healthy lives for everyone is a unifying and galvanizing force across all disciplines, all walks of life, and all political arenas. The research community must work with great urgency, especially since the U.S. life expectancy is low compared to peer nations, despite greater spending in the U.S. health care system. Life expectancy was declining in the United States long before the COVID-19 pandemic, and the increased life expectancy in 2022 has not compensated for the additional deaths caused by the pandemic.

According to the 2021 report *High and Rising Mortality Rates Among Working-Age Adults,* from the National Academies of Sciences, Engineering, and Medicine (NASEM), this decline in life expectancy seems largely related to an increase in mortality among working-age adults, ages 18 through 64. The main contributors to this decline are a dramatic increase in deaths due to drug poisoning, alcohol poisoning, and suicide and slow progress in reducing deaths due to cardiovascular disease. These contributors are some of the core issues in health that the research community can and must make an effort to reverse. The 2021 NASEM report highlighted this as a national population health crisis and a trend that threatens the future of families and the social fabric of communities, as well as the productivity and competitiveness of America.

Guiding Principles

Dr. Bertagnolli stated that as she meets with leaders across NIH, she is shaping her plans to identify what NIH can do to address this health crisis, especially in the current budget climate. She shared some of the principles that guide the NIH mission.

First and foremost, work is not finished when scientific discoveries are delivered but is finished when all people are living long and healthy lives. NIH and its partners must do whatever is necessary to achieve this ultimate aim, which requires robust, sustained attention to advancing scientific discoveries. Second, NIH research accomplishments are dependent upon the laboratory, clinic, and community. It is increasingly recognized that NIH is unable to achieve its aims without also considering the community to be its arena for research. NIH has an unprecedented opportunity to embrace and increase access to innovation. As a biomedical research institution, NIH must ensure that advances benefit the people who need them, especially residents in rural areas, which is one segment of society that has had disproportionately poor health outcomes. Third, progress is accelerated when advanced scientific methods, such as new data analytics, are applied to data that include everyone and when new discoveries are rapidly and equitably adopted into clinical care.

New advances in information technology and data science, while familiar to many researchers, have also captured significant public attention with the emergence of LLMs (e.g., ChatGPT). NIH and its researchers have been using this technology and have been developing new methods that present new opportunities. Knowledge and technology have developed to the point where it should be possible to deliver evidence-based, data-driven health care to every patient. The remaining problem is social engineering. NCATS is at the forefront of being able to solve this problem. AI is already revolutionizing what is possible in medical research and care, but to realize its potential for improving health, the research community needs to invest in a secure and sustainable data sharing infrastructure that reaches everyone.

Budget Climate

Dr. Bertagnolli remarked that NIH is facing critical needs—needs that extend into the future—in a time of very challenging fiscal restraints. The key for NIH is to focus on what it can do as a biomedical research institute to ensure that advances reach the people who need them. The NIH is very concerned about the budgetary pressures and the difficult decisions that will need to be made in the near term. Dr. Bertagnolli is optimistic that Congress will be able to avoid drastic cuts to NIH and sister agencies across the U.S. Department of Health and Human Services (HHS); however, the flat budget that is projected will have a significant negative impact on biomedical research. NIH has always sought the best new ideas and science; nonetheless, even current funding levels are not sufficient to fully realize great ideas and the potential of new discoveries.

What Should NIH Do?

Dr. Bertagnolli stressed that in times of uncertainty, the younger generation of researchers is always the most adversely affected. The field could lose a generation of researchers unless they receive all possible support. NIH needs to do everything it can to continue to fund the best science and to support those who will be leading in the future. Dr. Bertagnolli and NIH staff—who are thoughtful, dedicated, and focused—have been discussing what NIH should do to have the most positive impact for health. During this period of setting critical priorities, she is envisioning what to promote through her leadership at NIH.

Dr. Bertagnolli anticipates putting two primary priorities in place as NIH director. The first priority is to connect research with primary care to optimize outcomes for patients. This connection aims to better engage all communities, including those that are underrepresented, by meeting people where they already receive care; to use EHRs in partnership with sister agencies across HHS to engage people in research; to increase research capabilities and efficiency with innovative study designs that address common health issues, particularly prevention and implementation studies; and to rapidly disseminate evidence to guide patient and provider decisions. The technology and tools are available to assist these efforts but are not being fully harnessed. The biomedical field currently has an abundance of data, and federal regulations now require NIH-funded researchers to share their data publicly. The second priority is, therefore, to expand biomedical research data use to inform new research and improve health outcomes. To make the best use of this influx of data, Dr. Bertagnolli envisions the National Library of Medicine (NLM) as a revitalized hub for this effort. NIH will focus on identifying the data needed to improve health and ensuring that the people who are asking important questions have access to the right data.

Dr. Bertagnolli remarked that her vision is to integrate data from basic and social science research, public health, and clinical care in a way that focuses on the data's users, not just how the data are stored. NIH needs to increase capacity for data hosting, enable low-cost access to data using open industry data standards, support broad access to advanced analytics and computational power, and increase education and workforce development. The most effective approach to addressing the foreseeable data storage issue and preserving the creativity, autonomy, and responsibility of individual research teams is to employ a federated architecture for data use. This approach is not new and aligns with the recommendations regarding data quality and analytic methods conveyed in the 2013 NASEM report *U.S. Health in International Perspective: Shorter Lives, Poorer Health*. She emphasized that the U.S. health disadvantage has increased in the decade since this report was published, and solutions to this problem are required now.

Discussion

Marshall Summar, M.D. expressed a desire for EHRs to be transformed from a billing system to an information-gathering system that includes associated elements. He suggested that NIH find ways to transform the EHR into a true health driver. Dr. Bertagnolli commented on the long-standing observation that the obstacle to this transformation is the lack of willingness to work together across federal agencies, rather than the lack of technology or data standards. She also commented that NIH is aware that trust in biomedical research is a problem in the United States, and NIH does not want to convey the message to the public that the data are being handled inappropriately. NIH is working on a system that provides each individual the opportunity to (1) grant permission to use his or her data and/or (2) be contacted about future relevant studies, which would be critical to people with rare disorders. Dr. Summar added that nearly 90 percent of participants in rare disease registries (e.g., National Organization for Rare Disorders) are willing to be re-contacted about new findings relevant to their health and also are willing to share their data accordingly. Dr. Bertagnolli highlighted an ambitious goal to inform study participants when their data have been included and published in medical literature.

Paula K. Shireman, M.D., M.B.A., commented that clinicians often are performing data entry for EHRs rather than focusing on the patient. She pointed out that as a surgeon, one challenge of integrating with the primary care physician is trying to get the whole ecosystem to work. Simpler additions to research studies, such as addressing medication adherence and providing primary care physicians the associated billing codes to follow up with their patients, would be the most effective. Dr. Shireman asked about

NIH's perspective on using State Health Insurance Assistance Programs (commonly called SHIP) to improve dissemination and implementation research. Dr. Bertagnolli emphasized that NIH serves the patients, clinicians, and caregivers, and in terms of care, NIH aims to enhance and facilitate the clinician–patient relationship. Through research, NIH determines what works and what does not. Dr. Bertagnolli noted that she meets weekly with leaders from the Centers for Medicare & Medicaid Services, CDC, and FDA to discuss working across agencies to address both research and care delivery.

Sergio Aguilar-Gaxiola, M.D., Ph.D., commented on meeting patients where they receive care and asked for input on how this would reflect addressing barriers to access to care of many populations and their relative lack of service utilization. Dr. Bertagnolli commented on one example of where this model works. M. Margaret Kemeny, M.D., a surgeon and director of the Queens Cancer Center in New York, reports that three-quarters of her patients receive Medicaid, and many do not have insurance and are new immigrants. Dr. Kemeny opened a food pantry and daycare in the clinic to assist mothers who are receiving chemotherapy; she removed barriers to care by addressing the needs of that community. The needs will vary by community, and a one-size-fits-all model will not be suitable for every clinic.

Mattias Kretzler, M.D. commented on the approach of the Rare Diseases Clinical Research Network (that allows patients to take a leading role in the activities, which has reduced mistrust. Patients are engaging with stakeholders and are helping to ensure that the research is understood and adopted. The NIH *All of Us* Research Program is a model in which the patients are in charge of their data and scientists can work with patients where they are. Dr. Kretzler added that this principle has been demonstrated effectively in his field of kidney precision medicine, where they have built community consensus regarding research participation. He emphasized focusing on building trust by empowering patients to participate in the science.

Paul A. Harris, Ph.D., appreciates the focus on trust and emphasized that the return of value to the research participants in diverse communities is critical. He asked Dr. Bertagnolli her thoughts on building trust through making data sources accessible and available in a safe way to educators and students. Dr. Harris speculated that when they are taught with real-world information about real-world health problems, students will gain an appreciation for data and data methods. Dr. Bertagnolli explained that the NLM can be used as a home for many data initiatives. NLM's main focuses are education, access, and the provision of tools to the people who can actually use them. An approach that incorporates education into the doctor–patient relationship, which is a focus of NIH, can help build trust.

Dr. Bertagnolli envisions patients sharing their data with the clinician, who shares with the patient where their data resides, the results, what the disease means, and the clinical question being addressed. This approach promotes building the clinician–patient relationship. Dr. Rutter noted that NCATS is proposing new tenant models for data, of which education is one component. The aim is to encourage new data scientists, those experienced in medical science, and power users to participate in data science efforts to inform understanding the unmet data needs and making those data usable for addressing clinical or research questions. Dr. Bertagnolli called attention to the NCI Childhood Cancer Data Initiative (CCDI) that is building a user community of data shared from every child with cancer in the United States. The CCDI is linked to a molecular characterization protocol and recently launched a new program to increase the number of power users of these data.

VIII. PROGRAM UPDATE: Office of Special Initiatives (OSI): Danilo A. Tagle, Ph.D., M.S., Director, OSI, NCATS

Danilo A. Tagle, Ph.D., M.S., provided an overview of and update on Office of Special Initiatives (OSI) activities. OSI is composed of a diverse multidisciplinary team of scientists, including geneticists,

neuroscientists, molecular and cellular biologists, chemists, physicists, and biomedical engineers. 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. OSI's activities span the range of translational science from fundamental research to discovery development, preclinical development, clinical development, and regulatory acceptance. All the programs within OSI adhere to NCATS' operating principles of "the three D's": developing the technology, demonstrating its utility, and disseminating the technology for use by the community.

Overview: Programs and Initiatives

OSI has a number of programs at various stages across the three D's, encompassing AI-driven manufacturing technologies; diagnostics and detection technologies; quantum technologies; Common Fund–supported programs, such as Extracellular RNA Communication and Stimulating Peripheral Activity to Relieve Conditions; National Science Foundation collaborations on Cyber Physical Systems and the National Robotics Initiative; and *in vitro* modeling technologies, including 3-D bioprinting and tissue chips/microphysiological systems (MPS) for drug screening.

- **Synthetic Technologies for Advancement of Research and Therapeutics (START).** This program seeks to use synthetic biology approaches for the production of compounds or delivery therapeutics. START is led by Dobrila D. Rudnicki, Ph.D., program director, OSI.

- **A Specialized Platform for Innovative Research Exploration (ASPIRE).** The ASPIRE program involves a collaboration among NCATS intramural and extramural scientists to establish physical and virtual modules for automated synthetic chemistry, AI and machine learning, engineering, informatics, and biological testing. ASPIRE also is led by Dr. Rudnicki.

- **Sensing Conditions with Electronic Nose Technology (SCENT).** This program is led by Leah Toloso-Croucher, Ph.D., program officer, OSI, and Chariz P. Johnstone, Ph.D., scientific program analyst, OSI. SCENT uses volatile organic compound detection to identify specific signatures for particular human diseases.

- **Rapid Acceleration of Diagnostics (RADx®) Radical (RADx-rad).** OSI manages two RADx-rad programs. One, led by Drs. Croucher and Johnstone, uses electronic smell technology from skin and breath to detect signatures for SARS-CoV-2 and long COVID. The second—led by Christine M. Happel, Ph.D., program officer, OSI, and Dr. Johnstone—uses exosome-based isolation technologies to detect SARS-CoV-2 and host immune response.

- **Quantum Information Sciences.** This new program is in the early stages of development and leverages the latest advances in quantum technologies, focusing on early detection, diagnostics, and device and drug development. Geetha Senthil, Ph.D., deputy director, OSI, leads this program.

- **Exosome Therapeutics for Regenerative Medicine (ExTReMe) Initiative.** ExTReMe focuses on the industrialization and translation of extracellular vesicles for use in regenerative medicine. Dr. Happel leads this program.

Tissue Chip Program at-a-Glance

Dr. Tagle reminded the Council of the translational challenges in drug development. The average time to develop a drug that reaches the market is 10 to 15 years, and the average cost is $2.6 billion. Current tools used for drug development—such as 2-D cell culture and animal models—do not accurately predict human responses. Less than 12 percent of drugs entering clinical trials result in approved medicines; 55 percent fail because of lack of efficacy, and 28 percent fail because of toxic effects. To overcome these translational challenges, predictive tools must become more specific to humans, and therapeutic modalities must become more personalized. Tissue chips are one such predictive tool.

The NCATS Tissue Chip for Drug Screening Program was established in 2012 to provide a human cell–based solution to translational challenges in drug development. The program focused on safety pharmacology for the first 5 years (2012–2017), followed by disease models and efficacy (2018–2023), and it currently is addressing clinical trials and precision medicine (2021–2025). NCATS partners with 18 ICs; other federal agencies, including the FDA, EPA, Defense Advanced Research Projects Agency, National Aeronautics and Space Administration (NASA), and Biomedical Advanced Research and Development Authority; and private organizations, including the International Consortium for Innovation and Quality in Drug Development MPS Affiliate (IQ MPS Affiliate), to implement this program.

Dr. Tagle focused the remainder of his update on how NCATS is deploying the technology for use in personalized medicine, building confidence in the technology, working toward regulatory acceptance, and building community.

Tissue Chips Models of Human Disease for Predictive Toxicology

Dr. Tagle demonstrated the utility of human tissue chip models in predicting the human physiological response.

- **Liver-Chip: Drug-Induced Liver Injury (DILI) Modeling.** DILI is the most common cause of acute liver failure, and adverse drug reactions may result in discontinuation of a drug, hospitalization, liver transplantation, or even death. Fialuridine (FIAU) was developed as an antiviral agent against hepatitis B; animal models did not reveal any dangerous side effects, and the FDA approved the drug for clinical trials. Subsequently, FIAU was shown to be highly toxic in Phase 1 clinical trials and led to the deaths of 5 out of 15 trial participants due to the formation of steatosis. In a 2019 study evaluating human and rat tissue chips, FIAU treatment in human liver chips resulted in dose-dependent steatosis and reduced liver function that was not observed in rat liver chips. In a follow-up liver-chip study to predict DILI that evaluated 22 compounds previously withdrawn from use in humans, the results demonstrated that human liver chips exhibit 87 percent sensitivity and 100 percent specificity in predicting hepatoxicity, thus outperforming common animal models and liver spheroids (a common preclinical model). The human liver–chip was able to predict toxicity that the animal models were not able to identify.

- **Neuromuscular Junction–Chip: Rare Autoimmune Demyelinating Neuropathies Modeling.** Chronic autoimmune demyelinating neuropathies are a group of rare neuromuscular disorders that include chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN). Animal models to examine these disorders are limited. A tissue chip model consisting of co-culture of human primary Schwann cells (SC) and iPSC-derived motoneurons (MNs) was developed. Using this neuromuscular junction on a chip, serum isolated from 15

patients with CIDP or MMN and containing antibodies (i.e., anti-GM1 IgM and IgG) sufficient to activate the classical complement pathway in SC-MN tissue chips resulted in detection of the biomarkers C3b and C5b-9. Efficacy testing of a candidate drug, TNT005, which is a monoclonal antibody that inhibits complement component C1 protease, rescued the serum-induced complement deposition and functional deficits, whereas treatment with an isotype control antibody had no rescue effect. These efficacy data and other related data sets have been included in an FDA IND application and are being evaluated in a Phase 2 clinical trial sponsored by Sanofi.

Tissue Chips in Space: Age-Related Disease Modeling

Dr. Tagle explained that the aim of the Tissue Chips in Space program is to study human biology and disease that otherwise would be difficult or take longer on Earth, such as aging. Research has shown that the microgravity environment can accelerate the effects of aging. In partnership with NASA, the Center for the Advancement of Science in Space, and the International Space Station National Laboratory (ISS National Lab), NCATS has supported projects that examine these physiological changes in astronauts. Such projects have evaluated immunosenescence, drugs crossing the blood–brain barrier, the modulization of the immune system from the bone marrow as a consequence of lung infection, post-traumatic osteoarthritis, proteinuria and kidney stone formation, cardiac dysfunction, muscle wasting or sarcopenia, and gut inflammation and the microbiome.

Dr. Tagle shared a video of NASA astronaut Lieutenant Colonel Jasmin Moghbeli and Japan Aerospace Exploration Agency astronaut and heart surgeon Satoshi Furukawa, M.D., both stationed at ISS National Lab, endorsing NCATS' Tissue Chips in Space program. He further elaborated on the translational benefits for Earth of biomedical research in low-Earth orbit and in space. This program sponsored nine payloads to the ISS National Lab, which have identified age-related markers of cardiovascular deconditioning, among other achievements. The projects have enabled miniaturization and automation of MPS technologies and better understanding of the effects of cosmic radiation, microgravity, and isolation to develop interventions and countermeasures applicable to health on Earth. Other benefits include enabling capabilities in biomanufacturing (e.g., protein crystallization), 3-D bioprinting, regenerative medicine, and telemetry and robotics. One area of interest for future applications is long shelf-life pharmaceuticals and pharmacology on-demand capabilities. NCATS released two requests for applications (RFAs) (RFA-TR-23-017 and RFA-TR-23-018) to further advance the miniaturization and automation of MPS technologies. The Tissue Chips in Space program concept was renewed during the September 2023 Council meeting, and notices of funding opportunities are being developed.

Clinical Trials on a Chip Program and Precision Medicine

Dr. Tagle noted another area demonstrating the usefulness of tissue chips: prostate cancer metastasis to bone marrow. Metastatic castrate-resistant prostate cancer is lethal, and no curative therapies are available. NCATS' Clinical Trials on a Chip program is conducting a study in parallel with a Phase 2 single-arm clinical trial for sacituzumab govitecan-hziy, or IMMU-132 (Gilead Sciences, Inc.). Tumor biopsies and blood are collected from 50 participants enrolled in the study and are profiled using patient-derived bone metastasis chips, emulating the tumor microenvironment to identify responders versus nonresponders. Participants are then stratified for more efficient clinical trials.

Building Confidence in Tissue Chips

Dr. Tagle noted NCATS' validation efforts and highlighted an increased use of MPS in the pharmaceutical industry.

- **Tissue Chip Validation Framework.** NCATS has established a validation framework for tissue chips. Physiological validation is performed by the developers of the technology through publications of the findings. For analytical validation, NCATS funded the establishment of Tissue Chip Testing Centers (TCTC) at Massachusetts Institute of Technology and Texas A&M University and a federated MPS Database (MPS-Db) managed by the University of Pittsburgh. The aim is to independently test the results of the physiological validation for robustness through reproducibility, reliability, and relevance of the data generated. In the final stage of the validation framework—the industrial validation—NCATS encouraged the formation of self-sustaining business models to continue these efforts. The Massachusetts Institute of Technology TCTC transitioned to a contract research organization model, Javelin Biotech. The Texas A&M University TCTC switched to a pay-for-play model, forming the Texas A&M Tissue Chip Validation Consortium in collaboration with academia, government, and industry. The University of Pittsburgh leveraged the MPS-Db and launched BioSystics, Inc. (now Numa Biosciences, Inc.) and the BioSystics Analytics Platform (BioSystics-AP™).
- **Industry Uptake of Tissue Chips.** NCATS partnered with the IQ MPS Affiliate and co-authored a series of publications detailing MPS that are fit-for-purpose for industry use in terms of various organ systems, types of biomarkers, and assays needed, particularly in the areas of high need within industry and drug development. Commercial entities, such as Emulate, Inc. supply the tissue chips, and large pharmaceutical companies are the end users. MPS already are being used to inform internal portfolio decision-making by pharmaceutical companies across multiple phases of drug development, including target validation.

Dissemination: Microphysiological Systems Database/BioSystics Analytics Platform (BioSystics-AP)

Dr. Tagle noted that NCATS established the MPS-Db as a way to build confidence in tissue chips by allowing access to the data and disseminating the information. Experimental data from tissue chips or MPS are incorporated with metadata from clinical data sets, preclinical data, and data on universal compounds that have been tested in humans. Analytical tools have been developed and are available for determining experimental model reproducibility, compound safety and efficacy, and mechanisms of disease and actions of compounds. Researchers also will have the ability to develop computational models for absorption, distribution, metabolism and excretion, and toxicity and disease pathology. In addition, NCATS OSA encourages the formation of startup and spinoff companies with an interest in 3-D tissue models. These companies (30 to date) and projects have primarily been supported through NCATS and/or NIH SBIR funds.

Regulatory Acceptance

NCATS established the Translational Centers for Microphysiological Systems (TraCe MPS) to accelerate the translational use of MPS in drug development through regulatory acceptance and adoption for industrial use. A Letter of Agreement between NCATS and the FDA is required. NCATS intends to fund three or four centers across the United States. Each center would advance four or five validated MPS with a specific context of use and would work with the FDA to develop the required FDA qualification submission package to qualify the MPS as drug development tools. NCATS OSI expects that TraCe MPS

will result in MPS that are fit-for-purpose for industry needs, have specific context of use, and meet regulatory qualification criteria as a drug development tool for rapid dissemination.

Community Building: International MPS Community

Dr. Tagle highlighted another important aspect of dissemination: establishing an international MPS community. The goal is to engage major stakeholders across academia, industry, and regulatory agencies to connect, exchange, and educate one another on the use of tissue chips. NCATS has funded two MPS World Summits, one in New Orleans, Louisiana, in 2022, and the second in Berlin, Germany, in 2023. Both were well attended, and participation is growing. A third summit is planned for June 2024 in Seattle, Washington. To train the next generation of MPS scientists in existing and new MPS technology, NCATS is forming an International MPS Society. The goal is to accelerate the use of MPS to improve health, welfare, and the environment.

NCATS' investments in tissue chips and *in vitro* modeling have catalyzed interest in Novel Alternative Methods (NAMs), not only within NIH, but across federal agencies and the biomedical research community. NCATS' approaches and NIH's new initiatives, such as Complement-ARIE, provide an opportunity to integrate data sets to establish a common data ecosystem. Dr. Tagle expressed appreciation to the tissue chips program staff—Passley Hargrove-Grimes, Ph.D., Dmitriy V. Krepkiy, Ph.D., and Kris Sunderic, Ph.D.—and the Trans-NIH MPS Working Group for their support.

Dr. Tagle noted that OSI is seeking Council input on other areas of biomedical research applications to leverage tissue chip technologies, additional stakeholders to engage for dissemination, other activities to promote widespread adoption, ways that NIH can build on NCATS' investments to enhance the goals of Complement-ARIE, areas of integration with other NAMs, and coordination with international funding and regulatory agencies.

Discussion

Matthias Kretzler, M.D. noted three approaches NCATS can consider: Use AI-driven disease modeling to advance patient-derived materials, leveraging the rare disease networks and their established cohorts; use primary cells; and use gene editing to generate the mutations readily seen in a particular disease.

Marshall L. Summar, M.D. suggested engaging the FDA in the biomarker qualification program to accelerate clinical trials and examining rare disease cell lines, which can be acquired from the Rare Diseases Clinical Research Network or American Type Culture Collection repositories. He also encouraged developing rare disease models for the benefit of rare diseases.

Kelly Marie McVearry, Ph.D., Ed.M., will share information on an open-source biological digital twin program she facilitates and organizes with rare disease organizations. She encouraged engaging large aerospace companies as stakeholders.

IX. PROGRAM UPDATE: Office of Strategic Alliances (OSA): Krishna Balakrishnan, Ph.D., M.B.A., Director, OSA, NCATS

Krishna Balakrishnan, Ph.D., M.B.A., provided an update on Office of Strategic Alliances (OSA) activities and shared his vision for the future. NCATS pursues its mission by reengineering the translational pipeline for greater efficiency and greater speed. OSA supports NCATS' efforts at each step. OSA supports the translational mission of NCATS by combining science, law, and business into one usable, practical product. OSA oversees three main functions: intellectual property management, alliance management, and small business programs. Dr. Balakrishnan stated that this presentation would focus on intellectual property management and alliance management.

OSA aims to brand NCATS as the preferred partner for collaborating on translational projects by increasing efficiencies and reducing barriers. As a preferred partner, NCATS serves as the connector for enabling organizations to partner with OSA to advance translational progress. Other key elements of a preferred partnership include the trust that is vital to collaborations and the speed to accomplish tasks quickly, as well as innovation. OSA's vision is interwoven with NCATS' mission. The office implements the "more treatments" aspect through innovation and managing a large volume of negotiations with speed, as well as by having more short-term goals. OSA addresses the "more quickly" component by (1) using templates that allow speed and efficiency and (2) building networks and relationships. Lastly, OSA reaches "all people" by using platform technologies, playing a catalytic role in the drug development pipeline, utilizing NCATS' convening power, and reducing barriers. Dr. Balakrishnan acknowledged OSA staff, commending them for their expertise in science, law, and business.

NCATS Agreements and Licenses

Dr. Balakrishnan highlighted some of NCATS' recent agreements, intellectual property activities, and commercial licenses. OSA has several agreement types in place to align with the needs of the various collaborations. In FY22 and FY23, the office issued 4 Cooperative Research and Development Agreements (CRADAs), 234 Confidential Disclosure Agreements, and 172 Research Collaboration Agreements (RCAs). The CRADAs are the most complex and can take months to years to execute. The RCAs are considered the most robust agreement with highest efficiency and can be in place within days or weeks. During this same period, NCATS completed 62 intellectual property (IP) filings and at a lower cost than seven other ICs. This notable success can be attributed to using collaborations to expand the center's scientific research, focusing on platform technologies, and employing team science to derive greater synergies in ideation. The close working relationship between OSA staff and scientists (i.e., collaborators, partners) also contributed to this success. OSA has facilitated 66 commercial licenses, the majority of which are interinstitutional agreements with the external institution taking the lead; in the others, NIH is the lead institution.

Case Studies: Innovations in Alliances

Dr. Balakrishnan described case studies that exemplify how OSA is uniquely positioned to support the NCATS mission.

- **Cooperative Research Collaboration Agreement (C-RCA).** In 2020, OSA developed the Cooperative Research Collaboration Agreement (C-RCA), an innovative new type of CRADA agreement. The C-RCA combines the best elements of the RCA and the standard CRADA, layering the legal toppings of a CRADA onto the business efficiency of an RCA. Other NIH ICs have also signed on to use the C-RCA. Key benefits include requiring only days or weeks to execute versus the months needed for a CRADA and preserving the legal safeguards for background IP. The C-RCA has been used 25 times at NCATS.

- **Template Agreements.** Former OSA director Lili M. Portilla, M.P.A., and OSA staff were tasked with developing new agreements for the N3C Data Enclave during the COVID-19 pandemic. Template agreements became the foundation of the N3C. Three different agreements were developed: the Data Transfer Agreement (DTA), Data Use Agreement (DUA), and the agreement to participate in Privacy-Preserving Record Linkages (PPRL). OSA consulted multiple stakeholders across NCATS, NIH, and HHS for input on establishing the DTA, DUA, and PPRL criteria. More than 500 template agreements have been executed since development, with minimal changes necessary to the templates.

- **New Platform Technologies.** The NCATS Stem Cell Translation Laboratory generated a four-part cocktail, Chroman 1, Emricasan, Polyamines, Trans-ISRIB (CEPT), that revolutionized the stem cell field. CEPT increases cell viability, reduces DNA damage, facilitates single-cell cloning, enhances embryonic bodies and organoid formation, and supports the functioning of mature cells. To support dissemination of the cocktail, OSA employed tailored approaches to maximize its accessibility, including internal use of nonexclusive licenses, fee-specific patent commercial nonexclusive licenses, commercial evaluation licenses for clinical uses, and material transfer agreements with the academic community. The versatility of the CEPT cocktail and its wide access is quickly making it a broadly used and standard approach in cryobiology, drug development, and regenerative medicine, and CEPT is now widely commercialized.

- **Exclusive License Negotiation. Three-Way CRADA.** NCATS and Cincinnati Children's Hospital Medical Center developed small molecules for treating rare cancers. Ami Gadhia, J.D., LL.M., CLP, a senior technology transfer and patenting specialist in OSA, determined that an interinstitutional agreement was the most appropriate approach for this collaboration, allowing CCHMC to file the IP, marketing, and exclusive licensing applications. Subsequently, 86 patent applications were filed under five distinct structural series for these molecules. Ms. Gadhia negotiated a three-way CRADA with Kurome Therapeutics, which licensed the technology from CCHMC. Kurome Therapeutics later received venture capital funding, established a scientific advisory board, began manufacturing the product, and began conducting IND-enabling studies. An FDA IND application will soon be filed.

- **NIH/NCATS as Lead Institution.** In this collaboration, Sury Vepa, Ph.D., J.D., senior licensing and patenting manager, OSA, advised that metarrestin could be a revolutionary new first-in-class cancer drug and decided that the best course of action would be for NCATS to take the lead. NCATS filed the patent applications in collaboration with other partners. Funding was received from NCATS TDB to perform preclinical evaluation and IND-enabling studies. The Phase 1 clinical trial was sponsored by NCI. NCATS has a licensing partner to further advance metarrestin along the drug development pipeline.

- **NCATS Advancing Innovations Through Mentorship (AIM) Training Program.** NCATS launched its Advancing Innovations Through Mentorship (AIM) training program, which leverages the National Science Foundation Innovation Corps (I-Corps™). The goal is to train the next generation of translational scientists in the business aspects of science and in how to advance discovery. AIM is an experiential learning process that uses customer discovery methodology. The customer could be a user, top leader, competitor, or potential collaborator. Research teams of four are formed and begin conducting interviews of external subject-matter experts. Since inception, 14 teams consisting of 39 employees have been formed. Three of these teams were highlighted. The *Bunyavirus* team seeks to investigate why research in the field is dormant and identify some of the challenges. The team discovered that Merck & Co., Inc. could be a potential collaborator. The nicotinamide N-methyltransferase (NNMT) team found a partner with animal models for investigating new diseases. The Real-Time Cellular Thermal Shift Assay to Monitor Target Engagement (RT-CETSA) team filed patents and developed a prototype instrument.

In closing, Dr. Balakrishnan revisited the elements of OSA's vision, emphasizing that trust is the most important component of NCATS' collaborations. Partnerships established with speed and efficiency are beneficial to both parties. Innovative methods that can reduce the complexity of establishing collaborations will bring in partners, as will being flexible and building bridges. One challenge any

organization faces when developing partnerships is establishing networks. Being a productive, preferred partner requires a broad and deep network, which is one area where NCATS can improve.

Discussion

Sergio A. Aguilar-Gaxiola, M.D., Ph.D. commented on the critical nature of trust in developing, demonstrating, and disseminating information and resources developed in NCATS. He encouraged identifying those partners that stand to benefit the most and engaging them systematically in these three areas. Dr. Aguilar-Gaxiola was impressed that trust emerged as a key element across the various programs and encouraged NCATS to keep trust at the center of its activities, especially when working with underserved communities. Dr. Balakrishnan noted that trust has to be planned and built with a good track record, as NCATS has observed across the volume of agreements it manages. Dr. Aguilar-Gaxiola volunteered to share insight from the National Academies of Sciences, Engineering, and Medicine (NASEM) meeting on the power of community engagement. Dr. Rutter expressed appreciation to Dr. Aguilar-Gaxiola for his participation in NASEM conferences on community engagement and trust and then sharing ideas with NCATS on what has been effective in building trust and trustworthiness.

Paul A. Harris, Ph.D. emphasized that OSA is vital for dissemination, especially for the intramural research program. He appreciated the use case presented about the N3C platform, as well as the standard agreements to be able to observe projects at scale.

In response to questions from Dr. Harris about how licensing is handled in NCATS and whether the RCAs were standardized, Dr. Balakrishnan explained that rules and regulations govern licensing in NIH and that licensing principles exist, such that NIH can receive royalty monies. For IP that is out-licensed, NIH can ask for a commercial development plan from the group requesting the license. With nonexclusive licenses, the royalties and payments tend to be lower. Exclusive licenses require a detailed commercial development plan, with options for various models of payments (e.g., milestones, royalties). He further noted that although some text in the RCA is standard, the RCAs are flexible, and terms can be negotiated according to needs.

Paula K. Shireman, M.D., M.B.A. asked about plans to increase accessibility to N3C data, especially for clinicians who have patients at multiple facilities, and also about the next steps in data sharing that NCATS and OSA can innovate to prevent a stoppage of information. Dr. Balakrishnan noted that approaches exist to share data more broadly but explained that this question should be addressed at the NIH level, not just for the N3C data. He encouraged scientists who are not filing for patents to publish their results early and to share their knowledge with the translational science community. NIH scientists are leading in sharing their data, with interpretation and context in NIH's open platforms. Dr. Rutter added that most of the initial efforts had been focused on collecting input on and developing tailored templates for the N3C agreements, which have helped to speed processes downstream.

Annica M. Wayman, Ph.D. commented on using the NCATS AIM training program and building the knowledge of businesses resulting from the Tissue Chips program on how IP works, for example. She asked about ways OSA could build capacity, particularly with new tools, for small businesses and entrepreneurs to help them better traverse the drug development "valley of death." Dr. Wayman also noted the opportunity to build the knowledge base of venture capitalists about how best to interface with small businesses in biomedical research and, and to address bottlenecks for larger businesses. Dr. Balakrishnan explained that OSA publishes information about unique licenses or tools (e.g., C-RCA) and presents updates at trade conferences, including the annual meetings of the Association of University Technology Managers. In addition, the NIH Small Business Education and Entrepreneurial Development sponsors the Applicant Assistance Program to train entrepreneurs on preparing an SBIR

application. Other training options at NIH include I-Corps. Dr. Wayman emphasized ensuring that the innovative tools developed in OSA are integrated into the existing training programs at NIH.

Marshall L. Summar, M.D. suggested providing additional teaching materials and/or sharing best practices with smaller academic technology transfer offices to assist the commercialization process. Dr. Balakrishnan pointed out that the team-oriented approach used in NCATS makes technology transfer easier and is an approach similar offices can model.

Kelly Marie McVearry, Ph.D., Ed.M. asked whether NCATS had explored using smart contracts to automate the royalty agreements and will forward additional information via email.

X. PUBLIC COMMENTS

Comments from the public were accepted until February 9, 2024 (15 days after the meeting) and will be appended to the minutes.

XI. ADJOURNMENT OF THE OPEN MEETING

Joni L. Rutter, Ph.D., thanked the participants for their input. The next meeting is scheduled for May 23, 2024, and is planned as an in-person session. Dr. Rutter adjourned the meeting on January 19, 2024, at 4:22 p.m. EST.

XII. CERTIFICATIONS

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

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

_____ _____

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