

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

**30th Meeting of the  
Advisory Council**

**Minutes of Virtual Meeting  
May 19–20, 2022**

The National Center for Advancing Translational Sciences (NCATS) Advisory Council held a meeting in open session on May 19, 2022, from 1:01 p.m. to 4:34 p.m. EDT, and on May 20, 2022, from 1:01 p.m. to 4:46 p.m. EDT 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 May 19, 2022, from 11:01 a.m. to 11:49 a.m. EDT for the review and consideration of grant applications.

**NCATS ADVISORY COUNCIL MEMBERS PRESENT**

**Chair**

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

**Executive Secretary**

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

**Council Members**

Paul A. Harris, Ph.D.

Theodore R. Holman, Ph.D.

Rebecca D. Jackson, M.D.

Annie M. Kennedy, B.S.

Matthias Kretzler, M.D.

Andrew W. Lo, Ph.D.

Kelly Marie McVearry, Ph.D., Ed.M.

Keith J. Mueller, Ph.D.

Rajesh Ranganathan, Ph.D.

Paula K. Shireman, M.D., M.B.A.

Marshall L. Summar, M.D.

**Ad Hoc Council Members**

None present

**Representative Members**

None present

**Ex Officio Members**

None present

## **Others Present**

Marie A. Bernard, M.D., Chief Officer for Scientific Workforce Diversity (COSWD), Office of the Director (OD), NIH

Jessica Mazerik, Ph.D., Director, Helping to End Addiction Long-term<sup>SM</sup> Initiative, or NIH HEAL Initiative<sup>SM</sup> Data Ecosystem  
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**

Joni L. Rutter, Ph.D., adjourned the closed session of the NCATS Advisory Council meeting on May 19, 2022, at 11:49 a.m. EDT.

**May 19, 2022**

## **III. CALL TO ORDER, OPEN SESSION DAY 1**

Dr. Rutter called the meeting to order and welcomed members and guests to the 30th meeting of the NCATS Advisory Council. Anna L. Ramsey-Ewing, Ph.D., conducted the roll call and reviewed the meeting agenda. She pointed out that the meeting will span two days, May 19 and 20, 2022, from 1:00 p.m. to 5:00 p.m. EDT each day. Dr. Ramsey-Ewing 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 January 2022 Council meeting with 10 ayes, zero nays, and 1 abstention.

## **V. 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 2022, 2023, and 2024, noting that the remaining meeting for 2022 will be virtual:

- September 22, 2022 (virtual meeting)
- January 26–27, 2023 (virtual meeting)
- May 25, 2023
- September 28, 2023
- January 18–19, 2024 (virtual meeting)
- May 23, 2024

- September 26, 2024

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

Dr. Rutter began by announcing a new interactive approach to the NCATS Advisory Council meetings, which consists of quick response (QR) codes embedded throughout the PowerPoint presentations. When scanned, these QR codes will direct viewers to the Center's webpages to provide more in-depth information about the programs and initiatives. She next extended her appreciation to CAN Review Board representative member, Michael Rosenblatt, M.D., who has completed his four-year term. Dr. Rutter presented updates on the NIH and NCATS — including leadership transitions, announcements, and events — and reported on the NCATS fiscal year (FY) 2022 budget. She also discussed program updates, COVID-19 activities, and NCATS' follow-up to the Center's *FY 2019–FY 2021 Triennial Report*. Dr. Rutter noted that Clare K. Schmitt, Ph.D., acting deputy director, NCATS, will moderate the discussions.

### **NIH Announcements and Events**

Dr. Rutter highlighted recent NIH announcements and events.

### **Ongoing Leadership Searches**

Dr. Rutter reminded the Council that in December 2021 President Joseph R. Biden appointed Lawrence A. Tabak, D.D.S., Ph.D., as NIH acting director. The announcement is open and the search for a new NIH director, who is appointed by the President and approved by the Senate, is ongoing. The Advanced Research Projects Agency for Health (ARPA-H) was designated to be under the purview of the Department of Health and Human Services (HHS) and has been placed within the NIH. The leadership search for an ARPA-H director, who also is appointed by the President, is in progress.

The NIH Office of the Director (OD) has several other leadership searches open and positions to fill. In November 2021, a search for a new NCATS director began. On April 29, 2022, Norman E. Sharpless, M.D., stepped down as the director of the National Cancer Institute (NCI), and Douglas R. Lowy, M.D., now is serving as NCI acting director. Michael M. Gottesman, M.D., announced his plans to step down as NIH Intramural Program deputy director for internal research but is remaining in this position until a new deputy director is selected.

### **Advanced Research Projects Agency for Health**

Dr. Rutter explained that in the summer of 2021, a variety of listening sessions outlined the vision and goals of ARPA-H. On March 15, 2022, Congress passed the FY 2022 Omnibus Appropriations (also known as 2022 Consolidated Appropriations Act [P.L. 117-103]), which allotted \$1 billion for three years beginning in FY 2022 and ending in FY 2024 to initiate ARPA-H activities. After the director is appointed, other hiring and award flexibilities will be provided. ARPA-H will be complementary to and not duplicative of NIH programs and efforts. In April 2022, the responsibility of determining where ARPA-H will be located was delegated to the HHS secretary. This initiative subsequently has been transferred to the NIH. The President's FY 2023 budget request includes \$5 billion for ARPA-H. A new bill has been proposed in Congress that could transfer ARPA-H outside of NIH and into HHS.

## Reporting to NIH by NIH-Funded Institutions

Dr. Rutter noted that the 2022 Consolidated Appropriations Act included provisions for reporting to NIH by NIH-funded institutions. This reporting is mandatory and relates to hostile working conditions, harassment, and bullying. Prior to this Act, the NIH lacked clear authority to require funded institutions to report to the NIH whether personnel changes were related to harassment. A provision stated that such entities should report this information, but it was not a requirement. This Act ensures the NIH is made aware when personnel changes are due to harassment and strengthens NIH's ability to take necessary action to ensure safe work environments wherever NIH-funded activities are conducted. This gives the NIH more authority to improve student learning.

## NIH Policy for Data Management and Sharing (DMS) Policy and Implementation

The NIH DMS Policy is being updated and changes are scheduled to take effect on January 25, 2023. The updated DSM Policy will advance rigorous and reproducible research, enable validation of research results, make high-value data sets accessible, accelerate future research directions, and increase opportunities for citation. In addition, this policy aims to promote public trust in research, including aspects of transparency, stewardship, contributions, and research data. The NIH will be providing supplemental information, including budgetary considerations and privacy protections, as well as sample plans and additional webinars. Once the DSM Policy takes effect, the NIH will conduct ongoing assessments and provide incentives for data sharing. The Council was encouraged to visit the [Data Management and Sharing Policy Overview](#) website for further details.

## NCATS Announcements and Events

Dr. Rutter called attention to upcoming NCATS activities and announcements.

- **NCATS Organizational Changes.** NCATS has enacted the proposed changes announced during the January 2022 Council meeting. The Division of Extramural Activities (DEA) has replaced the Office of Grants Management and Scientific Review (OGMSR), and Dr. Ramsey-Ewing is the DEA director. The Division of Rare Diseases Research Innovation (DRDRI) has replaced the Office of Rare Diseases Research (ORDR). Philip John (P.J.) Brooks, Ph.D., will serve as the DRDRI acting director until a search is completed.
- **Awards and Recognitions.** Dr. Rutter congratulated leaders and trainees in the Clinical Translational Science Awards (CTSA) Program and in other NCATS research efforts on their recent accomplishments. Three CTSA leaders have received the Association of American Medical Colleges (or AAMC) 2022 Innovations That Bolster Community Trust in Science Award: Linda B. Cottler, Ph.D., M.P.H., FACE, University of Florida, College of Public Health and Health Professions, College of Medicine (first place winner); Sergio Aguilar-Gaxiola, M.D., Ph.D., University of California, Davis School of Medicine (second place winner); and Vineet Arora, M.D., MAPP, The University of Chicago Pritzker School of Medicine (tied for third place). In addition, two Ruth L. Kirschstein National Research Service Award training award (TL1) scholars received 2022 Association for Clinical and Translational Science outstanding trainee awards: Tara Bautista, Ph.D., Yale University, received the Postdoctoral Scholar Award, and Afaf Saliba, M.Sc., University of Texas Health San Antonio, was selected for the Predoctoral Scholar Award. Last, Dr. Brooks received the American Society of Gene & Cell Therapy 2022 Sonia Skarlatos Public

Service Award for his work in gene and cell therapy and for consistently fostering and enhancing the field. Dr. Rutter highlighted that within the governmental agencies, Dr. Brooks works tirelessly in this research area.

- **Somatic Cell Genome Editing (SCGE) Program.** NCATS and the National Institute of Neurological Disorders and Stroke (NINDS) co-lead the SCGE Common Fund program. The SCGE Program Phase 2 was approved by the NIH Council of Councils in September 2021, and new funding opportunity announcements (FOAs) are open. The focus of these FOAs is to develop novel technologies and gene editing to build foundations for clinical applications and then deliver resources to accelerate treatments.

### **NCATS Events and Meetings**

- **Assay Guidance Workshop.** On June 7 and 8, 2022, NCATS, the Bill & Melinda Gates Foundation, and National Institute of Allergy and Infectious Diseases (NIAID) will host a 3D Tissue Models for Antiviral Drug Development workshop. This workshop will provide high-level perspectives on infectious disease and the potential value of 3D tissue models for antiviral drug development, as well as tools for understanding and modeling those infectious diseases.
- **Helping to End Addiction Long-term<sup>SM</sup> Initiative, or NIH HEAL Initiative<sup>SM</sup> Annual Meeting.** On April 11 and 12, 2022, the NIH convened the third annual NIH HEAL Initiative investigator meeting, and more than 600 NIH HEAL Initiative awardees attended. The goals of this annual meeting were to explore trends and shared interests on the topic. Several community stakeholders joined and shared their concerns and ideas. Dr. Rutter conveyed that the NIH values this input to advance the science, research, and solutions for improving (and ameliorating) the opioid epidemic, pain-related symptoms, and pain-related diseases. Dr. Rutter moderated a session on advancing the pain and addiction therapeutic research pipeline and numerous NCATS-supported preclinical and clinical investigators presented their research.
- **NCATS Stakeholder Teatime.** Dr. Rutter relayed that on May 18, 2022, NCATS held its inaugural Stakeholder Teatime event. FasterCures Executive Director Esther Krofah, M.P.P., moderated the session, which was well attended. The goal of the event was to discuss how NCATS could engage stakeholder communities in conversations about advancing its goals. The overall focus areas of these events are building relationships, raising awareness, and working together to advance NCATS' mission.

### **FY 2022 Budget**

Dr. Rutter reported that the 2022 Appropriations Act included \$45.2 billion for the NIH, which is a 5.2 percent increase above the FY 2021 enacted budget. NCATS was appropriated \$882 million, which is a 3.1 percent increase above the FY 2021 enacted budget. This includes \$606 million for the CTSA Program, a 3.3 percent increase, and up to \$60 million to implement CAN. The President's FY 2023 budget, released two weeks after the FY 2022 enacted budget, begins the NIH/NCATS budget process. This request includes a 45.7 percent increase for the NIH and contains \$5 billion for ARPA-H and \$12 billion for pandemic preparedness; 2 percent increases for NCATS and the CTSA Program; and up to \$90 million to implement CAN. Congressional hearings on the NIH budget in the House occurred on May 11, 2022, and in the Senate on May 17, 2022.

Dr. Rutter briefly reviewed recently published FOAs that span NCATS programs, including those linked to concept clearances (e.g., Rare Diseases Clinical Research Network [RDCRN] and CTSA Program) and the 2022 targeted NCATS Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) awards.

### **NCATS Program Updates**

Dr. Rutter pointed out that detailed program updates from the Division of Preclinical Innovation (DPI) and the Office of Strategic Initiatives (OSI) will be provided later in the meeting. She highlighted some notable achievements since the last Council meeting.

- **LitCoin Program.** The LitCoin Natural Language Processing (NLP) Challenge was a two-phased prize competition conducted to examine the NLP of abstracts or concepts from PubMed. The aim was to assign relationships between those concepts based on the context by which they appear within the abstracts. As part of the Challenge, hundreds of different abstracts were processed and compared with hand-annotated abstracts to generate team scores to determine the winners. More than 200 teams worldwide participated. NCATS soon will award prizes totaling \$100,000 to the high scorers; U.S. citizens and permanent residents were eligible for the competition. Dr. Rutter noted that further details on this topic would be provided later in the meeting.
- **Accelerating Medicines Partnership® (AMP) Bespoke Gene Therapy Consortium (BGTC).** The BGTC is the first AMP initiative to focus on rare diseases. The application period for the adeno-associated virus biology workstream closed in February 2022, reviews have been completed, and four grants have been funded. A second round of AMP BGTC solicitations is soon to be released via the Foundation for the NIH (FNIH). To support the manufacturing workstream, activities include conducting biweekly subteam meetings to discuss critical quality attributes (CQAs). Efforts also are focusing on developing a proposal for a minimum set of CQAs for Phase 1/2 clinical trials in a tiered structure and establishing a good laboratory practice (GLP) and toxicology subteam. Disease nominations for the clinical workstream closed in February 2022 and are being reviewed by the subteam. Twelve to 15 candidates will be selected for full clinical trial proposals. Awards are anticipated to be announced in fall 2022.
- **Training and Education Program.** The Office of Policy, Communications and Education's (OPCE) Education Branch, led by Jessica M. Faupel-Badger, Ph.D., M.P.H., hosted a translational science roundtable in March 2022. Roundtable participants discussed challenges and opportunities in translational science as the field matures and how to best train and educate the next generation of researchers. Participants were asked to provide a one-word response to share their thoughts about translational science training and education. Overall responses were optimistic, and the Education Branch received several suggestions to improve NCATS' ongoing efforts.
- **NCATS Translational Science Education Digital Badging Program.** A key activity related to training and education in translational science is the establishment of a digital badging program. The goals of the program are to increase awareness of translational science, stimulate interest in translational science and related career paths, and increase engagement in translational science education. The digital badges are offered for NCATS-sponsored educational opportunities and can be shared via LinkedIn and other social media outlets.

- **NCATS–U.S. Food and Drug Administration (FDA) Jointly Sponsored Translational Science Interagency Fellowship.** NCATS and the FDA began sponsoring this fellowship in 2021 and inducted the first class of fellows. Two incoming fellows for 2022 for the second class are F31 awardees with industry experience: Kristin Altwegg, M.S., The University of Texas Health Science Center at San Antonio; and former NIH Graduate Partnership Program fellow and current FDA postdoctoral fellow Tsung-Jen Liao, Ph.D., University of Maryland, College Park. Fellows perform 18-month rotations with both the FDA and NCATS.

### NCATS COVID-19 Activities

Dr. Rutter provided an update on NCATS’ COVID-19-related activities. On May 12, 2022, during the second Global COVID-19 Summit, President Biden announced that the NIH has licensed 11 COVID-19 research tools and early-stage vaccine and diagnostic candidates to the [Medicines Patent Pool](#) through the World Health Organization (WHO) [COVID-19 Technology Access Pool](#) (C-TAP). C-TAP technologies are designed to benefit people living in low- and middle-income countries and include a research tool for drug and diagnostic development, which NCATS played a key role in developing. NCATS — along with the National Eye Institute (NEI), National Institute of Environmental Health Science (NIEHS), NCI, and NIAID — has been invited to contribute to C-TAP. Dr. Rutter acknowledged the NCATS laboratories for this development and the exciting activity within the COVID-19 space that is enabling the translation of these technologies more broadly.

- **National COVID Cohort Collaborative (N3C).** Dr. Rutter remarked that N3C plays a central role in NCATS’ response to COVID-19 and has been included in the HHS *FY 2022–2026 Strategic Plan* as a key tool for restoring trust and accelerating advancements in science and research for all. N3C is supplementing information from electronic health records (EHRs) with other data types. These include social determinants of health and data from the Centers for Medicare & Medicaid Services (CMS), as well as viral variant, mortality, clinical, and vaccine data. These external data sets will help create an overall view of patients within the N3C and improve understanding of SARS-CoV-2 in terms of diagnosis and treatment. As of May 19, 2022, the N3C Data Enclave contained data from more than 13 million patients, 5 million of whom have received a COVID-19 diagnosis.
- **Researching COVID to Enhance Recovery (RECOVER) Initiative.** NCATS is collaborating with the RECOVER initiative that is co-led by NINDS and the National Heart, Lung, and Blood Institute (NHLBI). The RECOVER study examines long COVID-19 or post-acute sequelae of SARS-CoV-2 infection (PASC). NCATS has identified more 200,000 adults within N3C with these sequelae who could be enrolled in interventional studies. The first RECOVER consortium findings were published in the May 16, 2022, issue of *The Lancet Digital Health*, in which researchers detailed a five-step analysis using machine learning processes to identify potential PASC patients before they are diagnosed. These steps are (1) retrieving EHRs for patients who are diagnosed with PASC based on the International Classification of Diseases (ICD) code; (2) identifying the pattern of PASC clinical features; (3) identifying previously unknown cases using these learned patterns; (4) identifying the presumed (or known) PASC patients; and (5) identifying the PASC subtypes. Subtyping is essential for comparative effectiveness of drugs and other interventions. The de-identified data in N3C can be used to identify potential cohorts for future studies, recruitment, and risk prediction. RECOVER investigators examined vaccine information related to long COVID-

19 records using the N3C database. The results showed that across different dosing regimens, vaccination prior to acute SARS-CoV-2 infections reduced the likelihood of PASC or long COVID-19 by 18 percent.

- **NCATS [COVID-19 OpenData Portal](#).** This COVID-19 resource is continuing to collect *in vitro* therapeutic data on known and emerging SARS-CoV-2 variants. Currently, the portal contains nearly 10,000 data points of therapeutic annotations, and users can now view and sort data by sublineage. Data on more than 18 Omicron variant sublineages have been added to the existing information.
- **COVID-19 Clinical Trials.** The CTSA's have been critical in managing the COVID-19 randomized controlled trials. These include the FNIH-led public-private partnerships Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) trials, Convalescent Plasma to Limit COVID-19 Complications in Hospitalized Patients Trial (commonly called CONTAIN COVID-19), and Passive Immunity Trial of the Nation for COVID-19 (commonly called PassItOn). Dr. Rutter informed the Council that most of the trials are Closed to enrollment and that results are anticipated within the coming weeks.

#### **NCATS FY 2019–FY 2021 Triennial Report Follow-up**

During the January 2022 Council meeting, NCATS Office of Translational Medicine (OTM) presented the Center's FY 2019–FY 2021 Triennial Report on monitoring adherence to the NIH Policy on the Inclusion of Women and Minorities in Clinical Research. Dr. Rutter provided an update in response to the Council suggestions to do more to address gaps in this inclusion. She highlighted some of the efforts in place to adhere to the NIH Policy on the Inclusion of Women and Minorities in Clinical Research. She noted that the CTSA Program and the RDCRN are the two major programs that address this topic. Dr. Rutter first reminded the Council of NCATS' three audacious goals to provide (1) more treatments (2) to all people (3) more quickly.

Regarding diversity, equity, inclusion, and accessibility (DEIA) in rare diseases, Dr. Rutter noted that the structural factors that lead to health disparities intersect with and may amplify the challenges also faced by patients with rare diseases. For example, pain management is a known health disparity facing African Americans and especially is amplified for those with sickle cell anemia. The diagnostic odyssey (i.e., journey to a diagnosis) is a known challenge for patients with rare diseases, which is further magnified for those from an underserved community.

- **RDCRN.** To better understand the current RDCRN enrollment and to develop strategies to address any disparities, NCATS analyzed inclusion enrollment records and grant applications from 22 prior longitudinal studies. Dr. Rutter explained that because individual rare diseases affect a very small population and the incidence in different races is mostly unknown, NCATS needs to ensure that these minority groups are represented in its inclusion efforts. Strategies include refining the FOA language to emphasize the importance of NIH inclusion policies; using administrative supplements to increase outreach to improve research participant diversity; promoting diversity special interest groups — including patients, families, and patient advocacy groups (PAGs) — in the RDCRN monthly meetings; and improving collaboration between the RDCRN and CTSA projects and initiatives, including the Trial Innovation Network (TIN) and Recruitment Innovation Center (RIC).



- **Genetics and Rare Diseases (GARD) Information Center.** NCATS is in the process of revamping the GARD information center, and upgrades are anticipated to be completed within a nine-month time frame. The GARD 2.0 beta test version of the website has launched and can be accessed from any GARD 1.0 disease page. NCATS is continuing to collect user feedback from the rare diseases community to refine the website.
- **CTSA Program.** Dr. Rutter highlighted activities focused on inclusion strategies for diverse population clinical enrollment managed within the CTSA Program. Two inclusion strategies are to implement the NCATS-sponsored SMART (Streamlined, Multisite, Accelerated Resources for Trials) institutional review board platform and utilize the RIC to facilitate community engagement, including with the Clinical and Translational Science Council of Faiths and mobile health vehicles. Other community engagements efforts within the RIC include using technology-enabled research recruitment and consenting processes (i.e., telehealth and teleconsent).
- **Community Engagement.** In broader terms of community engagement, NCATS will be releasing the Healing Power of Community Engagement one-page document and has revamped the community engagement webpage that features CTSA Program efforts. In addition, the CTSA Program Steering Committee has established a DEIA Task Force and this group has published details of its activities in the January 20, 2022, issue of the *New England Journal of Medicine*. The activities of this task force will be ongoing and the group has been integrated into the CTSA Program's leadership. NCATS is developing a manuscript in response to the *Journal of Clinical and Translational Science's* call for papers on diversity, equity, and inclusion. Additional DEIA activities of the RIC include assisting with a vaccine campaign, [Faster Together](#), and promoting the Community Engagement Studios model. A 12-member Community Advisory Board oversees the activities of RIC. Future efforts will include evaluating the impact of these activities and initiatives within RIC, many of which are not funded by NCATS.
- **Rapid Acceleration of Diagnostics for Underserved Populations (RADx-UP).** This program focuses on underserved populations and the communities most affected by COVID-19. The aim is to ensure that all people have access to testing. The RADx-UP projects span the CTSA sites.
- **American Indian/Alaska Native (AI/AN) Data.** N3C collects data from health centers across the United States, including AI/AN populations. NCATS has been meeting with the NIH Tribal Health Research Office, Indian Health Service Tribal Epidemiology Centers, and NIH experts regarding these matters. NCATS convened a virtual Tribal Consultation meeting to seek input from tribal nations on the use of these data within N3C, and a report is pending. Current AI/AN data in N3C are aggregated, and ZIP codes overlapping tribal lands are not available.

### **Diversity, Equity, Inclusion, and Accessibility at NIH and NCATS**

Dr. Rutter noted that a detailed report on NIH DEIA efforts will be provided later in the meeting and highlighted a few activities NCATS has engaged in. She called attention to a UNITE (NIH's ending structural racism initiative) listening session on health centers and systems that she moderated in January 2022. Participants discussed challenges in career opportunities and research pathways; opportunities for addressing health disparities; and barriers and solutions that the NIH can consider. NCATS has established an internal Inclusion, Diversity, Equity in Action Council and a Health Disparities Action Plan Working Group.

## **Discussion**

Paula K. Shireman, M.D., M.B.A., asked where specifically ARPA-H would reside, especially because the initiative has been funded. Dr. Rutter clarified that ARPA-H is within the NIH, but no interim director for the initiative has been named. Operational systems — such as the Electronic Research Administration (eRA) — can begin building allowances for ARPA-H using precedents of other federal agencies.

Paul A. Harris, Ph.D., commented on the goal that ARPA-H complement and not compete with existing efforts and noted that NCATS would be the most vulnerable in this area. He asked about plans to address the details of “complementary” activities. Dr. Rutter explained there would not be many complementary approaches to what NCATS currently is doing. NCATS does not focus on any single disease and has activities in several areas — such as Alzheimer’s disease, cancer, and diabetes — all of which have been mentioned as areas of research of ARPA-H. She anticipates that NCATS will have a seat at the table to discuss complementary approaches with the ARPA-H director. Dr. Harris inquired about ways that the Council could ensure the NCATS leadership is at the table for these types of discussions. Dr. Rutter responded that this conversation would continue during future Council sessions.

Annie M. Kennedy, B.S., commended NCATS and program officer, Eric W.K. Sid, M.D., M.H.A., on the GARD website upgrades to address interoperability of the ICD codes and Mondo Disease Ontology, emphasizing that this is a critical publicly available tool for the rare diseases community. Dr. Rutter explained that a goal for the GARD website is to have a one-stop shop for this information. The website connects to other resources in the rare diseases community, including the EveryLife Foundation for Rare Diseases and its ICD Code Roadmap. Dr. Brooks acknowledged the efforts of NCATS informatics staff in upgrading to GARD 2.0.

Dr. Rutter and NCATS leadership will consider ways that the Council could help emphasize the Center’s complementary approaches to ARPA-H.

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

13:53:13 From Kelly M McVeary to Everyone: it would be great to have the article just referenced.

14:16:07 From Joni Rutter to Everyone: @Kelly - here is the link to the paper I mentioned:  
<https://www.nejm.org/doi/full/10.1056/NEJMp2112233>. Thank you for your comment as well.

### **VII. INVITED PRESENTATION: Assuring That All Are at the Table — Viewpoint from the COSWD and UNITE: Marie A. Bernard, M.D., COSWD, OD, NIH**

Marie A. Bernard, M.D. who is the Chief Officer for Scientific Workforce Diversity (COSWD) and co-leader of the NIH UNITE, presented on the NIH Diversity, Equity, Inclusion, and Accessibility (DEIA) Strategic Plan, COSWD activities, and the NIH UNITE Initiative.

#### **NIH Strategic Plan for DEIA**

Dr. Bernard called attention to two mandates that led to the NIH DEIA strategic plan. First, the legislation (H.R. 7614) that led to the FY 2021 NIH budget required a DEIA Strategic Plan to address racial, ethnic, and gender disparities at the NIH. This law, which went into effect in December 2020, also required a plan to identify and address barriers to access to NIH funding faced by investigators

researching health disparities. The second mandate was Executive Order 14035: Diversity, Equity, Inclusion, and Accessibility in the Federal Workforce.

On November 23, 2021, the *Government-Wide Strategic Plan to Advance DEIA* in the federal workforce was released and served as a roadmap for implementing Executive Order 14035. This Government-wide plan charged agencies — including HHS — with developing a DEIA Plan by March 23, 2022, which the HHS completed. The NIH anticipates releasing its DEIA strategic plan in summer 2022. The COSWD will provide an update during the June 2022 Advisory Committee to the Director meeting. Dr. Bernard reviewed the overarching principles of the draft NIH DEIA Strategic Plan. It communicates the vision and aspirations for all NIH, conveys broad priorities and sample activities, and provides accountability. The scope encompasses articulating NIH's vision for strengthening DEIA, capturing activities that the NIH workforce will undertake to meet the vision of the strategic plan, and harmonizing to the framework of the *NIH-Wide Strategic Plan for Fiscal Years 2021–2025*. The three main objectives will be to implement organizational practices to center and prioritize DEIA in the workforce; improve and sustain DEIA through structural and cultural change; and advance DEIA through research.

### **COSWD Activities**

In March 2022, Dr. Bernard and her team released the *COSWD Strategic Plan for Fiscal Years 2022–2026*, which outlines the team's vision, mission, and goals. The vision is to enable the NIH and NIH-funded institutions to benefit from the nation's full range of talent and foster creativity and innovation in science. The mission is to serve as the NIH thought leader in the science of scientific workforce diversity by using evidence-based approaches to catalyze cultures of inclusive excellence. The goals are to build, disseminate, and act on the evidence to advance DEIA using the NIH as a test bed.

Dr. Bernard reminded the Council that the Notice of NIH's Interest in Diversity (NOT-OD-20-031) released in November 2019 defined the categories — not an exhaustive list of groups — considered to be underrepresented populations in the U.S. biomedical, clinical, behavioral and social sciences research enterprise. The four categories are (1) individuals from racial and ethnic groups that have been shown by the National Science Foundation to be underrepresented in health-related sciences on a national basis; (2) individuals with disabilities; (3) individuals from disadvantaged backgrounds; and (4) women from the first three categories at the graduate level and beyond in scientific fields. The NIH is thinking broadly about the different groups that need to be at the table to advance science.

Dr. Bernard next highlighted examples of current activities and initiatives that fit with the strategic plan goals.

- **21st Century Scholars Program.** In March 2022, the COSWD launched a new scholars program, which was modeled after the successful NIH Distinguished Scholars Program. The goal is to establish DEIA ambassadors composed of NIH extramural program staff who have built a community, received additional mentoring, and have had enhancements of their skills. The vision is to increase the diversity of extramural program staff in a manner that translates, for example, into differences in the way FOAs are written or who gets invited to scientific meetings. The inaugural cohort, consisting of 13 program participants and six mentors from across NIH ICs, is building a self-reinforcing culture of mentoring and support at the NIH, focusing on the science of scientific workforce diversity. The cohort meets monthly, hears from DEIA experts, and is conducting the COSWD Challenge pilot project to advance DEIA principles at the NIH.

- **Scientific Workforce Diversity (SWD) Seminar Series.** The COSWD conducted an SWD Seminar Series on the dissemination of the evidence that began in September 2021. The final session was held in May 2022, and more than 500 people attended to discuss how diversity impacts science. The video recordings and presentation materials can be accessed from the COSWD website.
- **Catalyzing Recognition of DEIA Mentoring.** The COSWD issued a Notice of Special Interest (NOSI): Administrative Supplements to Recognize Excellence in DEIA (NOT-OD-22-057). This NOSI provides administrative supplements to already-funded research. The requirement of the NOSI was to have a mentoring objective that was reviewed by a peer panel or a plan to enhance diverse perspectives. The NIH ICs are reviewing the applications, and the NIH is prioritizing funding mentors who will enhance outreach to scientists in keeping with the broader NIH NOSI on diversity.

### The [NIH UNITE Initiative](#)

The NIH developed UNITE with the ambitious goal of ending structural racism. This initiative was prompted by events in 2020. Evidence indicates that a disproportionate morbidity and mortality among African Americans and Black, Hispanic, Latino, and American Indian populations persists. Racial violence in the United States — such as the videotaped murder of George Floyd while in police custody in Minneapolis, Minnesota, and the killing of six women of Asian descent in Atlanta, Georgia — has continued.

The NIH UNITE initiative was launched to address what the NIH could do within the biomedical ecosystem to ensure racial and ethnic equity. Each letter of “UNITE” represents a committee that interacts with the supporting workstreams. UNITE focuses on three areas: health disparities, minority health, and health equity research; the internal workforce; and the external workforce. Dr. Bernard detailed NIH actions related to these areas.

### Health Disparities, Minority Health, and Health Equity Research Actions

The NIH is cognizant of the data illustrating a longevity of disparities. The life expectancy for African Americans and Blacks, non-Hispanic whites, and Latinos decreased with the onset of the COVID-19 pandemic. The disadvantages in health for these minority groups compared with whites persist. The NIH has engaged in several activities to begin to address these disparities.

- **Transformative Research to Address Health Disparities and Advance Health Equity FOAs.** In FY 2021, the NIH, through the Common Fund, committed up to \$58 million to support health disparities and health equity research. A request for applications (RFA) on Transformative Research to Address Health Disparities and Advance Health Equity (U01 Clinical Trial Allowed) awarded six grants. An RFA on Transformative Research to Address Health Disparities and Advance Health Equity at Minority-Serving Institutions (U01 Clinical Trial Allowed) awarded five grants. An additional competition is planned for FY 2022.
- **Community Partnerships to Advance Science for Society (CompPASS).** The NIH Council of Councils approved establishing CompPASS for FY 2023. This initiative includes community-driven, health equity structural interventions, a coordination center in collaboration with the National Health Equity Research Assembly, and health equity research hubs for scientific support and partnership. The intent is to commit \$23 million to \$52 million annually for a period of 10 years.

## UNITE Internal Workforce Actions

- **Power of an Inclusive Workforce Recognition Project.** Dr. Bernard pointed out that intramural investigator Sadhana Jackson, M.D., (not in attendance at this meeting) led the concept for this project. The aim of the project is to add diversity to the existing visuals (i.e., images) in NIH buildings with photographs depicting the variety of people who are necessary for success in the biomedical research enterprise (e.g., scientists, nonscientists, early- and late-career individuals).
- **NIH Executive Performance Requirements and DEIA.** The performance plan for NIH Institute and Center (IC) directors contains elements of leading change, leading people, and business acumen. In FY 2022, Racial and Ethnic Equity Plans (REEPs) have been included as a component of the DEIA performance metric. The expectation is that ICs develop a customized REEP, with both short- and long-term measures to implement related to outcomes and progress. REEPs are to be managed in four phases: assess, design, implement, and report. ICs submitted their reports in April 2022, and final reviews are in progress by the COSWD; Office of Equity, Diversity, and Inclusion; and Office of Human Resources. ICs will report and share REEPs annually.

## UNITE External Workforce Actions

- **Faculty Institutional Recruitment for Sustainable Transformation (FIRST).** The overarching goal of FIRST is to create cultures of inclusive excellence. The objectives are to establish a faculty cohort model for hiring, multilevel mentoring, and professional development; implement integrated institution-wide systems to address bias, faculty equity, mentoring, and work-life issues; and establish a Coordination and Evaluation Center (CEC). The estimated budget is \$241 million over nine years. The NIH issued awards in FY 2021 to six cohorts across seven universities and funded the CEC.
- **Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative FOA.** The BRAIN Initiative is the first to use the Plan to Enhance Diverse Perspectives in an NIH FOA as a consideration for scoring. The diverse perspectives are defined broadly and align with the NIH NOSI on diversity.

Dr. Bernard highlighted the effort to increase career opportunities for underrepresented groups by expanding the Science Education Partnership Awards Program NIH-wide. Other ongoing activities include supporting institutional climate and self-studies; supporting structured institutional needs assessment and action development grants for minority-serving institutions; promoting S10 Instrumentation grants for minority-serving institutions; expanding Sponsored Programs Administration Development services and activities for minority-serving institutions implementation; and sponsoring the Excellence in DEI Investigator Award.

Dr. Bernard announced that the COSWD released a request for information on the development of a prize competition for institutional excellence in DEIA. The aims are to acknowledge transformative cultures, systems, projects, and processes that institutions of higher education have developed to achieve inclusive excellence and to highlight practices that have resulted in measurable change and created a more inclusive environment for students and faculty. Responses are due by July 28, 2022.

## ***Discussion***

When asked by Dr. Harris what has been most surprising about being the COSWD, Dr. Bernard noted the high level of momentum in addressing DEIA from the Biden Administration to the NIH and across the biomedical workforce. A series of intense meetings with NIH IC directors during the summer of 2020 led to the first internal unveiling of the UNITE initiative and then to the external presentation. NIH leadership and staff were engaged heavily. UNITE has 85 volunteers, and the NIH anti-racism steering committee has more than 500 members. Dr. Bernard anticipates that the NIH's evidence-based approach to making the existing landscape equitable and welcoming will be a long-term approach.

Matthias Kretzler, M.D., expressed his enthusiasm for the COSWD activities. He remarked that as a unique model of what humankind can be on this planet, the NIH (and its investigators) is one of the few remaining institutions with respect in this society. He called attention to the American Society of Nephrology plea that its community, which has broad reach to underserved populations, take its DEIA efforts from the federal level to the local level.

Rebecca D. Jackson, M.D., commended Dr. Bernard and her team for embedding the scientific translational method into the DEIA activities.

### **VIII. PROGRAM UPDATE: Division of Preclinical Innovation (DPI): Elizabeth A. Ottinger, Ph.D., Senior Program Manager, Therapeutics for Rare and Neglected Diseases Program, DPI, NCATS**

Elizabeth A. Ottinger, Ph.D., presented an overview of the DPI and its mission. She explained that her update would focus on the Therapeutic Development Branch (TDB), which is led by Donald C. Lo, Ph.D. Dr. Ottinger addressed operations, advancement of therapeutic development projects and initiatives, and efforts on rare and neglected diseases.

The work of the DPI is focused on collaborations and the development of platforms. Functional groups work together to advance projects with high translational impact. Most such efforts are focused on the lead optimization and preclinical phases of therapeutic development. The TDB's portfolio includes the Therapeutics for Rare and Neglected Diseases (TRND) program, Platform Vector Gene Therapy (PaVe-GT) Pilot Project, Bridging Interventional Development Gaps (BrIDGs) program, NIH HEAL Initiative, and Antiviral Program for Pandemics. These programs contribute to NCATS' ultimate mission of advancing translation to bring new therapies to people. Presently, 15 projects have been initiated in the area of preclinical development. Four translational initiatives and two biotechnology development projects also are in place.

The phases of lead optimization and preclinical development are integrative and involve multiple scientific and operational challenges. Dr. Ottinger noted that although the TDB typically is not involved in every aspect of these efforts, the TDB has been involved at every step for certain projects. Some trials are conducted through the NIH Clinical Center, and the NIH can provide regulatory support or assistance with toxicology studies. NCATS employs a team science approach, and project management is an important component of this structure.

Therapeutic development for rare and neglected diseases involves numerous challenges and opportunities. The TDB is interested in advancing research on rare and neglected diseases to develop new therapies. Rare diseases comprise 49 percent of the TDB's portfolio, and neglected diseases comprise 5 percent. Rare and neglected diseases are incorporated in most of TDB's programs. These projects address a broad range of therapeutic areas and modalities. The TDB plays an important role in dissemination

throughout this process. Dr. Ottinger presented examples of TDB's efforts involving rare diseases of low prevalence, as well as neglected diseases.

- **Jansen's Metaphyseal Chondrodysplasia.** An ultra-rare disease with fewer than 30 known cases, Jansen's metaphyseal chondrodysplasia affects bone development and mineral ion homeostasis. This disorder is caused by genetic mutations in parathyroid hormone receptor type 1, which cause the protein to remain in an active state. No effective treatments are available. Researchers at Massachusetts General Hospital have identified a peptide that shifts the receptor to an inactive state. Drug development for small patient populations, however, remains a challenge. NCATS is building a collaborative ecosystem through engagement with Patient Advocacy Groups (PAGs), researchers and clinicians, and the NIH Clinical Center. The TDB provides drug development expertise to enable investigational new drug (IND) applications, coordinate all aspects of the project, and enable translation from preclinical to clinical studies. Dr. Ottinger emphasized that patient engagement is important at all stages of therapeutic development: outreach, academic research, preclinical drug development, clinical planning, and treatment.
- **Human African Trypanosomiasis.** The TDB also works in the space of neglected tropical diseases, which face many of the same challenges as rare diseases. The DPI is working with the Drugs for Neglected Diseases Initiative (DNDi) in the development of the drug acoziborole for the treatment of African trypanosomiasis. This disease spreads through bites of infected tsetse flies and ultimately penetrates the brain, causing severe headaches, disorientation, psychosis, and characteristic sleep disorders that can lead to coma and death. WHO has set a goal of eliminating African trypanosomiasis. Limitations of current treatments include adverse effects, cost, hospitalization, and duration. WHO is working toward an oral, single-dose treatment to increase accessibility and compliance. NCATS contributed to GLP toxicology studies for regulatory approval. Presently, the drug is being made available at no cost to patients in affected countries through their public health systems, and DNDi has completed a Phase 2/3 clinical trial in the Democratic Republic of Congo.
- **BENeFITS Trial.** NCATS also has been interested in repurposing drugs to treat rare diseases. Hemoglobinopathies are a group of inherited blood disorders (e.g., sickle cell disease, beta thalassemia) that affect the production and structure of red blood cells. Many current therapies are associated with adverse effects, and some treatments are inaccessible to patients. Benserazide, a drug for Parkinson's disease, could be used as a treatment for this disorder. Approval of benserazide for treatment of hemoglobinopathies required additional clinical studies. NCATS collaborated with the NHLBI to initiate the BENeFITS trial, which includes sites in the United States and Canada.
- **TRND Program.** About 85 percent of rare and ultra-rare diseases result from pathogenic variants in single genes that alter the function of gene products. Because many gene therapies have a low prevalence, gene therapies could serve as an effective solution. The TRND program was established in 2016 in partnership with the NCI at Frederick. Recent efforts have included the development of new gene therapies for aromatic L-amino acid decarboxylase deficiency and Pompe disease.
- **PaVe-GT.** Established in 2017 as a DPI, DRDRI (formerly ORDR), and Office of Strategic Alliances (OSA) collaboration, the PaVe-GT trial resulted in the PaVe-GT program. This program seeks to increase efficiencies, enhance collaborations, leverage existing resources and expertise, increase accessibility, and disseminate information. TDB's overall goal in this effort is to use common

processes across the platform and make the data publicly available. The TDB is overseeing IND-enabling studies focused on scale-up and process development, GLP, drug metabolism and pharmacokinetics studies, and GLP toxicology and safety. This effort requires multiple collaborations across the NIH. Dissemination activities include the platform launch, a preclinical playbook, regulatory submissions and communications, and a clinical playbook.

- **RARe-SOURCE.** Scientific knowledge far exceeds the degree of translation to therapeutics for rare diseases. NCATS is working to apply advances in information and technology to make information on rare diseases more accessible. NCATS has developed RARe-SOURCE, which uses a big data approach to understand how rare diseases can be grouped — using existing data — to identify common drugs. The development process has involved training the platform through manual literature curation, integrating known public databases, developing models to automate the mining of literature, and expanding to the more than 7,000 rare diseases. Pilot training projects have focused on creatine transporter deficiency, Farber’s disease, and congenital myopathy disease. This effort involves collaborations with NINDS, NCI at Frederick, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

Dr. Ottinger concluded by reflecting on the impact of TDB’s engagement in drug development activities. TDB’s recent efforts have resulted in 44 INDs, 49 Phase 1/2 clinical trials, 21 Phase 2 clinical trials, four Phase 2/3 clinical trials, four New Drug Applications/ Biologics License Applications, and six natural history studies. The TRND program worked with Viamet Pharmaceuticals to develop a novel azole class of antifungal drugs; TRND is developing critical process chemistry methods for large-scale manufacturing. In the decades ahead, the TDB will remain focused on NCATS’ goal of developing more treatments for all people more quickly.

### **Discussion**

Dr. Kretzler remarked that NCATS, the NIH, and the biomedical community can provide support for TDB’s efforts in rare and neglected diseases. Establishment of public–private partnerships is critical. Dr. Ottinger agreed, noting that the TDB continues to seek partnerships to help advance these projects. Andrew W. Lo, Ph.D., noted that NCATS played a critical role in supporting Agilis Biotherapeutics in their development of a gene therapy for L-amino acid decarboxylase deficiency.

Dr. Kretzler also pointed out that studies of rare diseases can provide numerous downstream benefits for understanding other diseases. Dr. Ottinger remarked that this topic has been discussed in scientific meetings; additional communication efforts in this area could be beneficial. Marshall L. Summar, M.D., expressed interest in participating in such efforts and explained that RARe-SOURCE also could be adapted for characterization of molecular variations.

Rajesh Ranganathan, Ph.D., inquired about NCATS’ investment in research leading to new INDs and approvals. Dr. Rutter explained that NCATS is working on calculating this metric and is looking closely at commercialization potential and the democratization of manufacturing as it relates to cost savings. Dr. Donald Lo added that NCATS contributes scientific value through de-risking of meritorious clinical projects.

Ms. Kennedy highlighted the value of PAGs in coordination for research, noting the importance of feedback loops and continued messaging throughout the process. Dr. Ottinger agreed, adding that PAGs



have served as a catalyst for research efforts. Kelly Marie McVeary, Ph.D., Ed.M., commented on the importance of disseminating information to the general public.

Dr. Andrew Lo pointed out that NCATS' involvement in research has contributed to downstream financial impacts for private organizations. Dr. McVeary expressed interest in ways that NCATS could benefit from these impacts. For example, the NCATS research pipeline could function as a value chain, and measurable impacts underscore that value.

Dr. Ranganathan, who has been involved in early discussions on the flow of royalties resulting from translational research, observed that academic administrators have been resistant to this approach. Legislative changes would be needed for changes in this area.

Theodore R. Holman, Ph.D., noted that a mechanism exists for sharing intellectual property through intramural funding. Dr. Summar has observed similar mechanisms through extramural funding, and Dr. Holman added that many extramural investigators are willing to share patent rights with federal funders in exchange for additional funding.

Dr. Andrew Lo commented on the importance of maintaining a distinction between public and private activities to prevent conflicts of interest. Public-private collaborations, however, can increase NCATS' impact. He added that the Rare Disease (RAD) Fund Act of 2018 sponsored by Reps. Vargas, Rooney, and Peters was proposed to grant the NIH the authority to create a public-private partnership, along with private-sector funding. He underscored the importance of demonstrating both the financial return and social impacts. Dr. Ranganathan commented that mechanisms can be established to prevent conflicts of interest, but support from the academic community will be needed. Dr. Rutter suggested that this topic could be discussed further in an Advisory Council Working Group.

Dr. Rutter, NCATS leadership, and the Council will explore establishing an NCATS Advisory Council Working Group to investigate how the research has contributed to downstream financial impacts for private organizations and to examine the flow of royalties resulting from translational research.

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

15:39:12 From Andrew Lo to Everyone: Case study on NCATS involvement in AADC gene therapy:  
<https://www.sciencedirect.com/science/article/abs/pii/S1359644618303404?via%3Dihub>

15:43:18 From Kelly M McVeary to Everyone: Thank you for the link - not all of us have institutional access to journal articles. There is a paywall for this article. Would it be possible to send the pdf to NCATS Council?

16:02:11 From Andrew Lo to Everyone: That roadshow was extremely effective and I know many biotech companies and VCs that were really surprised by how much expertise NCATS had and the kind of resources it could provide!

16:05:21 From Lili Portilla to Everyone: TDB considers Strategic Alliances part of the drug development team, which makes for better/responsive agreements to accomplish the goals of the specific project.

16:08:03 From Andrew Lo to Everyone: Just posted an older case study on NCATS's rare disease portfolio, which has some numbers Rajesh asked for.  
<https://www.science.org/doi/abs/10.1126/scitranslmed.aaa2360>

16:10:11 From Kelly M McVeary to Everyone: The phrase “The Power of Derisking” is a nice impact statement for NCATS communications.

16:11:47 From Joni Rutter to Everyone: Yes! @Kelly— great phrase to use.

16:20:57 From Lili Portilla to Everyone: @kelly if NCATS develops IP because of the collaboration(s), the collaborator will license the IP from the NCATS.

16:23:02 From Andrew Lo to Everyone: See Vargas Rooney Peters Bill!!

16:23:40 From Andrew Lo to Everyone: <https://vargas.house.gov/media-center/press-releases/rep-vargas-rep-rooney-and-rep-peters-announce-the-introduction-of-the>

**IX. ADJOURNMENT DAY 1: Joni L. Rutter, Ph.D., Acting Director, NCATS, Chair, NCATS Advisory Council**

Dr. Rutter adjourned Day 1 of the meeting at 4:34 p.m. EST.

**May 20, 2022**

**X. CALL TO ORDER, OPEN SESSION DAY 2**

Dr. Rutter called the meeting to order at 1:01 p.m. EDT and welcomed Council members and guests to the second day of the 30th meeting of the NCATS Advisory Council. Dr. Ramsey-Ewing reminded attendees that the open session is being videocast and reviewed the agenda.

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

13:01:32 From Andrew Lo to Everyone: <https://www.prnewswire.com/news-releases/ptc-therapeutics-receives-positive-chmp-opinion-for-upstaza-for-the-treatment-of-aadc-deficiency-301551996.html>

**XI. 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 update on programs and initiatives under the OSI and focused his report on tissue chips or microphysiological systems (MPS). The Office’s mission is to address translational problems with innovative solutions through disruptive technologies and novel partnerships. The majority of the OSI portfolio is supported through the Cures Acceleration Network (CAN), although the NIH Common Fund and OD support several initiatives. 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 2D 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 for Safety Studies, Efficacy Studies, and Precision Medicine

- **NCATS Tissue Chips for Drug Screening Program (Tissue Chips 1.0).** This program was established in 2012 to provide a human cell–based solution to translational challenges in drug development. The goal of the program is to develop *in vitro* MPS consisting of 3D-printed primary or stem cells representing various tissues on microfluidic chips. These tissue chips should emulate the physiology of organ systems to enable accurate assessment of the safety and efficacy of promising therapies. Since the initiation of the program, several commercially available platforms have been developed, including Emulate single-organ chips and Hesperos five-organ chip systems. With support from several NIH ICs, investigators across the nation have partnered with NCATS to incorporate tissue chips research into their research programs. Dr. Tagle presented an example of the drug fialuridine (FIAU), which was shown to be highly toxic in Phase II clinical trials and led to the deaths of several trial participants. Whereas animal model testing of FIAU did not reveal any dangerous side effects, FIAU treatment of human liver chips resulted in dose-dependent steatosis and reduced liver function that was not observed in rat liver chips. The same research group subsequently showed that liver chips exhibit 87 percent sensitivity and 100 percent specificity in predicting hepatotoxicity, outperforming animal models and liver spheroids.
- **NCATS Tissue Chips for Disease Modeling and Efficacy Program (Tissue Chips 2.0).** This program has supported MPS research since 2017. The goal is to develop models of human disease using tissue chip technology to evaluate the effectiveness of candidate drugs by assessing biomarkers, bioavailability, and on- and off-target engagement of candidate therapeutics prior to entry into clinical trials. Researchers across the nation have been funded to study such conditions as Alzheimer’s disease, arthritis, cardiomyopathies, diabetes, epilepsy, influenza infections, Parkinson’s disease, polycystic kidney disease, polycystic ovarian syndrome, and a number of rare diseases. The program has supported responses to such national health emergencies as the opioid crisis and the COVID-19 pandemic. For example, the effects of FDA-approved drugs on SARS-Cov-2 viral entry were compared in 2D epithelial cells versus 3D human airway chips. Although several drugs showed promising effects in 2D culture, only two inhibited viral entry in the 3D chip model.
- **NCATS Tissue Chips in Space Program.** A partnership with the National Aeronautics and Space Administration (NASA), the Center for the Advancement of Science in Space, and the International Space Station National Laboratory, this program aims to model age-related biology and diseases that are accelerated under microgravity and translate that understanding to improve human health on Earth. Automation and miniaturization requirements for spaceflight created technological innovation and commercialization opportunities for tissue chip instrumentation. In partnership with space engineers, NCATS scientists reduced tissue chip hardware from the size of a typical refrigerator to the size of a shoebox. Since December 2018, multiple tissue chip experiments have been delivered into orbit. Dr. Tagle shared preliminary results from these projects. Under microgravity conditions, immune cell aging is initiated within days, resulting in changes to cell markers of senescence, proliferation, and wound healing. In the same time frame, microgravity also causes functional deficits in heart tissues that continue to increase with time.

- **Clinical Trials on a Chip Program (Tissue Chips 3.0).** This effort seeks to incorporate validated tissue chips into rare diseases clinical trial frameworks. The goals of the program are to inform clinical trial design and execution by establishing recruitment criteria, stratifying patients, and developing clinically relevant biomarkers. The first phase of the program involves developing and validating disease models using patient-derived cells. The second phase of the program involves clinical trials to evaluate potential drugs for efficacy and safety. Researchers in the program are studying atopic dermatitis, dementia, dystrophin-deficient muscular dystrophy, preterm birth, progeria, and prostate cancer metastasis.

### **Building Confidence and Community Adoption**

NCATS has funded developers and testing centers for each step of the tissue chip validation framework, which comprises physiological, analytical, and industrial validation processes.

- **MPS Database (MPS-Db).** NCATS has helped establish MPS-Db, a data ecosystem to aggregate, analyze, and model MPS experimental data in conjunction with databases containing human and animal exposure data. The NIH is supporting more than 25 spinoff and startup businesses as they advance commercial activities related to tissue- and organ-on-chip technologies.
- **Alternative Methods Working Group.** From the tissue chip program's inception, the FDA has been a partner and functioned in an advisory role. The FDA recently established this working group to support non-animal-based methods for toxicity and efficacy testing and also is incorporating MPS technology into its research and development (R&D) environment.
- **International MPS Professional Society.** NCATS has funded the first MPS World Summit, which will be held May 30–June 3, 2022, in New Orleans, Louisiana, to support the establishment of an international MPS professional society. The International Consortium for Innovation and Quality in Drug Development has established an MPS affiliate (IQ Consortium MPS Affiliate) that has been joined by several pharmaceutical companies to outline needs in the MPS field. Pharmaceutical companies already are using MPS for internal portfolio decision-making. Within 5 years, tissue chips are predicted to save between 10 and 26 percent of drug development costs.

### **Discussion**

Dr. Rutter asked Dr. Tagle about his history with the Tissue Chips program. Dr. Tagle answered that he first led the initiative when it was established as an NIH Common Fund program in 2012, the same year NCATS was founded. Dr. Rutter pointed out that the program has produced impressive results after less than a decade.

Dr. Summar highlighted HemoShear Therapeutics, which was an early adopter of MPS technology and has received multiple NIH SBIR Program grants (including support from NCATS) since its founding in 2010. The company has received FDA clearance to conduct a Phase II clinical trial of one of its novel therapeutics.

Dr. Kretzler congratulated Dr. Tagle and the OSI for building a strong MPS research community that is supported by diverse and sustainable funding streams.

Dr. Jackson asked for more insight into the program's engagement with stakeholders and ability to quickly disseminate resources in the wider community. Dr. Tagle pointed out that early engagement, with the end goal of relieving translational bottlenecks, was at the forefront of every decision related to the program. End users and stakeholders (e.g., patients, regulatory agencies, pharmaceutical companies) provided input at every stage. Novel partnerships — particularly with consortiums and NIH ICs — helped accelerate every process.

In response to a question from Dr. McVeary about the process of fabricating tissue chips, Dr. Tagle explained that chips presently are custom made by injection molding. Full-scale production must address the challenges of standardization (e.g., regulations, manufacturing, cell sources, biomarkers), automation, and minimization.

With regard to clinical trial failures when preclinical trials had predicted success for a therapeutic, Dr. Andrew Lo speculated about whether retrospective tissue chip studies would recapitulate the human trial results. Dr. Tagle noted that this concept was built into the Clinical Trials on a Chip program, where several retrospective studies compared preclinical and tissue chip data for failed clinical trials. Additional prospective studies involved candidate therapies with animal data that were evaluated on human and animal chips. Dr. Kretzler added that the use of tandem chips that combine multiple organ systems can provide information about side effects related to organ–organ interactions and toxic secondary metabolites.

Dr. Tagle and the OSI will consider the Council's ideas on further examining clinical trial failures using other approaches for evaluating toxicity, such as tandem chips of multi-organ systems.

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

13:56:07 From Rebecca Jackson to Everyone: what an amazing program and an example of truly catalyzing a new approach to improve drug development. The promise for this in personalized medicine is incredible.

13:57:36 From Lili Portilla to Everyone: Thanks Marshall- that was one of first grants that we funded in the program.

13:58:41 From Kelly M McVeary to Everyone: Would you please comment on the progress in the manufacturing processes to fabricate these chips.

14:11:21 From Marshall Summar to Everyone: Here is what resulted from that first grant Lili. They have built up a very strong network saving explanted livers from inborn error patients. That "zoo" has over 20 diseases in it with multiple forms of each. <https://hemoshear.com/>

14:11:49 From Marshall Summar to Everyone: Great choice for the SBIR program with good results.

**XII. CLEARANCE OF CONCEPTS**

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

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

Dr. Tagle introduced the new concepts being proposed by the OSI that leverage the Tissue Chip program. He pointed out that the first five years (FY 2012 to FY 2017) of the NCATS Tissue Chip program focused on toxicity studies, followed by disease modeling for efficacy studies (FY 2016 to FY 2021), and then precision medicine (FY 2022 to FY 2025). NCATS OSI has established Tissue Chips Testing Centers (TCTCs) and partnerships with the FDA and IQ Consortium MPS Affiliate and has demonstrated significant return on the Center's investments.

**Translational Centers for Microphysiological Systems (TraCe MPS) Concept: Danilo A. Tagle, Ph.D., M.S., Director, OSI, NCATS**

Dr. Tagle presented a new concept to establish TraCe MPS, which leverages the fact that MPS hold promise as a leading new approaches method (NAM). NCATS continues to play a leadership role domestically and internationally in the development, implementation and adoption of this technology for the drug development process. Despite scientific advancements, the need to translate MPS in the direction of industrial use and regulatory acceptance is great.

NCATS proposes this concept to accelerate the translational use of MPS in drug development through regulatory acceptance and adoption for industrial use by drug developers. The aim is to develop tissue chips that are fit-for-purpose for industry needs and have specific context of use (CoU) that will satisfy regulatory approval criteria. The objectives are to establish translational centers focused on regulatory qualification of MPS with active input and engagement from key stakeholders and end users (e.g., FDA and pharmaceutical members of the IQ MPS Affiliate) and engage other NIH ICs in the formation and funding of these translational centers. The expectation is that the translational centers will, through the project period, be able to qualify several MPS models as drug development tools (DDTs).

In terms of key areas emphasis, the MPS models will need to meet end-user criteria for biomarkers and assays as defined by industry. The NIH, FDA, and the IQ Consortium will co-develop study designs for each organ system and MPS model that will be suited to have multiple CoUs, each of which could be the basis for qualification by the FDA as a DDT. In addition, discussions are underway to have FDA serve as a center hub.

This proposed initiative aligns with the Tissue Chips for Drug Screening program and will be the culmination of NCATS' investments in developing MPS as *in vitro* models for safety pharmacology, therapeutic efficacy, and precision medicine. NCATS' support of this concept is important to continue its leadership in this field and to further spur engagement and investments in using MPS as DDTs. NCATS anticipates that this initiative will pave the way for regulatory and industry use of MPS that will address scientific, legislative, and ethical needs for more predictive NAMs.

***Discussion***

Dr. Jackson thinks that the success of this natural next step for the Tissue Chips program will depend on the scientific rigor and meeting all the regulatory requirements. She emphasized clearly identifying the right stakeholders (e.g., PAGs) to move this initiative forward so that adoption is widespread.

Dr. Jackson also emphasized focusing on ways to promote awareness of this effort in the wider community and addressing sustainability as the technology advances. Dr. Tagle explained that since the inception of the Tissue Chips program, NCATS has created a consortium of investigators, established memoranda of understanding with the FDA and the pharmaceutical industry, and pre-competitively exchanged information (i.e., unpublished data) to benefit from the expertise and resources across the consortium. In addition, NCATS has received input from stakeholders to address and frame solutions to problems, which will be key in qualifying MPS as DDTs. He added that the investigators freely explore the technology and apply innovative methods to stay current on the advances.

Dr. Kretzler endorsed the concept and commended the OSI on this systematic and logical next step to bring the MPS to fruition, which will be challenging given the lower success record of diagnostic devices at the FDA compared with therapeutics. He called attention to discussions with the FDA on orphan diseases that might be useful to review and an upcoming workshop on drug-induced kidney injury that will focus on this topic. Dr. Kretzler recommended partnering the IQ Consortium MPS Affiliate with the FNIH, continuing to leverage the NCATS dollars with industry, and engaging the European Medicines Agency (EMA) for its expertise in addressing regulatory hurdles for startup biotechnology companies. He sought clarity on whether the translational centers would be expected to examine all the different organ systems or specialize on a subset. Dr. Tagle clarified that one center would focus on a particular organ system to develop fit-for-purpose tissue chips. He also agreed with continuing to leverage industry investments and noted ongoing discussions with the EMA on harmonizing approaches and outreach via the MPS world summit.

Dr. Andrew Lo commended NCATS and the OSI on the progress of the Tissue Chips program. He speculated on establishing a joint NCATS–FDA collaboration with the goal of using tissue chips to provide an example of an industry guidance for the appropriate surrogate endpoints for difficult-to-treat diseases. Dr. Tagle explained that another new OSI concept that will be presented during the meeting will provide an example of how this need can be addressed. Dr. Andrew Lo also suggested prioritizing diseases that the translational centers would focus on. Dr. Tagle noted that a 2018 collaboration with a drug information group, the FDA, and IQ Consortium MPS Affiliate to identify the greatest need resulted in establishing the Clinical Trials on a Chip program.

Dr. Summar commented on involving the FDA early in the project to provide general guidance to the field, especially if the wide adaptation of MPS will be the basis for accelerating cures for diseases. He suggested reverse engineering a rare disease that has been successfully treated with small-molecule therapy (e.g., tyrosinemia) to demonstrate how the tissue chip model works.

Dr. Tagle and the OSI will consider Council members' recommendations to further engage the EMA on advice to traverse the regulatory hurdles for startup companies; engage PAGs as additional stakeholders in the implementation of this concept; and demonstrate how a tissue chip model works in a successfully treated rare disease.

Dr. McVeary also emphasized engaging patients and PAGs. She shared that she represents a PAG, Lupus Research Alliance, that funds the Lupus Clinical Investigators Network (LuCIN), addressing this major health issue that disproportionately affects women and minorities. Because lupus is a model of a multi-organ system, Dr. McVeary suggested considering the resources of the LuCIN to help implement this concept. Dr. Tagle appreciated the information and noted that providing cell banks and cell resources for bioengineering the devices are key areas PAGs could engage in this project.

Dr. Tagle and the OSI will connect with the Lupus Research Alliance and Dr. McVeary on available resources to leverage.

Ms. Kennedy commented that the FDA User Fee Agreement has been proposed by Congress and provides an opportunity to enhance the language that addresses engaging the FDA for this and similar NCATS projects. She suggested including more statistics on the potential cost or cost savings of NCATS' investments in tissue chips in these concept presentations. Dr. Rutter agreed that this was a good recommendation and elaborated on providing such information at a future meeting.

Members unanimously approved the TraCe MPS concept.

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

14:34:19 From Kelly M McVeary to Everyone: Dan, I represent a patient advocacy group called the Lupus Research Alliance and its clinical trial network of 57 academic medical centers operating under a more-or-less common IRB. Lupus is a multi-organ disease affecting women (10:1) and minorities (80%). If it adds value to your consortia strategy, we are happy to help.

14:35:28 From Annie Kennedy to Everyone: A bit time sensitive but could something be included within the UFA to support FDA's engagement here?

14:39:47 From Annie Kennedy to Everyone: I also found the stat from Drug Dev Today re overall R&D cost savings from tissue chip investment to be extremely compelling. That needs to be the first soundbyte, along with how this technology helps improve patient outcomes.

14:46:54 From Matthias Kretzler to Everyone: @Kelly: We do have the framework in place in the RDCRN NEPTUNE network, happy to share protocols and regulatory frameworks.

**Introduction of the Helping to End Addiction Long-term<sup>SM</sup> Initiative, or NIH HEAL Initiative<sup>SM</sup> Concepts: Christine M. Colvis, Ph.D., Director, Office of Drug Development Partnership Programs (ODDPP), NCATS**

Christine M. Colvis, Ph.D., provided a brief review of ODDPP activities and introduced the Office's two new NIH HEAL Initiative concepts. Dr. Colvis explained that the concepts presented today, if approved, will be supported by the NIH HEAL Initiative and not NCATS funding. The two concepts will be presented in succession and then discussed; each concept will be voted on separately.

The LitCoin (i.e., academic currency) concept, approved by the Council during the June 2021 meeting, is a novel publication format that is citable and indexed by PubMed, with the goal of incentivizing data sharing. LitCoins are short, small publications of observations that would not normally be included in a major publication. One key aspect of this program is to build machine-readable, artificial intelligence-ready knowledge at the inception of traditional publications. An NLP algorithm generates a knowledge graph based on the LitCoin free text, which the author would confirm.

NCATS collaborated with the NASA Tournament Lab (NTL) to sponsor a LitCoin NLP challenge for government agencies. Through NTL, NCATS partnered with CrowdPlat, Inc. (San Francisco, California) to help with crowdsourcing, disseminating, and engaging the community. More than 200 teams



participated, and eight winning teams were selected. NCATS has been granted a broad license to use these eight NLP software systems for LitCoin concepts.

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

15:05:46 From Paul Harris to Everyone: Would a LitCoin submission include peer review?

**NIH HEAL Initiative LitCoin Pilot Program to Enable Pain and Addiction Research Discoveries Concept:  
Tyler F. Beck, Ph.D., Scientific Program Officer, ODDPP, NCATS**

Tyler F. Beck, Ph.D., presented a new contract concept on establishing an NIH HEAL Initiative LitCoin Pilot Program to enable pain and addiction research discoveries. ODDPP envisions LitCoin as a biomedical publication that allows researchers to share results normally not included in high-impact peer-reviewed journals and to do so computationally and without the burden of additional work. In the LitCoin framework, the authors (i.e., researchers) write an abstract-length description of their work and the conclusions and upload the text to the LitCoin server. The NLP algorithms generate knowledge assertions, which are displayed to the researcher for verification. The publisher partner reviews the assertions and approves them for publication.

Dr. Beck highlighted that the June 2021 NCATS [LitCoin Stakeholder Feedback Workshop](#) and [LitCoin Natural Language Processing \(NLP\) Challenge](#) — organized in collaboration with CrowdPlat, Inc., Bitgrit (Tokyo, Japan), and NTL — informed developing the NCATS LitCoin program. The goals of the broader LitCoin program are threefold: Encourage researchers to share their data their data in a computationally accessible manner; generate highly connected knowledge networks from published works with built-in curation; and encourage the reporting of research findings that may be separate from the researcher’s main hypothesis. In addition to the NLP challenge, NCATS soon will sponsor a conceptual challenge for the design of the LitCoin platform.

NCATS is proposing this concept to build a critical component of the LitCoin platform to pilot with pain and addiction research, because it fits with the NIH HEAL Initiative. The proposed platform extends from observation to open data reuse and involves converting human-readable knowledge to machine-readable knowledge. The deliverables of this pilot program and feasibility study are to create a sophisticated web interface that will allow researchers to upload free text describing their findings. A successful system should be able to run NLP algorithms on the text to extract knowledge assertions and display extracted assertions to researchers, allowing confirmations and edits. The system also will need to connect with publisher partners to facilitate easy journal submissions. After confirmation from the publisher of acceptance, the system would deposit the assertions into the LitCoin knowledge graph to allow reuse.

Regarding implementation of the project and its expected impact, this research has the potential to fundamentally change the manner in which researchers publish their work by allowing computational-accessible knowledge to be generated as part of the publication process. NCATS, which is well suited to conduct such pilot studies to assess feasibility of transformational concepts, anticipates that this

concept will result in findings that may not have been published or accessible to researchers. In addition, publishing failed drug discovery attempts could improve efficiency in drug development.

**NIH HEAL Initiative LitCoin Foundational Knowledge Graph Concept: Tyler F. Beck, Ph.D., Scientific Program Officer, ODDPP, NCATS**

Dr. Beck presented the second ODDPP new contract concept, the NIH HEAL Initiative LitCoin Foundational Knowledge Graph, which also is a critical component of the LitCoin platform to pilot with pain and addiction research. The objectives are to extract free text from existing research publications in the pain and addiction research space and generate knowledge assertions using the NLP systems that emerged from the 2022 LitCoin NLP challenge. The NIH HEAL Initiative investigators will review the NLP-generated assertions extracted from their own publications and verify that they are accurate. Some professional curation to ensure accuracy is expected.

The chief deliverable will be a robust knowledge graph with highly accurate knowledge assertions in the pain and addiction research space generated using NLP. This process will involve combining the algorithms received through the 2022 LitCoin NLP challenge into a single system that can generate knowledge assertions and run those assertions on PubMed abstracts in the pain and addiction space collected from a portfolio analysis of the NIH HEAL Initiative investigators. The contractor will build a simple web interface to allow researchers to curate their knowledge from prior publications and organize virtual events (e.g., workshops) to engage researchers in the creation of computationally accessible knowledge.

This concept is a continuation of the broader NCATS LitCoin initiative and will support the LitCoin Pilot Program. NCATS anticipates that normalizing the pre-curation of extracted knowledge will provide researchers more agency to ensure that their findings are discovered and widely reused. The generated knowledge graph complements other NCATS programs, such as the Biomedical Data Translator.

Dr. Beck summarized that NCATS proposes two new concepts to pilot a program that could fundamentally change the way that researchers publish their discoveries by providing a new currency of research consistent with present practices. NCATS anticipates that asking researchers to curate their own generated knowledge will energize them and help them understand how NLP can enhance their own work. If successful, this effort could expand to other fields, leading to a fundamental shift in publication practices, with far-reaching consequences for the generation and reuse of biomedical knowledge.

For these contract concepts, the reviewers are being asked to consider the scientific, technical, or programmatic significance of the goals of the proposed R&D activity; availability of the technology and other resources necessary to achieve the required goals; and the extent of identified practical, scientific, or clinical uses for the anticipated results. Comments on each of these features have been provided in the Council materials.

***Discussion***

Dr. Harris encouraged testing with researchers (in-person or virtually) the workflow associated with the algorithmic detections to evaluate the assumptions and to focus on a disease area that is of interest to NCATS. He asked about incentives for the NIH HEAL Initiative investigators to participate, which Dr. Beck noted as a general incentive of being able to upload and visualize data in the knowledge graph. Jessica

Mazerik, Ph.D., added that a special session could be convened in parallel to the NIH HEAL Initiative Investigators Annual Meeting, for example, to discuss LitCoins. She highlighted that the [HEAL Data Ecosystem](#) is building an infrastructure with guidelines for data sharing and includes incentivizing through FOAs and collaborations. LitCoin activities could be linked to this data ecosystem.

The ODDPP will explore, with the HEAL Data Ecosystem leadership, the potential of collaborating on the NCATS LitCoin program.

Dr. Kretzler agreed with Dr. Harris on identifying user personas of the LitCoin knowledge graphs to better understand the value, output, and challenges. This group also could infer new hypotheses and generate insight on research activities that could educate the wider NIH HEAL Initiative community.

Dr. Beck commented that this could be an opportunity to engage early-career investigators and postdoctoral researchers, who may have data that do not necessarily fit into a major publication.

Dr. McVeary noted the strengths of the program to engage the initial content creators and use pre-curation methods. She asked about the “coin” aspect of this title, specifically what does LitCoin represent. Dr. Beck commented that the “coin” aspect is referring to building a new currency of research. LitCoin will enable a link between the researchers and the generation of knowledge they create and use as the currency in the future. Dr. McVeary also emphasized expansion beyond machine learning to include ontological engineering and exploration of a decentralized architecture to further engage the broader research community to curate their knowledge assertions.

Dr. Jackson encouraged evaluating the LitCoins pre- and post-submission and considering incentives for the investigators. Dr. Summar commented that promotion and tenure committees drive publication behavior and having a metric similar to the cumulative impact factor for publications could be useful.

Members unanimously approved the NIH HEAL Initiative LitCoin Pilot Program concept.

Members unanimously approved the NIH HEAL Initiative LitCoin Knowledge Graph concept.

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

15:48:39 From Paul Harris to Everyone: Interesting paper on incentives on data sharing ...

### **Introduction of Division of Clinical Innovation (DCI) Concept: Michael G. Kurilla, M.D., Ph.D., Director, DCI, NCATS**

Michael G. Kurilla, M.D., Ph.D., introduced the new DCI concept that focuses on a CTSA Program broad area: providing a national resource for the rapid response to urgent public health needs. The CTSA supported several COVID-19-related clinical trials, specifically the convalescent plasma evaluations and two ACTIV trials, including ACTIV Randomized Master Protocol 1 of Immune Modulators (ACTIV-1 IM or ACTIV-1). This trial opened in FY 2020, focused on evaluating three immunomodulators (Remicade®, Orencia®, and cenicriviroc) for hospitalized patients with COVID-19, and was funded by HHS Operation Warp Speed (OWS). The majority of U.S. clinical sites were CTSA Hubs. ACTIV-1 is now closed, and the data are being reviewed. Dr. Kurilla explained that with additional funding from OWS, the DCI is proposing a new concept that addresses the need for time-limited biospecimen storage and related services.

**Contract Topic: ACTIV-1 Time-Limited Biospecimen Storage and Related Services (COVID- 19) Concept: Soju Chang, M.D., M.P.H., Medical Officer, DCI, NCATS**

Soju Chang, M.D., M.P.H., presented a contract concept for ACTIV-1 time-limited biospecimen storage and related services. Dr. Chang noted that Cynthia Boucher, M.S., project manager for ACTIV-1 and Samuel A. Bozzette, M.D., Ph.D., Chief Medical Officer, OTM, NCATS, would be available for the discussion of this concept. ACTIV-1 is funded through a task order under the Biomedical Advanced Research and Development Authority (BARDA) contract and is managed by NCATS. The period of performance for the BARDA task order is from August 8, 2020, to September 30, 2022. Research samples of whole blood, serum, and plasma were collected from consented participants during the trial and stored in the ACTIV-1 biospecimen storage facility for future use.

NCATS proposes this new contract concept to continue the support of existing activities under the BARDA task order and provide additional services after the conclusion of the trial. The objectives are to provide (1) time-limited storage and distribution of deidentified biospecimens, (2) regulatory support and data management of clinical data, and (3) additional statistical analyses. The key areas of emphasis are biospecimen management, clinical data management, and biospecimen analyses.

NCATS will manage the biorepository contract funded by OWS. Regarding the expected impact, this resource will permit the medical community to better understand the role of inflammatory markers and cytokines to predict the clinical course of COVID-19 disease and the disease's response to treatments evaluated in ACTIV-1. The outcome will be publications describing finding related to the results of the biospecimen analyses.

For this contract concept, reviewers are being asked to consider the scientific, technical, or programmatic significance of the goals of the proposed R&D activity; availability of the technology and other resources necessary to achieve the required goals; the extent of identified practical, scientific, or clinical uses for the anticipated results; and the adequacy of the inclusion of women, minorities, and individuals across the lifespan in clinical research. Comments on each of these features have been provided in the Council materials.

Dr. Chang explained that the ACTIV-1 clinical trial recruited hospitalized adults (age 18 and older) who had COVID-19. Enrollments span across the United States and in Latin America. The trial had no exclusions by gender or race and ethnicity; children, however, were excluded because this was the first trial evaluating two repurposed drugs and one experimental drug to treat COVID-19. NCATS will contribute towards the scientific evidence to better understand the clinical course of COVID-19 and treatment response of immunomodulators tested in ACTIV-1.

***Discussion***

In response to questions from Dr. Harris about the location of the biospecimens, changing the funding mechanism, and new statistical and regulatory support, Dr. Chang replied that the plan is for the biospecimens and clinical data to remain with the current contractor. He clarified that this concept would support a three-year contract and a new activity to provide statistical services to evaluate the clinical data combined with the biomarker and cytokine assay information. Dr. Kurilla pointed out that these data comprise a finite set of samples and that no new biospecimens will be added. Dr. Bozzette commented that the current statistical team has worked with the complex database linked to ACTIV-1 to

streamline the process for deriving variables and has been incorporating biological factors into the developed mathematical models.

Dr. Shireman asked about the long-term plans for these data to maximize their usefulness to inform the research community before the next SARS-CoV-2 variant or the next pandemic and how these data would be made accessible to the broader public for future studies. Dr. Chang explained that the NIH has no plans to share these individual-level data with the scientific community, noting that aggregated data are shared via the [clinicaltrials.gov](https://clinicaltrials.gov) database. Dr. Rutter noted a lesson learned that it is best to determine how data will be handled up front than to add activities on the back end of a project.

Dr. Bozzette explained that a decision cannot be reached about the ACTIV-1 data alone; a broader discussion at the NIH level will involve all the ACTIV trials.

Dr. Shireman asked about the possibility of generating an ACTIV-1 deidentified data set that can be shared with the scientific community to address research questions of interest. Dr. Kurilla commented that the aspiration is to combine ACTIV data sets, but the protocols and case report forms differ. He reminded the Council of the updated NIH data sharing guidelines that will be forthcoming and noted that NCATS has considerable experience in deidentifying data.

Regarding the scope of work, Dr. Jackson encouraged including quality control and harmonization across the different biomarkers, which will be critical for using secondary data. Dr. Bozzette explained that the cytokine analysis is contracted out and noted that the pharmaceutical companies are completing analysis of antibody levels and pharmacokinetics, all of which will be incorporated into the current database.

Members unanimously approved the ACTIV-1 Time-Limited Biospecimen Storage and Related Services (COVID- 19) concept.

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

16:09:57 From Paul Harris to Everyone: NCATS has really played a strong and important role in these ACTIV trials - kudos to Mike, Sam, Clare, Jane, Soju, and other program leaders.

**Introduction of Small Business Innovation Research (SBIR) Concepts: Lili M. Portilla, M.P.A., Director, Office of Strategic Alliances (OSA), NCATS**

Lili M. Portilla, M.P.A., provided an overview of the NCATS SBIR program. Small Business Innovation Research (SBIR) and Small Technology Transfer (STTR) are congressionally mandated programs, with 3.2 percent set aside for SBIR and 0.45 percent for STTR. NCATS receives most of its applications through an Omnibus Solicitation. Other avenues include Grant Solicitations in Targeted Areas or SBIR Contract Solicitations. The benefits of the SBIR and STTR programs include stability, predictability, non-diluted funding, retention of intellectual property rights, and technical assistance for commercialization. Companies are provided the opportunity to participate in the innovation core training program at no cost. In addition, projects in this program undergo a rigorous scientific peer review, and awards can be leveraged for other funding and collaborative opportunities.

NIH SBIR/STTR is a three-phase program: Phase I, a feasibility study, provides support for up to one year. Phase II, full research and R&D, provides funding over two years. Fast-Track combines Phase I and Phase II. Direct-to-Phase II allows skipping Phase I. Phase IIB, competing renewal for Phase II/R&D, provides up

to three years of support. Phase III, commercialization, establishes a public–private partnership using non-SBIR/STTR funds.

SBIR contract solicitations are issued once per year, have a statement of work, and accept proposals on targeted topics in October. NCATS conducts the review for contracts. Grants have multiple solicitation dates, and the NIH Center for Scientific Review conducts the review, except for the cooperative agreements (U series funding mechanism), which are reviewed by the respective IC.

Ms. Portilla introduced the SBIR concepts. Two new SBIR proposals are being presented: a U44 grant focusing on tissue chips and a contract topic addressing tissue-cell culture cleaning processes.

**SBIR Grant Topic: Botulinum Toxin Potency Assay Using Tissue Chips (BoT PATCh) Concept: Danilo A. Tagle, Ph.D., M.S., Director, OSI, NCATS, and Lili M. Portilla, M.P.A., Director, OSA, NCATS**

Dr. Tagle presented the SBIR grant topic for BoT PATCh. In terms of the gap or need for this research, the mouse lethality bioassay (MLB) or the model dose that kills 50 percent of the population (LD50) assay has been the standard FDA-approved method to determine the safety and potency of each batch of botulinum toxin manufactured for medical and cosmetic uses since 1928. The challenge is that MLB is laborious and expensive and requires a sophisticated animal facility with a skilled and dedicated workforce. Ethical concerns have led to bans on the sale of cosmetic products or their components, which have been tested in animals. These concerns have resulted in rigorous efforts to develop alternative testing methods for the safe use of botulinum toxin in humans. In partnership with the FDA, NCATS has sought to develop such methods. NCATS has matured and validated human neuromuscular junction tissue chips that can provide a useful alternative platform for a NAM for quantitative analysis and titer evaluation of botulinum neurotoxins.

NCATS proposes to use the Center’s SBIR program to solicit U mechanism grants to develop and commercialize neuromuscular junction tissue chip platforms that will replace the MLB as a potency assay for botulinum toxin. The two main objectives are to develop and qualify neuromuscular junction tissue chips for BoT PATCh in partnership with the FDA and to establish commercialization avenues through the NCATS SBIR program after the platform has qualified as a DDT.

Although several alternative strategies and methodologies have been proposed for botulinum toxin testing, including both *ex vivo* assays (e.g., mouse phrenic nerve hemidiaphragm tests and non-lethal mouse flaccid paralysis assays) and *in vitro* assays (e.g., cell-based and nucleic acid tests), all have fallen short of replacing the MLB assay. Qualification as a DDT with the FDA will involve a side-by-side concordance study between the BoT PATCh and the conventional MLB assay.

This proposed initiative would leverage the Tissue Chips for Drug Screening program and complement ongoing activities supported by NCATS in developing MPS as *in vitro* models for safety pharmacology, therapeutic efficacy, and precision medicine. NCATS support of this concept is important to continue its leadership in this field and to spur engagement and investments in developing MPS as DDTs.

NCATS anticipates that this initiative will have a great impact on the field by replacing the MLB potency assay or LD50 assay for botulinum toxin. The successful outcome of this activity will lead to a DDT for the assessment of botulinum toxin potency during manufacturing, which will not only affect the cost and ease of use for the assay but also support the reduction, refinement, and replacement (known as the three Rs) of animal testing.

For this contract concept, reviewers are being asked to consider the scientific, technical, or programmatic significance of the goals of the proposed R&D activity; availability of the technology and other resources necessary to achieve the required goals; and the extent of identified practical, scientific, or clinical uses for the anticipated results. Comments on each of these features have been provided in the Council materials.

### ***Discussion***

Dr. Kretzler commented on how this concept is an exceptional use case, given the large numbers of research animals required for the MLB assays. He noted that this research fulfills one of the main missions of the tissue-on-a-chip platform to reduce animal usage and simplify robust testing. Dr. Kretzler emphasized stating in the RFA the expectations that the companies have a proven record of accomplishment of effectively qualifying tests and that they be familiar with the FDA approval process.

Dr. Tagle pointed out that the OSA has a signed letter of agreement defining the governance and interactions with the FDA, NCATS, and entities through a joint NCATS–FDA steering committee.

Members unanimously approved the BoT PATCh concept.

### **SBIR Contract Topic: Device or Process for the Cleaning of Cell Tissue Culture Flasks Concept: Sam G. Michael, Director, Automation and Compound Management, Chief Information Officer, NCATS, and Lili M. Portilla, M.P.A., Director, OSA, NCATS**

Sam G. Michael presented a new SBIR contract concept for a device or process for cleaning cell-tissue culture flasks, which addresses an unmet need. The use of consumable plastics is prevalent in biomedical research, with well over 90 percent being used once and then disposed. There are many challenges to such a practice. These products are expensive and generate large quantities of laboratory waste. Supply chain shortages have made these products even more expensive or difficult to acquire, impacting the ability of laboratories to perform research.

NCATS proposes this SBIR contract topic to identify a small business that can develop a device or a process capable of cleaning, sterilizing and treating tissue culture flasks. Such a process would allow repeated use of flasks before they are discarded in a burn box for incineration. A key requirement will be that the device or process has the ability to clean flasks while also applying a surface treatment to make them amenable to cell growth.

NCATS will help draft evaluation criteria, to be included in the solicitation, for verifying the characteristics of the flask after a cleaning process, including the sterility assurance level and cell viability measurements. Another key area of emphasis will be how to handle the caps, which may prove difficult to clean and may require that each flask have a replacement cap. In terms of implementation, this contract concept aligns with existing Information Technology Resources Branch efforts in laboratory sustainability, particularly in saving plates, tips, and reagents.

Regarding the expected impact, NCATS is a proven leader in laboratory sustainability, and its efforts in this space (e.g., IonField Systems SBIR) have saved tons in plastic wastes and hundreds of thousands of dollars. The ability to reuse tissue culture flasks could reduce overall laboratory waste and save laboratories substantial consumable costs, given their general expense. This concept provides an

opportunity to a U.S. small business to develop a solution to this problem. The metric of success will be a product or process that can clean flasks for reuse.

For this contract concept, reviewers are being asked to consider the scientific, technical, or programmatic significance of the goals of the proposed R&D activity; availability of the technology and other resources necessary to achieve the required goals; and the extent of identified practical, scientific, or clinical uses for the anticipated results. Comments on each of these features have been provided in the Council materials.

### ***Discussion***

In response to questions from Dr. Holman about plans to leverage existing, older cleaning methods that have been successful and the concern for the potential to use large quantities of water, Mr. Michael explained that the SBIR solicitation language is descriptive and will be responsive to other cleaning techniques. He noted that experience with high-throughput technology has shown that water can be recirculated and recycled in cleaning processes.

Dr. McVeary commended NCATS for elevating a fundamental operational issue to an opportunity for sustainability. She looks forward to a future SBIR opportunity not requiring large, expensive equipment for this type of cleaning method and noted her connection with Thrive Bioscience, Inc., which has made progress in cell culture automation. Mr. Michael expressed interest in following up with Thrive Bioscience, and Dr. McVeary volunteered to assist him.

Mr. Michael clarified that this SBIR contract concept will be responsive to approaches that lessen the environmental impact, including systems using degradation, renewable, or plant-based cleaning methodologies.

Members unanimously approved the Device or Process for the Cleaning of Cell Tissue Culture Flasks concept.

### **XIII. PUBLIC COMMENTS**

Comments from the public were accepted until June 4, 2022 (15 days after the meeting), and will be appended to the minutes.

### **XIV. ADJOURNMENT OF THE OPEN MEETING**

Dr. Rutter thanked the participants for their input. The next meeting is scheduled for September 22, 2022, and is planned as a virtual session. Dr. Rutter adjourned the meeting on May 20, at 4:46 p.m. EDT.



**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.  
Chair, NCATS Advisory Council  
Acting Director, National Center for Advancing Translational Sciences, NIH

\_\_\_\_\_  
Date

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

\_\_\_\_\_  
Date