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

31st Meeting of the
Advisory Council

Minutes of Virtual Meeting
September 22, 2022

The National Center for Advancing Translational Sciences (NCATS) Advisory Council held a meeting in open session on September 22, 2022, from 1:00 p.m. to 5:14 p.m. EDT via the 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 September 22, 2022, from 11:31 a.m. to 12:06 p.m. EDT for the review and consideration of grant applications.

NCATS ADVISORY COUNCIL MEMBERS PRESENT

Chair

Joni L. Rutter, Ph.D., 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.
Annie 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

Amy C. Lossie, Ph.D., Program Director, National Institute on Drug Abuse (NIDA), NIH
NCATS leadership and staff

I. CLOSED SESSION OF THE NCATS ADVISORY COUNCIL

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

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

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

Dr. Rutter adjourned the closed session of the NCATS Advisory Council meeting on September 22, 2022, at 12:06 a.m. EDT.

III. CALL TO ORDER, OPEN SESSION

Dr. Rutter called the meeting to order and welcomed members and guests to the 31st meeting of the NCATS Advisory Council. Anna L. Ramsey-Ewing, Ph.D., conducted the roll call and reviewed the meeting agenda. She noted the meeting logistics and reminded attendees that the open session was being videocast.

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

Members approved the minutes from the May 2022 Council meeting unanimously.

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 2023 and 2024:

- 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 welcomed new CAN Review Board member, Lisa Schill, B.S. Dr. Rutter presented updates on the NIH and NCATS—including staff and leadership transitions and announcements—and reported on the fiscal year (FY) 2022 budget. She highlighted progress in some of the NCATS offices, divisions, and programs and COVID-19 activities. Dr. Rutter noted that Clare K. Schmitt, Ph.D., acting deputy director, NCATS, will moderate the discussions.

NCATS and NIH Transitions

- **NCATS Staff Transitions.** Dr. Rutter announced staff changes. Randall J. Redmond, deputy executive officer, Office of Administrative Management, is retiring after 38 years of service to NIH. Mr. Redmond has worked behind the scenes assisting NCATS in setting up procedures and processes for operations. Bekah E. Geiger, M.S.W., is the new deputy executive officer. Carol Lambert, Ph.D., chief, Scientific Review Branch (SRB), Division of Extramural Activities, is retired after 20 years of service to NIH. Dr. Lambert, with her innovative ideas, was instrumental in helping NCATS sponsor prize challenge competitions and internal activities and was key to developing the NCATS emergency funding opportunity announcement (FOA) template and review processes. A search for a new SRB chief is in progress. Donald C. Lo, Ph.D., director, Therapeutic Development Branch (TDB), Division of Preclinical Innovation (DPI), is taking a position outside of the NIH with the European Infrastructure for Translational Medicine (commonly called EATRIS) headquartered in Amsterdam, The Netherlands. Dr. Lo led the TDB in achieving numerous milestones during the past 5 years, including enabling several U.S. Food and Drug Administration (FDA) investigational new drug (IND) applications, launching translational efforts in gene therapies, and securing the first two FDA-approved drug candidates for DPI. Elizabeth A. Ottinger, Ph.D., will serve as acting director, TBD.

- **Ongoing NIH Leadership Searches.** Dr. Rutter reminded the Council that the NIH Office of the Director has several leadership searches open and positions to fill. The search for a new NIH director is ongoing. Lawrence A. Tabak, D.D.S., Ph.D., is continuing to perform the duties of NIH director. Anthony S. Fauci, M.D., announced his plans to step down as director of the National Institute of Allergy and Infectious Diseases (NIAID) in December 2022. The search for a new NIAID director will be forthcoming. In addition, the search for a new NCATS director is ongoing, and Dr. Rutter is continuing to serve as NCATS acting director. President Joseph R. Biden has selected Monica M. Bertagnolli, M.D., to become the new National Cancer Institute (NCI) director. Dr. Bertagnolli will be the first woman to serve in this leadership position for the NCI. President Biden also announced his intent to appoint Renee Wegrzyn, Ph.D., M.S., as new director of the Advanced Research Projects Agency for Health (ARPA-H), Department of Health and Human Services (HHS). HHS Secretary Xavier Becerra announced Adam H. Russell, D.Phil., as ARPA-H acting deputy director.

Announcements and Events

Dr. Rutter highlighted recent NIH announcements and events.

- **NCATS Director's Corner.** Dr. Rutter, with assistance from the Communications Branch led by Emily Carlson Marti, M.A., Office of Policy, Communications and Education (OPCE), has been updating messages to the stakeholder community in the Director's Corner. The latest message focuses on working with stakeholders to advance the mission of NCATS. Other messages include a series on the bold goals of the Center. NCATS also launched a new NCATS stakeholder listserv, for which the Council members were encouraged to sign up. Dr. Rutter emphasized bidirectional communication across these platforms and noted the ongoing NCATS Stakeholder Teatime series.

- **FY 2023 Budget.** Dr. Rutter reported on the FY 2023 budget process. Eight days are remaining in the fiscal year, and a continuing resolution to operate the government from October 1, 2022, is anticipated. The House Appropriations Committee passed its bill out of committee on July 5, 2022 and includes a 3.2 percent increase for NIH Institutes and Centers (ICs). The Senate draft bill was released on July 28, 2022, with overall increases to the ICs similar to those proposed by the House, at 3.1 percent. The increases to the Clinical and Translational Science Awards (CTSA) Program are consistent with the increases to the ICs but not the increases in the non-CTSA budget, which has been experiencing smaller growth. NCATS is monitoring budget decisions and their potential impact on the concept clearances approved by the Council. In the next step, the House and Senate will conference and consider the final budget.

- **HHS 2022 Departmental Awards.** Several NCATS staff have received the Secretary's Award for Distinguished Service for their work on the Rapid Acceleration of Diagnostics (RADx) Initiative. The National Institute of Biomedical Imaging and Bioengineering organizes RADx, which is anticipated to extend beyond COVID-19-related activities. Bernard Talbot, M.D., Ph.D., who retired from the NIH in July 2021 after 5 decades of service, received the 50-year-length-of-service award. Dr. Talbot had worked with NCATS since 2011.

- **Genetics and Rare Diseases (GARD) Information Center.** NCATS is in the process of modernizing the GARD information center, and users may experience delays in retrieving information. GARD is one of the leading NIH websites; its user base is diverse, seeing visits from patients, clinicians, and other stakeholders. The first two phases have been completed, and NCATS staff transferred GARD and its Contact Center to the new platform to answer inquiries more rapidly. Phase 3 to rebuild the website to offer more information on additional rare diseases has started. Upgrades are anticipated to be completed in early 2023, potentially by the next Rare Disease Day. NCATS is continuing to collect user feedback from the rare diseases community to refine the website.

- **LitCoin Program.** The LitCoin Natural Language Processing (NLP) Challenge was conducted to examine the NLP of abstracts or concepts available from PubMed. More than 200 teams worldwide participated, and eight winning teams were selected. NCATS has been granted a broad license to use these eight NLP software systems for LitCoin concepts. Dr. Rutter noted that LitCoin has the potential to fundamentally change the way researchers publish their work. The next phase will be the LitCoin Pilot Design Challenge, focusing on the platform and associated requirements needed to build the submission system. The challenge opens on October 31, 2022, and the total award sizes will be $25,000 for each of the top five designs.

- **The Hever Group 2022 Meeting.** Dr. Rutter attended the 2022 Hever Group meeting, with prompting from then-NIH director, Francis S. Collins, M.D., Ph.D. This meeting convenes research and development leaders from different industry sectors or companies. Several current NIH programs were the outcome of ideas that Dr. Collins proposed to this group. These include the Accelerating Medicines Partnership® (AMP) and the AMP Bespoke Gene Therapy Consortium (BGTC). Discussions at the 2022 meeting focused on artificial intelligence (AI), the advent of AlphaFold Protein Structure Database that was developed by DeepMind and the European Molecular Biology Laboratory's European Bioinformatics Institute, and methods to leverage this effort for drug development.

NCATS Events and Meetings

Dr. Rutter noted upcoming events, including workshops and meetings. Some are directly addressing NCATS' three audacious goals to provide (1) more treatments (2) to all people (3) more quickly.

- **Quest for Innovative Molecular Treatment Modalities for Intractable Disease Targets.** On November 17 and 18, 2022, NCATS will collaborate with the National Institute of Neurological Disorders and Stroke (NINDS), NCI, and NIAID to host a virtual workshop on innovative molecular treatment modalities for intractable disease targets. This workshop aligns with NCATS goal 1, and the purpose is to identify "pain points" for developing treatments against targets that traditionally are considered intractable to current methods of drug discovery. One main area of focus includes identifying protein families, molecular entities, and disease areas most in need of innovative therapeutic modalities. It is expected that the outcomes from this workshop will expand the pool of therapeutic approaches for treating human diseases.

- **Minimizing Bias and Maximizing Long-Term Accuracy of Predictive Algorithms in Health Care.** The challenge focused on predictive algorithms in health care fits with NCATS goal 2 and will open for submissions on October 30, 2022. Dr. Rutter explained that previously designed AI and machine learning (ML) algorithms have not shown their full potential in clinical applications or clinical decision support. Even well-designed algorithms and models can become inaccurate or unreliable over time due to a variety of factors. These factors—such as how data are captured, distributed, and used in real-world applications—now can be further addressed. This challenge invites groups to develop bias-detection and -correction tools that foster good AI/ML algorithmic practice and mitigate the risk of inadvertent bias in clinical decision support algorithms in health care environments.

- **Assay Guidance Manual (AGM) Program Workshop.** On October 18 and 19, 2022, NCATS will host the in-person Assay Guidance Workshop for High-Throughput Screening and Lead Discovery on the NIH main campus. This AGM workshop is designed to disseminate critical information about the implementation of robust assay methods and is particularly relevant for researchers developing molecular probes and/or clinical drug candidates.

- **2022 In-Person CTSA Program Annual Meeting.** NCATS will convene the 2022 CTSA Program Annual Meeting on November 1 and 2 in Washington, D.C. The theme is "Achieving Health Equity Through the Science of Translation." FDA Commissioner, Robert Califf, M.D., and Dr. Rutter will be keynote speakers during the general session.

- **Funding Opportunity Announcements (FOA).** Dr. Rutter briefly reviewed recently published FOA that span NCATS programs, including those linked to concept clearances. The Division of Rare Diseases Research Innovation (DRDRI) released a Shared Molecular Etiologies (SaME) FOA—Basket Clinical Trials of Drugs Targeting SaME in Multiple Rare Diseases (U44 Clinical Trial Required)—that focuses on therapeutic approaches for commonalities across rare diseases. The Office of Drug Development Partnership Programs (ODDPP) released a FOA—Pilot Projects Investigating Understudied Proteins Associated with Rare Diseases (R03 Clinical Trial Not Allowed)—that leverages the NIH Common Fund Illuminating the Druggable Genome (IDG) Program. New FOAs are open to support the second phase of the Somatic Cell Genome Editing Program. Promising therapeutic approaches are starting to reach the clinic, including CRISPR-based gene editing therapies for liver and eye diseases, and initial results are positive. Other approaches include *ex vivo* editing trials, IND-enabling studies, and platform clinical trials of somatic genome editing for multiple diseases, which has a FOA that closes on November 10, 2022.

- **Children's Inn at NIH Visit.** NCATS hosted a dinner at the Children's Inn at NIH to serve the community of families who are lodging at the Inn while their children receive treatment at NIH. The Children's Inn has a long-standing tradition of having different groups serve dinner. Dr. Rutter; Jessica M. Faupel-Badger, Ph.D., M.P.H., chief, Education Branch, OPCE; and Mark J. Henderson, Ph.D., biology group leader, Early Translation Branch, DPI, attended this event. Dr. Rutter expressed appreciation to Audie A. Atienza, Ph.D., program officer, Digital & Mobile Technologies Section, Division of Clinical Innovation (DCI), for organizing this effort.

NCATS Program Updates

Dr. Rutter pointed out that detailed program updates from the DCI will be provided later in the meeting. She highlighted some notable achievements since the last Council meeting.

- **AMP Bespoke Gene Therapy Consortium (BGTC).** Dr. Rutter reminded the Council that several industry partnerships have been established in the BGTC. Philip J. (P.J.) Brooks, Ph.D., acting director, DRDRI, leads the BCTG, along with his Pfizer Inc. counterpart and with input from FDA's Peter Marks, M.D., Ph.D. To date, 11 NIH ICs have joined. Programs have been funded that are related to adeno-associated virus (AAV) biology that aim to improve the dosages required during AAV gene therapies. In addition, NCATS is in the process of developing chemistry, manufacturing, and quality control and preclinical proposals. Disease nominations for the clinical workstream closed in February 2022; 61 nominations were received, and 14 leading proposals were selected.

- **Gene Therapy Collaboration.** Dr. Rutter announced DPI's TDB second collaborative FDA approval, with partner Agilis Therapeutics (now PTC Therapeutics Inc.) for Upstaza™ (eladocagene exuparvovec). Upstaza is the first disease-modifying treatment for aromatic L-amino acid decarboxylase deficiency and is the first marketed gene therapy that is infused directly into the brain. PTC Therapeutics was granted European Commission approval in July 2022 for use of this therapy in patients 18 months and older. Council member Dr. Andrew Lo completed a case study on this topic that can be shared with the attendees.

- **Tissue Chips in Space Program.** In July 2022, the NCATS Office of Strategic Initiatives (OSI) supported two tissue chip projects on the program's second flight to the International Space Station National Laboratory. One project, led by the University of Florida, is studying the causes and prevention of muscle wasting; the second project, led by the University of California, San Francisco, is investigating immune aging and healing outcomes. The next launch is scheduled for October 2022. 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.

NCATS COVID-19 Activities

Dr. Rutter provided an update on NCATS' COVID-19-related activities.

- **Humanized Nanobody Phage Display SARS-CoV-2 Library.** The DPI, led by scientific director Anton M. Simeonov, Ph.D., and his team, has built a library of synthetic antibodies against the SARS-CoV-2 spike protein. The intent is to accelerate the identification and development of these antibodies into preclinical evaluation and, ultimately, clinical applications. The assay methodology, which was provided to the World Health Organization (WHO) to enable manufacturers from around the world to use these technologies, was published in the August 10, 2022, issue of *PLoS One*. Dr. Rutter commented on how this is but one way NCATS is disseminating its demonstrated work in the DPI.

- **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 (Alpha, Delta, Omicron), including the efficacy of the vaccines against these variants. Currently, the portal contains nearly 13,000 data points of therapeutic annotations from more than 370 sources, and users can now view and sort data by sublineage. The Omicron variant is the most prevalent, and data on more than 18 sublineages have been added to the existing information. NIH Chemical Genomics Center biochemist, Kyle R. Brimacombe, M.S., and DPI investigator, Matthew D. Hall, Ph.D., chief, Therapeutic Development Branch, have enabled a view of the shift in SARS-CoV-2 therapeutic activity across variants and monoclonal antibodies over time. Recent *in vitro* data are demonstrating that the imdevimab antibody has sustained effectiveness against the Omicron variants. In addition, the OpenData Portal added a monkeypox page and now includes data for treating this disease.

- **National COVID Cohort Collaborative (N3C).** As of the date of this meeting, the N3C Data Enclave contains data from more than 15 million patients, 6 million of whom have received a COVID-19 diagnosis. More than 3,000 researchers are participating in this platform. In response to a request from the White House COVID-19 Response Coordinator, Ashish K. Jha, M.D., NCATS examined Paxlovid™ (nirmatrelvir/ritonavir) use in the N3C Data Enclave and prepared a report. The N3C Paxlovid use characterization report to the White House shows that of the 22,000 COVID-19 patients who were prescribed Paxlovid, less than 1 percent had to be hospitalized within 3 weeks of administration or had severe outcomes. Data suggest that adverse outcomes appear to be attributed to viral behavior effects. In fact, despite receiving Paxlovid, people who were older or had more comorbidities tended to have more severe outcomes post-COVID-19 infection. Other research groups, some of which include NIH-funded investigators, have reported real-world use of Paxlovid, and the findings are similar.

- **American Indian/Alaska Native (AI/AN) Data.** N3C collects data on racial categories, including AI/AN populations, from health centers across the United States. NCATS is sensitive to the privacy and sovereignty of tribes and has been communicating with tribal groups to ensure understanding of how best to use these data. NCATS has solicited input from the NIH Tribal Health Research Office, Indian Health Service Tribal Epidemiology Centers, and NIH experts. Beginning in February 2022, NCATS convened consultations with the NIH Tribal Advisory Committee and Tribal Consultation Group and received written testimony from tribal nations to provide input on the plans for these data. During the August 2022 meeting, an update was provided on the process to integrate AI/AN data within the N3C database. Further details can be accessed on the N3C Tribal Consultation webpage. NCATS has updated the N3C four pillars of data protection—regulatory and policy, privacy measures, security testing and monitoring, and researcher responsibilities—to increase awareness in the research community about the sensitivities of using AI/AN data. For example, full five-digit ZIP codes will never be shown in AI/AN demographic data to ensure privacy with the communities.

- **Foundation for the NIH (FNIH) COVID-19 Clinical Trials.** FNIH public–private partnerships have been critical for advancing understanding of COVID-19 vaccines and other therapeutics in the scientific community. One such partnership is the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) clinical trials. NIH has activated six ACTIV trials investigating clinical targets across all stages of the disease. NCATS CTSAs have played a key role in managing the ACTIV Master Protocol 1 of Immune Modulators (ACTIV-1 IM) and ACTIV-6 trials. To date, the ACTIV trials have enrolled more than 25,000 patients in 620 sites across multiple networks and have collectively issued 26 scientific publications, receiving more than 500 citations. Of the 800 agents evaluated, 29 were examined in trials, and six have been effective. The majority of these agents were repurposed drugs for other indications.

  Dr. Rutter highlighted some major findings of the COVID-19 trials. In ACTIV-1 IM, Orencia® (abatacept) and Remicade® failed to acceptably reach the primary endpoint (time to recovery at day 28), but the data on key secondary endpoints, day 28 mortality, and clinical outcomes were promising compared with placebo. ACTIV-6, an outpatient trial, evaluated the efficacy of repurposed drugs—ivermectin, fluvoxamine, and fluticasone—for the reduction of COVID-19 symptoms in self-administered doses at home. No major differences were observed with ivermectin-400 or fluticasone. Studies examining ivermectin-600 and fluticasone-50 and -100 will start soon.

- **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 goal is to rapidly improve understanding of and ability to predict, treat, and prevent long COVID-19 or post-acute sequelae of SARS-CoV-2 (PASC) infection. RECOVER is considering clinical trials and is partnering with FNIH. NCATS has identified more than 200,000 adults within N3C with these sequelae who could be enrolled in these studies. RECOVER investigators examined vaccine information related to those who have long COVID-19 using the N3C database. The RECOVER consortium's first findings reported results of electronic health record (EHR) and health systems studies that were published in the May 16, 2022, issue of *The Lancet Digital Health*. The data showed different subgroups of long COVID-19, specifically cardiopulmonary, neurological, and metabolic phenotypes. The consortium also found that

difficulty breathing was associated with higher risk of PASC and that vaccination was associated with a lower risk of PASC.

To address long COVID-19 beyond the RECOVER initiative, the White House released a National Action Plan on Long COVID-19 prepared by HHS, which includes references to these N3C data. In addition, the NHLBI RECOVER–NCATS N3C, NIH *All of Us*, and National Patient-Centered Clinical Research Network (commonly called PCORnet) are collaborating to use ML tools to identify PASC/long COVID cases within these large databases. An N3C ML algorithm was successfully deployed within *All of Us*.

NCATS Trainees and Council Accolades

Dr. Rutter noted that each year, NCATS trainees (Intramural Research Training Award Postdoctoral Fellows and Intramural Research Training Award Postbaccalaureates) in the Intramural Research Program volunteer to enter the NIH Three-Minute Talk (TmT) Competition. During the 2022 NCATS–National Human Genome Research Institute (NHGRI) annual fellows retreat, trainees were provided an opportunity to develop compelling TmT scientific research presentations, which are posted to the NHGRI YouTube channel. Haley A. Chatelaine, Ph.D., who works with the NCATS Metabolomics Operations Workflow project, was selected as a finalist to enter the competition at the NIH level.

In closing, Dr. Rutter congratulated Council member, Marshall Summar, M.D., on receiving the National Organization for Rare Disorders (commonly called NORD®) Lifetime Achievement Award for his work in rare diseases research.

Discussion

Paula K. Shireman, M.D., M.B.A., agreed with the approach of not revealing the full ZIP codes and asked whether Social Deprivation Index data collected by the U. S. Census Bureau will be made available as deidentified data. Dr. Rutter replied that a 3-digit ZIP code will be the identifier for AI/AN data for areas in which 20,000 people reside. The 5-digit ZIP codes will remain in place for other racial groups. Dr. Shireman commented that a 3-digit and 5-digit ZIP code has limited usefulness for data on social determinants of health, that smaller geographies such as census tract and block group were needed to understand neighborhood deprivation. Dr. Rutter explained that this has been a topic of the tribal consultations and noted that conversations about other methods to collect such data are ongoing.

Annie Kennedy, B.S., commended NCATS on its work in highlighting the need for innovation that directly translates to optimized outcomes for the patient community. She also noted the global reach of these efforts. Dr. Rutter called attention to Translation Together, a global partnership of translational research, noting that such a collaboration will be critical to NCATS for building on the smaller rare diseases clinical trials to enroll patients from across the globe.

VII. PROGRAM UPDATE: Division of Clinical Innovation (DCI): Michael G. Kurilla, M.D., Ph.D., Director, DCI, NCATS

Michael G. Kurilla, M.D., Ph.D., provided an overview of FY 2022 activities, including Funding Opportunity Announcements (FOA), staff updates, Clinical and Translational Science Award (CTSA) consortium activities, and COVID-19 and regular program efforts.

CTSA Suite of FOAs

Constructive feedback on the new CTSA suite of FOAs issued in 2021 has been extensive, which the DCI addressed in discussions with various stakeholders, including the CTSA Program Steering Committee, Coalition for Clinical and Translational Science, and individuals. In response to this feedback, the Division issued notices of correction, scheduled new technical assistance webinars, developed and published enhanced frequently asked questions (commonly called FAQs), and enhanced its communications. Currently, 63 CTSA Program Hubs operate throughout the United States.

DCI Staff Updates

Dr. Kurilla presented a summary of staff updates for FY 2022. Senior staff include Salina P. Waddy, M.D., chief, CTSA Program Clinical Affairs Branch; Josh Fessel, M.D., Ph.D., senior clinical advisor; and Christopher M. Hartshorn, Ph.D., chief, Digital & Mobile Technologies Section. Newly hired program and administrative staff complement the existing full-time employees, providing increased flexibility to respond to inquiries.

CTSA Scholars, Trainees, and Community Engagement Leaders

Dr. Kurilla highlighted recent recognition of CTSA investigators, Institutional Mentored Career Development Award (KL2) scholars and Ruth L. Kirschstein National Research Service Award Training Award (TL1) trainees.

- **Academic and Medical Societies.** Within the societies, Toluwalasé Ajayi, M.D., Scripps Research Translational Institute, was elected to the American Medical Association Board of Trustees; Yasmin Hurd, Ph.D., Icahn School of Medicine at Mt. Sinai, was elected to the National Academy of Sciences; and Consuelo Wilkins, M.D., M.S.C.I., Vanderbilt University Medical Center, was elected to American Society for Clinical Investigation.

- **Emerging Leaders.** Two next-generation CTSA leaders recognized include Sidney Hankerson, M.D., M.B.A., Icahn School of Medicine at Mt. Sinai, who was named Emerging Leader in Health and Medicine by the National Academy of Medicine, and Olajide Williams, M.D., M.S., Columbia University Irving Institute, who was honored by The New York Academy of Medicine as a Rising Leader.

- **Nursing Societies.** Demonstrating the breadth and depth of the CTSA program, KL2 co-director Victoria Vaughan Dickson, Ph.D., RN, was bestowed leadership awards by Eastern Nursing Research Society and the Heart Failure Society America Nursing; KL2 co-director Miriam Bredella, M.D., was selected by The National Academy of Medicine for the 2022 Scholars in Diagnostic Excellence program; D3 (Drug Discovery & Development Core) co-director Linda Dwoskin, Ph.D., was bestowed the Innovator Award by the College on Problems of Drug Dependence; and former KL2 scholar, Shanina Knighton, Ph.D., RN, was awarded National Black Nurses Association Nurse of the Year for Community Service Award.

- **Minority Health.** KL2 Scholar Alexandra Sims Corley, M.D., M.P.H., Cincinnati Children's Hospital Medical Center, and former KL2 Scholars Miraj Desai, Ph.D., Yale Center for Clinical Investigation, and Nakiya Naomi Showell, M.D., M.H.S., M.P.H., Johns Hopkins University School

of Medicine, received the 2022 National Minority Quality Forum's 40 Under 40 Leaders in Health Award.

- **Innovation/Community Engagement.** CTSA investigators received Association of American Medical Colleges Awards: Linda B. Cottler, Ph.D., M.P.H., University of Florida, for Community Engagement Model That Bolsters Trust and Trustworthiness; Sergio Aguilar-Gaxiola, M.D., Ph.D., University of California, Davis School of Medicine, for Solano County Interdisciplinary Collaboration and Cultural Transformation Model Innovations Project; and Vineet Arora, M.D., The University of Chicago Medicine, Pritzker School of Medicine, for Empowering Healthcare Workers to Bolster Trust in Science and Vaccination During the Pandemic: Making Illinois Medical Professionals Action Collaborative Team (IMPACT) Using a Place-Based Approach.

CTSA Program Consortium Activities (FY 2022)

- **R03 Awardees.** NCATS awarded 10 R03 grants that span a spectrum of research activities. Additional junior faculty are among the awardees and are establishing their independent research programs.

- **CTSA Collaborative Innovation Awards (CCIA).** NCATS awarded four CCIAs across three different areas of the CTSA program, focusing on engaging patients, innovating processes, and advancing use of cutting-edge informatics. Dr. Kurilla provided an update on one of the four projects. NCATS and the NIH Office of Disease Prevention co-funded the Analytics & Machine-Learning for Maternal-Health Interventions (AMMI) project. The North Carolina CTSAs—The University of North Carolina (UNC) at Chapel Hill, Duke University, and Wake Forest University—are collaborating on this effort. AMMI's main goal is to develop, implement, and evaluate ML-based technology to link biological, clinical, and social determinants of health data.

- **CTSA Consortium-Wide Centers: Resources for Rapid Demonstration and Dissemination (C3-R2D2).** NCATS awarded one C3-R2D2 project, ENACT: Translating Health Informatics Tools to Research and Clinical Decision Making. ENACT aims to create a federated system to promote a user-friendly, collaborative research and computing environment. Natural Language Processing (NLP) is being used to create a platform for statistical and machine learning (ML) capacity.

Dr. Kurilla noted that NCATS collaborates with other ICs and offices to co-fund projects related to their missions.

CTSA Emerging Research, Impact and Success Stories

Dr. Kurilla noted that NCATS' most valuable resources are the people and highlighted recent translational science research progress.

- **KL2 Scholars.** Amir Manbachi, Ph.D., M.Sc., is developing implantable ultrasound devices for spinal cord injury. Dr. Manbachi's KL-2 project led to a $13.5 million award from the Defense Advanced Research Projects Agency (DARPA) to advance his research. Laura F. Sartori, M.D., M.P.H., is studying multisystem inflammatory syndrome in children and has published findings

on emerging data (e.g.., COVID-19), highlighting knowledge gaps. Colleen S. Kraft, M.D., M.Sc., is professor, Department of Pathology and Department of Medicine Division of Infectious Diseases, Emory University School of Medicine. Dr. Kraft, a 2013 KL2 scholar, is investigating wastewater surveillance for SARS-CoV-2 in the university setting. Renee Hsia, M.D., M.Sc., is associate chair for Health Services Research, University of California, San Francisco. Dr. Hsia, a KL-2 scholar from 2009 to 2013, led a retrospective study that shows how race, income, and location play a role in who receives optimal treatment regarding stroke interventions. Dr. Hsia was the first emergency medicine physician inducted into the American Society for Clinical Innovation.

- **TL1 Trainees and Scholars.** TL-1 trainee, Yoni Ashar, Ph.D., Weill Medical College of Cornell University, through his project under the Helping to End Addiction Long-term® Initiative, or NIH HEAL Initiative®, is investigating the hypothesis that psychological treatment for primary chronic back pain could provide substantial and durable pain relief. Findings have recently been published. A TL-1 scholar from 2019 to 2020, Uriel Kim, Ph.D., Case Western Reserve University School of Medicine, previously examined the impact of the Patient Protection and Affordable Care Act on cancer disparities. Dr. Kim currently is an M.B.A. candidate at the Kellogg School of Management, Northwestern University.

- **CTSA Program Diversity, Re-entry, and Reintegration Supplement.** Dr. Kurilla acknowledged the six FY 2022 awardees and highlighted recent efforts of three. Cecelia Calhoun, M.D., M.P.H.S., M.B.A., assistant professor, Yale University, uses implementation science methods to promote the increased uptake of American Academy of Pediatrics guidelines into clinical practice for the treatment of adolescents and young adults with sickle cell disease. Jamila Kwarteng, M.S., Ph.D., Medical College of Wisconsin, is assessing the extent to which COVID-19 has affected proximal factors associated with church readiness to engage in health promotion programming and research. The long-term goal is to examine church readiness to engage members in health promotion and leadership support. Natalie D. Hernandez, Ph.D., M.P.H., executive director, Center for Maternal Health Equity, Morehouse School of Medicine Center, a 2019 Diversity Supplement Awardee, currently is researching the disparate rates of maternal mortality and morbidities among Black women in Georgia and nationally.

COVID-19 Activities

Dr. Kurilla reported on CTSA ongoing and new COVID-19-related activities.

- **National COVID Cohort Collaborative (N3C).** The amount of N3C data far exceeds expectations, and investigators have collectively published 47 articles and 17 preprints, two of which Dr. Kurilla highlighted. N3C investigators reported on a study revealing higher hospitalization and mortality rates in people infected with SARS-CoV-2 in rural America, which highlights a major disparity in health care. In another study, N3C aggregated data provided sufficient populations to characterize COVID-19 outcomes in children. In addition, N3C, as a centralized database, is enabling studies on data quality and is being referenced in policy documents and national plans.

- **CTSA News.** The Case Western Reserve University CTSA evaluated Paxlovid and molnupiravir rebound in a study extending from January to June 2022 using N3C data. Similar results were found for both drugs, suggesting that the effect was not unique to any single drug. The N3C conclusions were also similar to other published data. The Indiana University CTSA led the Development of Immunity after SARS-CoV-2 Exposure and Recovery (commonly called DISCOVER) statewide study evaluating antibody serology. The results showed that COVID-19 antibodies last longer in children than adults but diminish over time. The University of Colorado CTSA coordinated a real-word evidence (RWE) study following patients receiving monoclonal antibodies against SARS-CoV-2 and demonstrated that these data supported the limited available clinical trial data. RWE data also demonstrated the effectiveness of sotrovimab treatment in reducing hospitalizations among COVID-19 outpatients during the Delta variant phase, but not during the Omicron variant phase. Last, the Scripps Research Translational Institute CTSA developed smartphone applications for health emergencies during the COVID-19 pandemic, which have been widely used.

Non-COVID-19 Activities

Dr. Kurilla next reported on CTSA non-COVID-19-related activities.

CTSA Research

- **Asthma Studies.** NCATS CTSAs supported asthma studies evaluating the effectiveness of the monoclonal antibody mepolizumab, in populations at high risk for the disease. The data showed a 27 percent decrease in asthma attacks for Black and Hispanic children and adolescents treated with mepolizumab and who live in low-income urban neighborhoods.

- **Translational Therapeutics Accelerator (TRx) Pilot Awardee.** Fatemeh Momen-Heravi, D.D.S., Ph.D., received pilot funding administered by the Columbia University CTSA. Dr. Momen-Heravi's project focused on using engineered exosomes for genome editing of lung cancer targeting the *KRAS* mutation and was one of four recipients selected for the 2021 American Association for Cancer Research (AACR)-Bayer Innovation and Discovery Grant.

- **Pilot Project: Interactive Video App.** The University of Arkansas for Medical Sciences CTSA developed an interactive video application called Safe Use to educate adolescents about opioid misuse so that they can make decisions and review outcomes.

- **Pilot Project: Pulse Oximetry.** The University of Georgia CTSA analyzed the discrepancies between pulse oximetry and arterial oxygen saturation measurements and the association with organ dysfunction and mortality, stratified by race and ethnicity. The data revealed significant disparities in pulse oximetry accuracy across racial and ethnic subgroups. The pulse oximetry devices showed interference with skin pigmentation and follow-up studies are planned.

- **Gut Microbiome Proof-of-Concept Study.** The University of California, San Diego CTSA developed a transgene delivery system with native *Escherichia coli* chassis, which they evaluated in a proof-of-concept study in mice. With this potential model of bacterial therapeutics, they were able to demonstrate persistent physiological changes.

CTSA Impact: Policy, Clinical Guidance, and Workforce

Dr. Kurilla noted that the CTSAs have had numerous publications over the years of the program, which have informed various policy documents and also have informed recommendations and guidelines from the Centers for Disease Control and Prevention and WHO.

Dr. Kurilla highlighted workforce efforts in the CTSA Program.

- **CTSA 500 Stars Initiative.** The Medical College of Wisconsin sponsors the 500 Stars initiative, which has been ongoing since 2016. Stars 500 promotes community engagement and translational workforce development for the future. The vision is to enrich the Southeast Wisconsin translational research workforce by promoting diversity, inclusion, and access to underrepresented minority and underprivileged students from underserved communities. The program has been successful and trains 50 area high school and college students annually. A former Stars 500 participant, Harsimran Kalsi, now a medical student, has received several research awards, and recently started his own company.

Discussion

Matthias Kretzler, M.D., commended DCI and NCATS on the efforts of N3C, which is serving as a national, comprehensive information source. He suggested leveraging this infrastructure beyond COVID-19 to build a critical resource for the research community.

Participants discussed COVID-19, its impacts, and future considerations for translational research. Dr. Kretzler detailed his perspective on the wave of misinformation into the health care domain during COVID-19 and the nation's failure to protect its people, noting how NCATS' efforts are steps in the right direction to systemically educate the workforce about minority and rural community issues. He underscored developing a strategy, as a medical society, with the tools and resources NCATS has developed to address this misinformation pandemic. Dr. Kurilla agreed that any approach to this issue begins with a U.S. health care system that is divided regarding information and data across hospitals. He called attention to pre-COVID-19 efforts to address interoperability in hospital data, such as establishing the National Center for Data to Health as a technological approach. Dr. Rutter added that N3C has resolved major problems that existed prior to COVID-19, such as the lack of communication across health systems electronically (i.e., interoperability) and lack of understanding about what the information within the EHRs was conveying. N3C also is enabling the data ecosystem, increasing awareness of rare diseases in the EHRs, and helping to incorporate International Classification of Diseases (ICD) codes and Standardized Nomenclature of Medicine Clinical Terms (commonly called SNOMED CT). One potential outcome would be improving understanding of rare diseases.

Dr. Summar commented on the importance of applying the N3C tools of using EHRs for conducting natural history studies in rare diseases. Dr. Kurilla noted the N3C Clinical Domain Teams that are examining individual diseases and how they are represented in the EHRs.

In response to a question from Ms. Kennedy on the downstream findings of the RECOVER EHR project, Dr. Kurilla explained that an ICD code for long COVID-19 has been established as a result of the algorithm-based approach to examining the N3C database. Efforts are ongoing to develop validated, reliable, clinical phenotypes for various diseases.

Dr. Rutter highlighted another EHR initiative, the NCATS-led Impact of Rare Disease Patients and Healthcare Systems (commonly called IDeaS) study that evaluated the prevalence of 14 rare diseases in EHRs to better understand the financial burden of rare diseases.

Dr. Shireman commented on the need for common definitions for diseases, noting that some ICD codes are used differently across hospitals, can be unreliable, and also are not sufficient as a standalone for research. Dr. Rutter spoke on using clinical terminology more specifically for research, such as the Human Phenotype Ontology.

Council members agreed with Dr. Kurilla's suggestion of developing an electronic clinical phenotype that can be used to examine EHRs to identify patients with common diseases that would replace the ICD codes.

Dr. Summar commented on unpublished data from mapping Orphanet ICD-10 codes for rare diseases to patients that he could share with NCATS and noted discussions with Cerner Corporation to incorporate sequence data into the EHR.

Penny W. Burgoon, Ph.D., director, Office of Policy, Communications and Education (OPCE), NCATS, informed the Council of discussions with the NIH Office of Science and Policy about genomic data and that Office's request for comments on this topic from the research community.

Dr. Kretzler highlighted efforts in biobanks and safe and secure links with genomics databases and EHRs and explained that a federated approach is probably the best starting point.

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

14:48:54 From Kelly M McVearry to Everyone: Michael, Thank you for an excellent update. I agree with Matthias -- The infrastructure you have built and scaled is a national treasure. Thinking downstream, are there any barriers or risk you foresee that could place this infrastructure and its sustainability at risk?

VIII. CLEARANCE OF THREE (3) CONCEPTS

The Council received presentations on three new initiatives that NCATS is considering for funding. At the end of each presentation, the members discussed the concept 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 Drug Development Partnership Programs (ODDPP) Concept: Christine M. Colvis, Ph.D., Director, ODDPP, NCATS

Christine M. Colvis, Ph.D., provided a brief review of ODDPP activities and introduced the Office's new concept. Dr. Colvis noted that each ODDPP program corresponds to a different stage of the drug development pipeline. Currently two programs—the NIH HEAL Initiative and Illuminating the Druggable Genome (IDG)—are NIH-wide efforts managed by NCATS. Four programs are NCATS-initiated, including the new concept, which is focusing on cutting-edge technologies for translational science. NCATS will provide 2-year seed funding awards for investigator-initiated development of technologies that are high-risk, high-reward.

Awards Supporting Cutting-Edge Technology for Translational Science (ASCETTS) Concept: Tyler F. Beck, Ph.D., Scientific Program Officer, ODDPP, NCATS

Tyler F. Beck, Ph.D., presented a new concept on establishing ASCETTS, which is filling a gap in research funding opportunities for translational researchers. NCATS proposes this concept to allow early-stage development of new biomedical technologies, which traditionally have been challenging to fund. A distinct lack of funding for investigator-initiated innovation in translational sciences programs for basic science remains a priority. The framework for this concept is the successful Cutting-Edge Basic Research Awards (CEBRA) sponsored by the National Institute on Drug Abuse (NIDA). Though CEBRA has resulted in several exciting projects' being funded, they are not in the translational sciences. This funding gap in NIH, as well as National Science Foundation, grants has been recognized by other research groups, such as the University of North Carolina (UNC) Office of Technology Commercialization.

The objectives of this concept are to create a funding opportunity for innovative technology development and stimulate development of technologies that could be further developed under the Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) program or supported by other investors.

Regarding implementation, the aim is to support the development of new technologies leading to translational science advancements, thus bringing more treatments to more people more quickly. The anticipation is that successful ASCETTS should lead to STTR awards or direct engagement with technology and pharmaceutical industry leaders. The long-term outcome would be uptake of new technologies by translational researchers. Examples of potential projects include nanoparticle packaging for alternative drug delivery modalities; dermal implants for monitoring or delivery of drugs; and development of new algorithms to predict threatening drug interactions.

Discussion

Dr. Summar asked about coordinating with FDA to ensure that the funded technologies could be used in clinical trials and suggested a platform showcasing the new technologies developed in this program.

Dr. Beck noted that ODDPP has not had those discussions with FDA and agreed with the suggestion of showcasing the technologies over time.

Dr. Andrew Lo asked whether the technologies being solicited will focus on any specific genre, such as IND-enabling technologies. He elaborated on his experience with the Kidney Health Initiative to fund essential projects. Dr. Lo also emphasized funding technologies that will be transformative for patient

health and, additionally, providing economic incentives. He suggested partnering with entities in the private sector that are developing medical technologies and could provide non-diluted financing, such as the Wellcome Trust and its nonprofit, Wellcome Leap. Dr. Beck commented that the focus will be on technology development across a broad range of translational science–related projects, which can include such critical areas as kidney health.

Keith J. Mueller, Ph.D., strongly supports this concept and the seed-funding approach and noted that the examples of potential projects were appropriate, and that technology development will help with dissemination and adoption of NCATS programs. Dr. Mueller suggested including software development in the scope of the concept.

In response to questions from Dr. Ranganathan about reviewing the broad range of applications and addressing limited preliminary data in the NIH review process, Dr. Beck explained that the aim is to seek reviewers who could provide the level of review necessary. Amy C. Lossie, Ph.D., health scientist administrator, NIDA, described the process to review the CEBRA awards, which has been successful. The reviews are performed in-house; a single review session can encompass projects ranging from designing new pill packets, a nanobasket, and an encapsulated drug to single-cell technologies. The NIDA scientific review officer solicits scientists or researchers who have expertise in a specific set of variables. During the orientation process, the reviewers are clearly informed that this is not a routine R21 review, and that the expectation is that 50 percent of the projects will be successful. Dr. Lossie added that innovation is highlighted, and special instructions and questions are provided to the reviewers. Dr. Ramsey-Ewing assured the Council that NCATS, building on NIH's record, has the capability to assess vastly different research projects and can structure the review(s) accordingly, thus providing ample consideration for each proposal.

Dr. Harris inquired about the requirements for having a continuation or next-steps dissemination plan for the funded projects. Dr. Beck responded that the aim is to include the appropriate level of follow-up, with the expectation that these awards will lead to other funding opportunities (e.g., STTR).

Dr. Kretzler remarked on reviewing successful prize challenges across HHS and other organizations, being intelligent with the critical investments, and identifying unmet research areas with limited access to seed funding.

The ODDPP and Dr. Beck will explore coordinating with FDA on proposed and subsequently funded technologies to ensure a fit for clinical trials and will consider expanding the scope to include software development and unmet research areas.

Members unanimously approved the ASCETTS concept.

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

15:51:24 From Keith Mueller to Everyone: I strongly support seed funding, including this concept. I admit to having to think about "technology" differently in the realm of software development, but the description provided helped me understand the context of the term. So, I am supportive -- the examples in the presentation were exactly what I needed to see. I think software development should be included.

15:53:29 From Keith Mueller to Everyone: I had a similar question to Andrew's, as expressed in my previous chat comment.

15:56:03 From Matthias Kretzler to Everyone: https://www.nibib.nih.gov/news-events/newsroom/ucsf-researchers-win-kidneyx-prize

15:56:13 From Keith Mueller to Everyone: Technology that helps with dissemination and adoption (use of software and platforms are examples) would be responsive to the previous discussion

16:00:08 From Kelly M McVearry to Everyone: Tyler -- This is an important initiative. What is the range of seed funding awards you envision?

16:00:48 From Tyler Beck to Everyone: To clarify, Kelly, do you mean the total funds we would expect to give per award?

16:00:53 From Kelly M McVearry to Everyone: clarification: $ range

16:01:07 From Kelly M McVearry to Everyone: for an individual award.

16:01:39 From Tyler Beck to Everyone: We expect to see a total award across 2 years of up to around $275k or less

16:02:04 From Kelly M McVearry to Everyone: Great. Thank you.

Overview of the NCATS Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) Program: 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. SBIR and STTR are congressionally mandated programs, with 3.2 percent and 0.45 percent of the NIH budget set aside for SBIR and STTR, respectively. NCATS receives most of its applications through an Omnibus Solicitation. Other avenues include Grant Solicitations in Targeted Areas and 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 Corps (I-Corps) 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 1 year. Phase II, full research and research and development (R&D), provides funding for 2 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 3 years of support. Phase III, commercialization, establishes a public–private partnership using non-SBIR/STTR funds.

Ms. Portilla explained that the SBIR contract solicitations are issued once per year, have a statement of work, and accept proposals on targeted topics each October. NCATS conducts the peer review for these contract proposals. 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.

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

Danilo A. Tagle, Ph.D., M.S., provided a brief overview of the OSI and introduced the two new OSI-OSA SBIR concepts. The OSI mission is to address translational problems with innovative solutions through disruptive technologies and novel partnerships. Dr. Tagle noted that the new concepts being proposed leverage the A Specialized Platform for Innovative Research Exploration (ASPIRE) Tissue Chip Drug Screening programs.

SBIR Grant Topic: Miniaturization and Automation of Tissue Chip Systems (MATChS) Concept: Danilo A. Tagle, Ph.D., M.S., Director, OSI, NCATS

Dr. Tagle presented a new SBIR grant concept to establish MATChS, which is addressing a translational science gap. Although tissue chips have been successful, have been widely used, and are well-positioned as an alternative method for drug development, widespread adoption of this methodology by industry, regulatory agencies, and biomedical research has been impeded. This can be attributed to the complexity of the supported instrumentation necessary, and the specialized expertise needed to operate those systems. A partnership among NCATS, the National Aeronautics and Space Administration (NASA), and the Center for Advancement of Science in Space, the Tissue Chips in Space program has made key technological innovations toward the automation and miniaturization required for space flight. Since 2018, NCATS scientists have worked with NASA and Space Exploration Technologies Corp. (commonly called SpaceX) payload developers and space implementation partners (e.g., Techshot, Inc., Space Tango) to reduce tissue chip hardware from the size of a typical refrigerator to the size of a shoebox.

The objectives are twofold: Translate the lessons learned in re-engineering tissue chip platforms toward a smaller footprint and simplification of systems for ease of use and increase commercialization of the improved tissue chip platforms for widespread use in drug development and in biomedical research. Areas of emphasis include creating bench-top, portable, automated, self-contained systems that maintain 3-D tissue constructs and provide biologically relevant outputs of tissue health and function (e.g., fluid sampling, electrode incorporation, microscopy, biosensors). Emphasis also will be on producing demonstrable pathways to commercialization.

NCATS is proposing to use the cooperative agreement small business SBIR/STTR solicitation and will continue to use and implement tissue chips as a promising drug development tool across NIH and other government agencies. NCATS anticipates that more cost savings will be realized in drug development. In its current state, tissue chip technology is estimated to save up to 26 percent of drug development research and development cost in 2024. The success of MATChS will result in the increased availability of automated tissue chip platforms with a smaller and simpler footprint for use beyond drug development and across multiple applications and settings. In the clinical setting, the application will be for personalized patient-specific chips; on the battlefield, for assessment of countermeasures against developing threats; and in drug treatment and spaceflight, in evaluating long-term effects of stressors, including chronic disease.

Discussion

Dr. Tagle noted that Passley Hargrove-Grimes, Ph.D., program officer, OSI, and Marc Ferrer, Ph.D., director, 3-D Bio-Printing Laboratory, DPI, would be available to address questions.

Dr. Kretzler, who has been a private tissue chips investigator for some time, strongly endorsed this concept and commended NCATS for integrating kidney-on-a chip into the Tissue Chips in Space program. He was interested in additional funding opportunities to engage key partners and suggested connecting with Biomedical Advanced Research and Development Authority (BARDA) and the Assistant Secretary for Preparedness and Response (ASPR), which may have similar efforts. Dr. Tagle explained that NCATS has been in communication with ASPR and BARDA through the Division of Research, Innovation and Venture (commonly called DRIVe) and has been partnering on projects.

Dr. Ranganathan expressed his support for the concept, which is utilizing the right funding mechanism to achieve the appropriate endpoints. From a diagnostic perspective, he suggested expanding the scope of the next phase of the project to include solar-powered, economical technologies that can be deployed in remote areas (i.e., non-industrialized areas) with less dependence on electricity. Additionally, Dr. Ranganathan suggested connecting with Dan Wattendorf, M.D., director, Innovative Technology Solutions, Bill & Melinda Gates Foundation**,** and former project manager at DARPA for his input on potentially using tissue chips in remote settings.

Dr. Andrew Lo remarked on the advances with tissues chips technology primarily enabled by NCATS' sustained efforts and fully supports the improvements in this area. He suggested focusing on using tissue chips in IND-enabling studies and coordinating with FDA. Dr. Tagle cited several examples of NCATS and FDA interactions and related tissue chip initiatives and projects, including recently approved concept clearances on developing neuromuscular junction-on-a chip and establishing translational centers.

Dr. Ranganathan commented on the need for clear guidance from FDA that the data from tissue chip models are acceptable in lieu of animal data in the IND submissions.

Dr. Ferrer noted that the aim of this concept is to enable tissue chip technology in basic research and clinical research laboratories to better understand the biology and predictive applications of these models.

Council members suggested generating a review article that details the various tissue chip applications and provides data on the validity and positive and negative results of toxicity studies. Another option they noted was providing a dedicated NCATS webpage containing these data, not necessarily accessible to the public.

When asked about standardizations of tissue chips, Dr. Tagle called attention to a series of publications from partners in pharmaceutical companies and industry that provide information on standards on fit-for-purpose use in industry settings.

The OSI and Dr. Tagle will consider connecting with experts in diagnostics for remote areas and generating a review article or establishing a dedicated website to showcase the tissue chip applications.

Members unanimously approved the MATChS concept.

SBIR Contract Topic: Small Manufacturing Systems to Produce Research-Grade Pharmaceutical Intermediates Concept: Danilo A. Tagle, Ph.D., M.S., Director, OSI, NCATS

Dr. Tagle presented the SBIR contract topic Small Manufacturing Systems to Produce Research-Grade Pharmaceutical Intermediates. The development of preclinical drug candidates is time and cost intensive, averaging 10 to 15 years and costing $2.6 billion. Quality and access to pharmaceutical intermediates (i.e., raw chemical ingredients) by medicinal chemists are among the limiting factors. Most preclinical development involves the chemical synthesis of the candidates. NCATS recognizes that chemists' on-demand access to pharmaceutical intermediates will speed up the design-synthesize-test cycle.

Exploring chemical space in drug development requires two components. The first is access to bulk specialized pharmaceutical intermediates, made in-house or via a contract research organization. The second is focused efforts toward synthesis of drug candidates by medicinal chemists. The hypothesis is that leveraging automation in synthetic chemistry will facilitate access to bulk specialized pharmaceutical intermediates and treatments, with the ability for rapid scale-up.

NCATS proposes this concept to develop tools to increase synthetic chemistry throughput to reduce development time for preclinical candidates. The objectives are to (1) develop automated tools for use by synthetic chemists to improve access to pharmaceutical intermediates and (2) increase the rate of exploration of chemical space by accelerating chemical synthesis in drug discovery. The key areas of emphasis for this contract solicitation include utilization of current automation technology in synthetic chemistry adaptable to multiple chemical methodologies and the rapid scale-up of technology that is amenable to real-time data acquisition and monitoring.

Current activities related to this concept include the ASPIRE Program and NCATS–DARPA Collaboration for Flexible Manufacturing of Fine Chemical Reagents. This research will provide additional support to develop non–good manufacturing practice reagents for laboratory use. NCATS support will recognize

that higher throughput synthetic chemistry will improve the rate of development of preclinical candidates. Improving access to pharmaceutical intermediates will increase the rate of drug candidate development and biological data generation for exploring chemical space. The success of this project will be the creation of an automated synthetic chemistry device to prepare pharmaceutical intermediates quickly on-demand, such that a chemist can focus efforts toward preparing drug candidates for biological testing.

For this contract concept, reviewers are being asked to consider the scientific, technical, or programmatic significance of the goals of the proposed research and development 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. Tagle noted that OSI staff who are resident medicinal chemists, Sean R. Gardner, Ph.D., and Chariz P. Johnstone, Ph.D., would be available to address questions.

Theodore R. Holman, Ph.D., asked about the types of chemical reactions being considered. Dr. Gardner noted that chemical reactions will need to be considered in the context of the specific technology an automated system would use. He explained that flow chemistry frequently introduces new reactions to smaller scale systems, and the number of transformations that automated systems support is rapidly increasing. Dr. Gardner also confirmed that a menu of reactions that could be expanded over time could be included with any system.

When asked about a purification step, Dr. Gardner pointed out that in-line recrystallization for solid intermediates, for example, could reduce impurities. Several purification strategies are available that could be coupled to an automated system.

Alexander G. Godfrey, Ph.D., NCATS, remarked on the challenge of performing oxidation–reduction chemical reactions with automated systems. He suggested combining continuous processing capabilities with electrochemistry to help address this gap in chemical synthesis development.

Ms. Kennedy asked whether NCATS has within its mission workforce development and training that fits with the new technologies and instrumentation being solicited or proposed. Dr. Tagle responded that the goal is that this small business activity will result in commercialization and engagement with companies that will be developing the new instrumentation; these companies would provide the necessary services and training. He added that the contract solicitation can include language emphasizing that the expertise to operate the proposed system would not be at the Ph.D. level.

Ms. Kennedy underscored the importance of further development of automated synthetic chemistry devices for data collection and standardization as deliverables.

Dr. Ranganathan commented on implementing technologies addressed in this concept and how that might have a negative impact on the workforce performing this work. Dr. Godfrey emphasized developing a short explanatory message that speaks to the augmentation strategy of these automated systems, rather than job replacement. Ms. Portilla added that the expectations are that the vendor will clearly detail the commercial development plan in Phase II of the contract.

Dr. Andrew Lo noted how this concept will reduce the variability and increase the quality of academic translational work, especially with small-molecule drug candidates. He offered to make introductions to potential industry partners, including AI-based drug discovery companies, if NCATS decides to establish a consortium for this initiative.

Members unanimously approved the Small Manufacturing Systems to Produce Research-Grade Pharmaceutical Intermediates concept.

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

16:31:30 From Matthias Kretzler to Everyone: https://insight.jci.org/articles/view/95978

16:32:46 From Matthias Kretzler to Everyone: https://c-path.org/c-path-launches-acute-kidney-injury-project-with-support-from-fda/

16:38:47 From Andrew Lo to Everyone: Is there a good review article that covers all the studies demonstrating the clinical value of tissue chips? For example, something in the Annual Review of Medicine or Sciences Translational Medicine? Is this something that NCATS should write, given its pivotal role in this remarkable technology?

16:46:30 From Passley Hargrove to Everyone: https://www.iqmps.org/organotypic-manuscripts-1-0

16:46:44 From Passley Hargrove to Everyone: Organotypic manuscripts from pharmaceutical partners in IQ Consortium

16:54:40 From Andrew Lo to Everyone: This is another terrific project that will reduce the variability and increase the quality of academic translational work involving small-molecule drug candidates. I would imagine that there would be multiple industrial partners---including AI-based drug discover companies---that could be tapped to join a consortium to contribute resources and expertise to this pre-competitive initiative. Happy to make introductions if that would be of help. Congratulations on great progress and an inspirational day!

16:56:09 From Andrew Lo to Everyone: For the avoidance of doubt, I support this concept wholeheartedly!

17:00:10 From Chariz Johnstone to Everyone: Approach would be via step change based on the type of chemistries involved in a "boxed," reconfigurable system. Ideally change reagents within the "boxes" to make various molecules. Solution is a new chemistry coupled with engineering approach.

17:00:50 From Chariz Johnstone to Everyone: Idea not far from reality as can be seen with the Vapourtech R series using reactor blocks that can run multiple reactions in tandem

17:01:09 From Chariz Johnstone to Everyone: https://www.vapourtec.com/products/r-series-flow-chemistry-system-overview/

17:10:23 From Lili Portilla to Everyone: The vendor needs to lay out this strategy in their Commercial Development Plan that is part of the Phase 2 contractor.

IX. PUBLIC COMMENTS

Comments from the public were accepted until October 7, 2022, (15 days after the meeting) and will be appended to the minutes.

X. ADJOURNMENT OF THE OPEN MEETING

Dr. Rutter thanked the participants for their input. The next meeting is scheduled for January 26 and 27, 2023 and is planned as a virtual session. Dr. Rutter adjourned the meeting on September 22, 2022, at 5:14 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. Date
Chair, NCATS Advisory Council
Acting Director, National Center for Advancing Translational Sciences, NIH

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