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

24th Meeting of the
Advisory Council

Minutes of Virtual Meeting
May 14, 2020

The National Center for Advancing Translational Sciences (NCATS) Advisory Council held a meeting in open session on May 14, 2020, convening at 11:30 a.m. ET via WebEx. Christopher P. Austin, M.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 joint meeting, the NCATS Advisory Council met in closed session from 10:01 a.m. to 11:00 a.m. for the review and consideration of grant applications.

NCATS ADVISORY COUNCIL MEMBERS PRESENT

Chair

Christopher P. Austin, M.D., Director, NCATS

Executive Secretary

Anna L. Ramsey-Ewing, Ph.D., Director, Office of Grants Management and Scientific Review, NCATS

Council Members

Ronald J. Bartek, M.A.
Theodore Holman, Ph.D.
Andrew W. Lo, Ph.D.
Brad Margus, M.B.A.
G. Lynn Marks, M.D.
Todd B. Sherer, Ph.D.

Representative Members

None present

***Ex Officio* Members**

James B. Petro, Ph.D., M.S.S.I., Director, Human Systems Directorate, Office of the Undersecretary of Defense for Research and Engineering
Rachel Ramoni, D.M.D., Sc.D., Chief Research and Development Officer, Office of Research and Development, U.S. Department of Veterans Affairs (VA Research)

Others Present

Richard Dickinson, Ph.D., National Science Foundation
Kiran Reddy, M.D., Blackstone Life Sciences
Michael Rosenblatt, M.D., Flagship Pioneering
Elizabeth Stoner, M.D., MPM Capital
Frank F. Weichold, M.D., Ph.D., U.S. Food and Drug Administration (FDA)
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

Christopher P. Austin, M.D., adjourned the closed session of the NCATS Advisory Council meeting at 11:00 a.m. ET.

III. CALL TO ORDER, OPEN SESSION

Dr. Austin called the meeting to order and welcomed members and guests to the 24th meeting of the NCATS Advisory Council. He reminded attendees that the open session was being webcast. Dr. Austin introduced the members of the Council and previewed the meeting agenda. He noted that by statute, 13 members are required to convene a Cures Acceleration Network (CAN) Review Board meeting compared to a quorum consisting of a majority of the members necessary for a meeting of the Advisory Council. Dr. Austin introduced the CAN Review Board members who are officially attending as guests at today's meeting.

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

Anna L. Ramsey-Ewing, Ph.D., confirmed the schedule for the meetings of the NCATS Advisory Council and CAN Review Board for 2020 and 2021:

- September 17, 2020
- December 11, 2020 (virtual meeting; CAN Review Board only)
- January 14, 2021
- May 20, 2021
- September 23, 2021
- December 10, 2021 (virtual meeting; CAN Review Board only)

V. APPROVAL OF MINUTES: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council and CAN Review Board

Members unanimously approved the minutes from the January 2020 joint meeting.

VI. STAFFING ANNOUNCEMENTS: Christopher P. Austin, M.D., Director, NCATS, Chairperson, NCATS Advisory Council; Michael G. Kurilla, M.D., Ph.D., Director, Division of Clinical Innovation, NCATS,

Dr. Austin introduced NCATS' first chief medical officer, Samuel A. Bozzette, M.D., Ph.D., Office of the Director. He noted that prior to coming to NCATS, Dr. Bozzette was chief scientist, Services Division, Premier Inc., and had spent his academic career primarily in the U. S. Department of Veterans Affairs (VA), San Francisco VA Health Care System. Dr. Bozzette expressed his appreciation to NCATS for the opportunity to serve the National Institutes of Health (NIH) and noted his training and academic career

in infectious diseases and health policy analysis. His industry-related experience spans 10 years and includes implementation research and retrospective studies using large-scale health care databases. Although his current activities are primarily supporting the COVID-19 response, Dr. Bozzette looks forward to increasing the availability of clinical and clinical policy expertise within NCATS when conditions improve worldwide.

Michael G. Kurilla, M.D., Ph.D., announced that Mary Purucker, M.D., Ph.D., former director, Clinical and Translational Science Award (CTSA) Program, Division of Clinical Innovation (DCI), retired in April 2020. He expressed appreciation to Dr. Purucker for her service to NCATS in helping to shape the DCI and the CTSA Program. Dr. Kurilla next announced the appointment of Erica Rosemond, Ph.D., who has served as the deputy director of the Program since 2015, as acting director.

Dr. Kurilla welcomed two new program directors to the DCI: Mercedes Rubio, Ph.D., who comes to NCATS from the National Institute of General Medical Sciences where she served as Research Training Officer and Science Administrator and also was former program chief at the National Institute of Mental Health; and Gallya Gannot, Ph.D., D.M.D., former program director at the National Cancer Institute and National Institute for Dental and Craniofacial Research.

VII. DIRECTOR'S UPDATE: Christopher P. Austin, M.D., Director, NCATS, Chairperson, NCATS Advisory Council

Dr. Austin began by welcoming new Advisory Council and CAN Review Board *ex officio* member representing the Department of Defense (DoD), James B. Petro, Ph.D., M.S.S.I. Dr. Austin reported on the NCATS COVID-19 response across the NCATS offices, divisions and programs; regular NCATS business; and the look ahead to 2021.

NCATS and COVID-19

Dr. Austin recalled the events leading up to the identification of SARS-CoV-2 (the novel coronavirus that causes COVID-19), declaration of a U.S. public health emergency by the Department of Health and Human Services (HHS) and declaration of a pandemic by the World Health Organization (WHO). He remarked that the SARS-CoV-2 gene was sequenced rapidly, and the results published quickly, both of which enabled the translational aspects to be addressed. Dr. Austin informed the Council that on March 13, 2020, the NIH suspended nonessential laboratory operations, except for mission-critical activities, and implemented mandatory teleworking for all staff.

Regarding guidance during this phase of operations, the NIH and NCATS provide up-to-date information and communications to staff through their intranet pages. NCATS conducts (1) weekly virtual town hall meetings for staff, contractors and trainees and (2) daily COVID-19 leadership meetings for staff engaged in those activities. In addition, a new NCATS COVID-19 webpage—A Translational Approach to Addressing COVID-19—was launched on May 14, 2020. This new webpage features NCATS-supported research, funding information, grantee and partner news, and NIH and the Centers for Disease Control and Prevention (CDC) resources. Dr. Austin expressed appreciation to Emily Carlson Marti, M.A., director, Communications Branch, Office of Policy, Communications and Education, NCATS, and Communications Branch staff for their efforts in designing and launching the COVID-19 webpage and related pages.

Dr. Austin explained that NCATS is rapidly advancing research to address this public health crisis and has issued several notices of special interest (NOSI) concerning regular and emergency COVID-19 funding opportunities. He next detailed the NCATS-wide COVID-19 efforts.

- **Clinical and Translational Science Award Program.** Dr. Austin informed the Council that NCATS in its CTSA Program—a national network of academic, health and medical centers addressing translational issues—initiated a consortium discussion forum on March 11, 2020. This forum allows the 60 or more organizations to share information about COVID-19 activities and has resulted in establishing best practices across the consortium. NCATS and the CTSA Program Coordinating Centers developed a publicly accessible clinical research information platform to serve as a central location for investigational research studies and the CTSA Hubs are involved in numerous clinical activities. In addition, the CTSA Trial Innovation Network (TIN) is supporting many COVID-19 clinical trials. The University of Utah CTSA is addressing questions on shortening the time of SARS-CoV-2 shedding after hydroxychloroquine treatments, and the Johns Hopkins University CTSA and others are evaluating convalescent plasma for pre-and post-exposure prophylaxis. Dr. Austin acknowledged the 2020–2022 CTSA Program Steering Committee members.

- **National COVID Cohort Collaborative.** Dr. Austin introduced a 3-year shared translational vision of NCATS—NCATS National COVID Cohort Collaborative (N3C)—which has been accelerated for understanding COVID-19. The N3C aims to deliver real-time, rapid collection of clinical, laboratory and diagnostic data. The critical design elements concerning data collection are speed, fast and easy access, and scalability to support clinical trials; all are essential when responding to a pandemic. The N3C is leveraging the DCI's efforts in helping to establish a common data model, which involves the CTSA Hubs, common data standards, data harmonization and the NCATS cloud. The aim is to replace the existing federated data models and formats that allow asking only specific questions with a centralized data model capable of investigating broad iterative questions. The CTSA National Center for Data to Health (CD2H) drives the N3C in collaboration with the CTSA Hubs, NCATS-supported informatics teams, NCATS multidisciplinary leadership and program teams, and collaborators and data partners. The goal is to have the N3C platform functional by June 2020.

  :: Emily Marti posted in Chat to all panelists:: Want to know more about the N3C? Just minutes ago, we posted information about the effort on the NCATS website: https://ncats.nih.gov/n3c

- **Tissue Chips (or Microphysiological Systems) Program.** Because SARS-CoV-2 is a new infectious agent and existing animal models that recapitulate the disease in humans are limited, Dr. Austin emphasized that the Tissue Chips (or Microphysiological Systems [MPS]) Program was utilized early in NCATS' response to COVID-19. NCATS rapidly issued NOSIs to develop tissue chip models for COVID-19.

- **Division of Preclinical Innovation.** Dr. Austin reported that 25 percent of the NCATS staff, particularly the Division of Preclinical Innovation (DPI), are supporting COVID-19 efforts. Ongoing are assay development, high-throughput screening (HTS) and drug development, and generation of three-dimensional (3-D) tissue models. DPI staff also are engaged in drug repurposing and supporting FDA investigational new drug-enabling drug development for the COVID-19 therapeutic targets (viral and human). More than 30 NCATS SARS-CoV-2 assays are at various stages of development and many drug-screening collaborations have been established. All data and information soon will be publicly available via the NCATS open science data portal.

- **Office of Rare Diseases Research.** Dr. Austin explained that the Office of Rare Diseases Research (ORDR) recognized early that the COVID-19 pandemic is impacting people with rare diseases.

People with rare diseases are a medically vulnerable population. Most rare diseases are serious, chronic conditions. On May 1, 2020, the ORDR—through the Rare Diseases Clinical Research Network (RDCRN)—launched a voluntary, online survey to evaluate the impact of COVID-19 on rare disease patients and their families. The ORDR anticipates that the survey will reveal the primary COVID-19 related concerns of people who live with a rare disease and their caregivers, as well as provide an estimate of the number of rare disease patients with COVID-19. The RDCRN anticipates enrolling 5,000 or more people in the survey and expects to learn more about the characteristics of COVID-19 in rare disease patients, one of the most vulnerable subgroups of patients, and potential interactions of patient treatments and COVID-19.

Looking Ahead to the Remainder of FY 2020 and FY 2021

Dr. Austin reminded the Council that the President's fiscal year (FY) 2021 Budget proposal was released on February 10, 2020 and includes a 7.2 percent decrease to the NIH compared with the FY 2020 enacted budget and a 5.4 percent decrease for NCATS. The House Congressional hearing occurred on March 4, 2020, and the Senate is postponed until operations return to regular appropriations work, likely in the summer of 2020. Dr. Austin noted that Congress approved three aid packages to address COVID-19 concerning the American economy, biomedical research and hospitals: Phase 1—Coronavirus Preparedness and Response Supplemental Appropriations Act—enacted 3 March 2020; Phase 2—Families First Coronavirus Response Act—enacted 18 March 2020; and Phase 3—Coronavirus Aid, Relief and Economic Security Act—signed into law 27 March 2020. The Phase 3 coronavirus aid bill includes funding for the NIH, of which $36 million was appropriated to NCATS.

Non-COVID-19 Activities

Dr. Austin was glad to report that the 2020 Rare Disease Day (RDD) at the NIH hosted by NCATS on February 28, 2020, was again successful and that the enthusiasm and the record-breaking attendance of prior RDD events continued. The new NCATS Rare Diseases Are Not Rare! 2020 Challenge opened on February 29, 2020, and will close on June 15, 2020.

VIII. SPECIAL DISCUSSION OF COVID-19-RELATED ISSUES: Joni Rutter, Ph.D., Deputy Director, NCATS

Joni Rutter, Ph.D., moderated the discussion of challenges to restarting research unrelated to COVID-19. She emphasized that the current pace at which NCATS researchers are working to address the pandemic is unsustainable and noted that many processes have been streamlined amid the pandemic. The question remains as to whether NCATS may be able to implement these new practices more broadly in its activities and programs after COVID-19.

Dr. Rutter explained that NCATS is seeking input from the Council (and CAN Review Board members attending as guests) on issues related to (1) translational science, both preclinical and clinical; (2) workforce, training and career development; and (3) administrative and operational hurdles. NCATS' goal is to continue these types of discussions beyond today's meeting. Dr. Rutter invited participants who had been assigned to issues to provide a brief introduction, including their affiliation, and to describe the key challenges and potential solutions, as well as key areas where NCATS could facilitate a solution to some of these issues.

Translational Science

Theodore Holman, Ph.D., professor of chemistry, Department of Chemistry and Biochemistry, University of California, Santa Cruz, is tasked with developing a plan for opening the basic research laboratories. Dr. Holman explained that his laboratory staff have discussed issues related to how to test people who enter the laboratory for COVID-19, how to determine how many people can occupy the laboratory safely, whether to implement a 24/7 work model to support distancing, and how COVID-19 might rebound later in the pandemic.

G. Lynn Marks, M.D., senior advisor, Tunnell Government Services, pointed out that this pandemic will result in the loss of patent exclusivity, and many companies will need to reexamine their budgets to adjust for lost revenue or time. Some personnel may be lost through death, and talent also is lost when researchers are on hold. Data also are on hold; future approaches to data collection might include greater focus on critical information, clinical trials and adding more exploratory components to research. Dr. Marks also noted disappointment in the number of clinical trials conducted without a control, and encouraged greater scientific rigor.

Dr. Rutter highlighted the need to ensure that current studies of COVID-19 can continue into longer term study of the disease and address the issues noted by Council members. She also noted the need to ensure adequate personal protective equipment for researchers.

Brad Margus, M.B.A., chief executive officer, Cerevance, Inc., commented on the need to progress research on other diseases, as well as review workflow to ensure that researchers can distance sufficiently and continue work. He suggested gathering best practices from across all biotechnology companies and wondered about ways to harness the rapid pace model observed in COVID-19 research activities to advance research progress into other diseases.

Michael Rosenblatt, M.D., chief medical officer, Flagship Pioneering, cautioned that less rigorous clinical trials, as mentioned by Dr. Marks, not only could saturate the field with difficult-to-use information but also could take patients needed for other clinical trials. Clinical trials that have slowed or been interrupted or terminated lead to missing data, and patients are reluctant to visit clinics for trial follow-up during the pandemic. Differences in global response also affect global clinical trials. Additionally, some patients in trials may contract COVID-19, and medications prescribed to these patients could complicate trial results. Dr. Rosenblatt suggested that ongoing trials include a pre-COVID and a post-COVID mirror with a clear demarcation. His company is reviewing its clinical trial protocols to determine if the frequency of visits can be decreased or if any nonessential components can be eliminated to reduce the burden on participants, as well as adding telemedicine and remote visits—although he noted that such modifications are a change to protocols in the middle of the trials. He noted that many trials have shifted from academic to community centers to accommodate the number of COVID-19 patients treated in academic centers, which will require careful record-keeping. Dr. Rosenblatt also suggested that an opportunity exists to demonstrate safety and efficacy mathematically by identifying the incidence of adverse experiences, which could be used to request conditional approval.

Workforce, Training and Career Development

Andrew Lo, Ph.D., Charles E. and Susan T. Harris professor of finance, Massachusetts Institute of Technology, presented his perspective as an economist outside the biomedical community, explaining that the economy will not recover until progress is made in public health. The shutdown of most laboratories and research will affect career development and workforce considerations, but the pandemic has demonstrated the value of biomedical research. The shift to online education has revealed high levels of interest in the intersection of business and biotechnology, and Dr. Lo suggested

that NCATS add content to online educational platforms and increase education on effective trial construction. NCATS also could convene a conference with bioethicists to discuss human challenge trials for COVID-19.

:: Christopher Austin posted in Chat to all panelists:: Andrew: could you send us the link to the BMJ article you mentioned?

:: Andrew Lo posted in Chat to all participants:: Sure, here's the link: https://www.bmj.com/content/bmj/369/bmj.m1847.full.pdf

Dr. Petro, director, Human Systems Directorate, Office of the Under Secretary of Defense for Research and Engineering, DoD, commented on the need to ensure that strict animal husbandry practices are followed to prevent unintentional infection in COVID-19 studies.

Kiran Reddy, M.D., managing director, Blackstone Life Sciences, noted that many biotechnology companies have experienced delays in functions beyond clinical trials, such as drug manufacturing and shipment and preclinical work. Many biotechnology companies are financed with objectives that require hitting milestones, which may be difficult to adjust in the pandemic. Dr. Reddy also noted that innovations in trial design prompted by COVID-19 could be supported by NCATS for long-term change.

Administrative and Operational Hurdles

Ronald Bartek, M.A., co-founder and founding president, Friedreich's Ataxia Research Alliance, agreed with previous comments and planned to expand on his ideas in a future discussion.

Todd B. Sherer, Ph.D., chief executive officer, Michael J. Fox Foundation for Parkinson's Research, suggested reviewing how to better direct the investment in the CTSAs and pivot them toward COVID-19 studies, as well as field systematizing standard assays or questionnaires. NCATS also could provide policies on science start-up plans for laboratories, as well as consider cost extensions for restarting research. Nonprofit organizations and foundations supporting rare disease research also likely are significantly affected by the economic impact of the pandemic, and NCATS could consider unique partnerships to support these patient networks.

Elizabeth Stoner, M.D., executive partner, MPM Capital, pointed out that venture firms and investors have supported companies in continuing research, but many researchers, particularly within academic institutions, have been diverted to COVID-19 research. CTSA institutions could take a lead role in smoothing the administrative tasks necessary to initiate new studies. Dr. Stoner added her support for previous comments encouraging NCATS to play a role in making clinical trials more robust.

Dr. Rutter organized the key points of the discussion into five thematic categories: (1) safety of researchers, (2) integrity of science, (3) non-COVID work, (4) clinical trial considerations, and (5) working toward economic recovery. She thanked the participants for their comments, noting that NCATS will continue the discussion at a future date.

IX. PROGRAM UPDATE: DIVISION OF PRECLINICAL INNOVATION: Matthew D. Hall, Ph.D., Acting Chief, Early Translation Branch, DPI, NCATS

Matthew D. Hall, Ph.D., presented an update on DPI activities. He noted that some of DPI's efforts are focused on understanding the prevalence of COVID-19. NCATS, in collaboration with other NIH Institutes and Centers, is supporting the NIH SARS-COV-2 Pandemic Serosurvey and Blood Sampling clinical trial

with assay development and also in automating an enzyme-linked immunosorbent assay (ELISA). Dr. Hall provided a historical overview of the NIH Chemical Genomics Center (NCGC), which was officially renamed the Early Translation Branch (ETB) as a part of NCATS' reorganization in 2019. ETB's mission is to kick-start the discovery pathway toward new cures by creating the tools needed to de-risk targets. Dr. Hall stated that collaboration across disciplines, dissemination of tools and technologies, and training a new generation of translational scientists represent crucial components of ETB.

ETB's mission is focused on the creation of probe molecules, which can be used to demonstrate the proof of concept of therapeutic development and as starting points for drug development programs. Dr. Hall spoke on the value of ETB's scientists and research infrastructure in these efforts. Experts from various disciplines (e.g., chemistry, biology, informatics) cross academic boundaries to work collectively as translational scientists. Dr. Hall also highlighted opportunities for intramural and extramural partnerships.

Biological assays represent the first step in probe development; assays are used to identify potential drug targets and to uncover promising therapies against those targets. The assays are simplified to enable high-throughput screening and the development of screening libraries for potential probes. Additionally, the Assay Guidance Manual represents a publicly available resource. Dr. Hall also highlighted collaborations, publications, and other research accomplishments across ETB. He emphasized the importance of data sharing, and he highlighted newly created probe molecules. With the creation of a new website, investigators will have the option to request samples of the molecules for testing.

Dr. Hall concluded by speaking about ETB's efforts in response to COVID-19. Scientists are creating assays and screening molecular probes against SARS-CoV-2. In addition, the team has created a portal to share drug repurposing data with the scientific community. He emphasized that ETB's existing platforms and translational science principles have enabled a rapid response to COVID-19.

Discussion

Rachel Ramoni, D.M.D., Sc.D., asked about prioritization for screening. Dr. Hall explained that each team focuses on specific areas of interest. ETB provides tools and guidance to researchers and is interested in pursuing collaborations to explore or create new biological tools. He added that therapeutic opportunities, particularly those relevant to rare diseases research, represent areas of interest.

Mr. Margus asked whether improvements to predictions of biological processes will negate the need for screening. Dr. Hall stated that ETB is leveraging its own platforms to integrate multiple approaches. He also reiterated the importance of data sharing and dissemination.

:: Brad Margus posted in Chat to all participants:: Too bad we don't understand biology better... If we did we wouldn't have to try hundreds of thousands of compounds at multiple doses... Have all of the academics and companies who have claimed to be able to predict chemical and biological interactions been disappointing?

:: Brad Margus posted in Chat to all participants:: And I LOVE that you're making new tool compounds available for the community!!! I've often been frustrated by scientists insisting on taking a lot of time to test new targets with KO animals etc that may not even answer the question of the target's validity. Getting a tool compound in-hand right away will be much faster and more useful! THANKS FOR DOING THIS.

Dr. Holman asked about the challenge of chemical diversity in screening libraries. Dr. Hall noted that the A Specialized Platform for Innovative Research Exploration (ASPIRE) Program is pursuing efforts to build an automated chemistry platform with predictive approaches to guide the synthesis of molecules.

X. CLEARANCE OF CONCEPTS

The Council received presentations on six new projects that NCATS is considering for funding. At the end of each presentation, the members discussed the proposal and voted on whether to approve NCATS' moving forward with the initiative. Dr. Anna L. Ramsey-Ewing noted a change in the order in which the concepts will be presented: the second concept will be Machine Intelligence in Health Care and the fourth concept, Extended Longevity Tissue Chips for Modeling Chronic Exposures.

A Specialized Platform for Innovative Research Exploration—ASPIRE-ing Beyond HEAL: Danilo A. Tagle, Ph.D., M.S., Associate Director for Special Initiatives, NCATS; Samuel G. Michael, Director, Automation and Compound Management, DPI, NCATS

Danilo A. Tagle, Ph.D., M.S., presented a new concept to expand the ASPIRE Program. He reminded the Council that the ASPIRE initiative originally was proposed in September 2017 to address key translational challenges: (1) the uninterrogated vast chemical space (10^{63}) of potential pharmacologically active molecules, (2) the undrugged biological space (5×10^5), and (3) an outdated reaction toolkit for accessing the relevant chemical space. To address these issues, NCATS convened the "Workshop on Automated Chemical Synthesis" on October 19–20, 2017, to identify the associated research opportunities, challenges and roadblocks. Subsequently, NCATS officially launched ASPIRE in 2018, as a pilot program funded by the Helping to End Addiction Long-term℠ Initiative, or NIH HEAL Initiative℠ with an extramural component through prize competitions and challenges, and an intramural component to build an automated chemistry infrastructure.

For this new concept that goes beyond the initial HEAL investment, Dr. Tagle noted the goals will be to establish a collaborative structure involving multidisciplinary expert teams from NCATS intramural and extramural scientists that takes advantage of the validated open-source infrastructure as well as tools and technologies within NCATS Division of Preclinical Innovation toward general translational challenges in synthetic chemistry.

Samuel Michael described the intramural components of the ASPIRE modular platform, which includes automation, informatics, consumables, chemistry, analytical, and biology modules, as well as technology development. The initial platform will be a 16-module design with integrated automation and technology components.

Dr. Tagle highlighted that the outcome will be a disseminatable platform for automated chemical synthesis, biological testing, and machine learning–driven optimization. NCATS anticipates that this platform will broadly enable the identification and synthesis of novel biologically active chemical structures with drug-like characteristics. The potential exists for a much-needed expansion of the chemical space toward new and improved therapeutics, which would catalyze an innovative and collaborative ecosystem.

Discussion

Drs. Holman and Sherer expressed their support for the concept. Dr. Holman asked whether computational docking studies—which would complement the proposed efforts to expand the available chemical space and potentially would increase chemical diversity—were planned. Mr. Michael explained that a virtual experimental modeling strategy is being considered. Additionally, collaborative efforts would be pursued. These strategies would serve to expand the chemical space if methods are validated.

In response to a question on prioritization of less-sought-after targets, Mr. Michael called attention to the NIH Common Fund Illuminating the Druggable Genome program and Pharos, a user interface that contains data on targets not being investigated in the pharmaceutical industry.

:: Sam Michael post in Chat to all participants:: https://pharos.nih.gov/

Members unanimously approved the ASPIRE-ing Beyond HEAL concept.

Artificial Intelligence in Health Care: Karlie R. Sharma, Ph.D., Program Officer, Drug Development Partnership Program, Office of the Director, NCATS; Christine M. Cutillo, M.M.C.i., Special Assistant to the Director, Office of the Director, NCATS

Karlie R. Sharma, Ph.D., presented a concept on advancing artificial intelligence (AI) in health care. The concept was developed in collaboration with Christine M. Cutillo, M.M.C.i. and will leverage NCATS' existing AI and informatics efforts. The importance of using AI in health care is well emphasized in the clinical community but translating such innovative tools for clinical applications remains a challenge. In recent weeks, many laboratories and companies have attempted to use AI for COVID 19 treatments. These, in addition to other recent examples, illustrate the urgent need for new paradigms for the development and application of these innovative AI-based tools before and as they are deployed into clinical care settings, because misdiagnoses from AI systems can result in fatal consequences.

Dr. Sharma highlighted several unique challenges that have impeded the progress of AI in health care; these challenges include barriers to data sharing, ineffective implementation into clinical care workflows, and transparency in ethical issues. To address these issues, NCATS sponsored a workshop focusing on machine intelligence in health care in July 2019. Three key topics emerged from the discussion that rose to the top as timely and aligning with the NCATS purview: testing algorithms in the real world prior to their implementation, prioritizing reproducibility and robustness of AI systems, and improving communication across groups developing these systems and the community that will use them. This concept aims to (1) develop a pipeline for testing algorithms prior to implementation in the clinic, and (2) in the long-term, improve trust in and uptake of AI systems in the health care setting. In a proof-of-concept approach, NCATS will develop and test the pipeline with use case algorithms and demonstration projects (Stage 1), then use the tested pipeline to assess newly developed algorithms focused on urgent clinical needs in a variety of disease areas (Stage 2).

The outcomes of the research will be (1) a fully formed and vetted pipeline equipped with standard operating procedures, creating a framework for comprehensive algorithm assessment in real-world environments; (2) distributable algorithms that can be implemented across health systems worldwide; and (3) dissemination of results and resources to the broader research community to facilitate the creation of other AI pipelines by the community modeled after the initiative-developed pipeline. NCATS anticipates that the incorporation of these algorithms into clinical practice will create new sources of reliable information for clinicians to better diagnose and treat patients.

Discussion

Mr. Margus remarked that the concept of AI in health care systems, in this proof-of-concept approach, fits the NCATS model of accelerating and applying technologies.

Dr. Sherer thinks this is a good area for NCATS and suggested determining whether the approach works for evaluating the metrics of success early in the algorithm development process. He also suggested clarifying which questions the algorithm is being developed against, and he encouraged collaboration between the clinicians and the mathematicians in formulating those questions.

Because an AI algorithm tends to lose its predictive power over time, Dr. Ramoni noted the challenge in applying a single algorithm across multiple systems without the context of a hyperlocal AI and performance monitoring. She suggested a concept update as the project progresses.

:: Christopher Austin posted in Chat to all panelists:: To Rachel's important point: what Anna said is correct that when a concept is cleared it is done with the understanding that the suggestions of the Council members are incorporated. I don't think there has ever been a concept approved with no suggestions for improvement that have been incorporated, and that is why I am so insistent on having adequate time for discussion so we can get those suggestions. The concepts are invariably improved by Council suggestions. In this specific case, the suggestions each of you made (e.g., explainability, stability, bias) are most definitely part of what we have considered internally (and were raised at the workshop we had last summer) and we will particularly emphasize them now that we have your input that we should do so.

Action Item: Dr. Sharma, Ms. Cutillo and the Drug Development Partnership Program will present a concept update at a future Council and/or Board meeting.

Dr. Lo called attention to a recent focus in the AI community—interpretability—the development of methods to interpret machine learning forecasts, which is related closely to the issue of trust. He noted the importance of AI applications in medicine, in which forecasts can have life-and-death consequences. Dr. Lo suggested that NCATS launch a program or host a conference on interpretability of health care in AI.

Action Item: The Drug Development Partnership Program leadership will consider launching a program or hosting a conference on interpretability in health care AI.

Members unanimously approved the machine intelligence in health care concept, with additional considerations to provide an update after approval.

Drug Screening with Biofabricated 3-D Disease Tissue Models: Dobrila D. Rudnicki, Ph.D., Program Director, Office of Special Initiatives, NCATS

Dobrila D. Rudnicki, Ph.D., presented a concept on drug screening with biofabricated 3-D disease tissue models. This concept expands existing NCATS initiatives, including the Pilot Program for Collaborative Drug Discovery Research using Bioprinted Skin Tissue and the Drug Screening with Biofabricated 3-D Skin Disease Tissue Models. The goals and primary objectives are threefold: (1) to synergize extramural and NCATS intramural expertise and resources, (2) to develop physiologically relevant and validated 3-D models that can be incorporated into novel drug screening platforms, and (3) to advance discovery and development of more effective and safe treatments for a number of diseases.

Dr. Rudnicki explained that the program will support intramural-extramural collaborations for the development of these models and will provide important resources and protocols enabling the extramural community to continue development in this area. The program will help shift the paradigm from 2-D to 3-D models for drug screening and enhance the strength and value of intramural-extramural collaborations to advance translation.

Discussion

Dr. Lo expressed his support for the concept and is looking forward to the progress. Dr. Marks commented that the intramural and extramural collaborations will be key to NCATS' shifting from 2-D cell culture to 3-D tissue model approaches. Developing safe and effective medicines using tissue models also reduces the reliance on animal models to recapitulate human disease.

Dr. Stoner asked about the potential of existing NCATS models to mature to commercialization. Dr. Rudnicki explained that the advancement of any models would depend on the success of the program. The Office of Special Initiatives is open to the commercialization of NCATS models. Mr. Michael pointed out that commercial entities often express interest in models as they become mature. Dr. Rutter added that the CAN Review Board and NCATS are interested in exploring advancing mature projects to commercialization and has established a CAN Review Board Working Group to address this topic.

Members unanimously approved the biofabricated 3-D disease tissue models concept.

Extended-Longevity Tissue Chips for Modeling Chronic Exposures: Lucie A. Low, Ph.D., Program Director, Office of Special Initiatives, NCATS

Lucie A. Low, Ph.D., presented a concept on extended-longevity tissue chips for modeling chronic exposures. Dr. Low noted that NCATS has been the leader in developing and advancing the tissue chip/MPS technology and remains key leaders in the field to guide and facilitate ongoing efforts across the NIH, FDA, industry and other government agencies. As tissue chip technology is becoming more mainstream and industrialized, other funding agencies now are supporting their own tissue chip programs. This initiative would be a joint initiative between two divisions within the National Aeronautics and Space Administration (NASA), the Biomedical Advanced Research and Development Authority and the Translational Research Institute for Space Health. In addition, six NIH Institutes and Centers have expressed interest in joining. The partner agencies are in the process of obligating funds for this initiative. NCATS and NASA recently signed a memorandum of understanding to express interest in this joint initiative.

Tissue chips generally are designed to last up to 28 days in culture per FDA requirements for drug testing. However, participants attending two NCATS and NASA co-sponsored workshops on the "State of the Science" for tissue chips identified the need to extend the tissue chip lifespan beyond 6 months (i.e., extended longevity tissue chips). This enables broader use of tissue chip technology for a number of applications. Therefore, the goals of this concept are to extend the lifespan of tissue chips beyond 6 months and to model their exposure to perturbations (e.g., drugs or compounds, radiation and environmental hazards) during the 6-month period.

The outcome will be reproducible and viable platform operation for long-term tissue chip function with proficiency for continuous monitoring, probing and sampling of the biological tissues. The research will enable *in vitro* assessment of long-term safety and toxicity studies and provide platforms that can be used for testing drug candidates, drug combinations and drug-drug interactions over extended time

periods (e.g., platforms that can give accurate readouts at 18 or 180 days). NCATS hopes the initiative will spur development of robust automated platforms that are amenable to remote operation and sensing of tissue function. A key aim of Cures Acceleration Network (CAN) programs is the "handoff" of mature technologies to new users. In line with this aim, and unique to this tissue chip initiative, is that external partners will provide 75% of funding, and NCATS investments will be minimal.

Discussion

Mr. Bartek remarked that this concept could help advance mature NCATS programs to real-world applications. He noted that a significant amount of the resources would come from stakeholders outside the NIH. He pointed out that an extended-longevity tissue chip would have broad applications to chronic exposures, potentially addressing challenges amid a pandemic like COVID-19 (e.g., laboratory closings resulting in loss of cultured cells and animals).

Dr. Marks commented that this concept is taking a logical next step in evaluating extended-longevity tissue chips in a robust experimental design.

Dr. Petro called attention to similar efforts in the DoD and volunteered to make introductions between the DoD and NCATS program staff who are managing these initiatives.

Mr. Margus wondered whether any breakthrough tissue and cell culture techniques could benefit other areas in science. Dr. Low is confident that technological breakthroughs from this program could be useful in other scientific areas (e.g., in other cell culture projects).

Members unanimously approved the extended-longevity tissue chips for modeling chronic exposures concept.

Introduction of Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) Topics: Lili Portilla, M.P.A., Director, SBIR/STTR Program, NCATS

Ms. Portilla introduced two new SBIR/STTR contract concepts. She explained the differences between SBIR grants and contract mechanisms. Contract topics are defined by NCATS, whereas grant topics are defined by the investigator and are within NCATS' mission. Contract topics are reviewed internally, but grants are reviewed by the Center for Scientific Review. Contracts solicitations occur annually, but grants have three submission deadlines each year.

Multisensory Virtual/Augmented Reality (VR/AR) Systems and Rehabilitation for Rare Disease Patients: Samuel G. Michael, Chief, Information Technology Resources Branch, DPI, NCATS

Mr. Michael presented the SBIR contract concept on the topic multisensory VR/AR and rehabilitation for patients with rare diseases. The senses (e.g., audio, visual and hand haptics) are limited in current VR/AR systems but could benefit from taking advantage of other senses that include full-body haptics (e.g., TESLASUIT), smell and taste. Research has shown that VR/AR immersive experience can reduce pain and discomfort in rehabilitation and, potentially, in clinical settings. In addition, the AI and machine learning algorithms can generate individualized immersive experiences, which must be verified for efficacy, user needs, and preferences. The challenge is that individuals respond differently to these environments and systems must be tailored.

This contract concept will support the development of multisensory VR/AR systems that adapt intelligently to each individual for the assessment and rehabilitation of patients with rare diseases. The aim is to assess the efficacy of the systems in clinical and rehabilitation settings for these patients through biofeedback readings and user self-reports. Developing such systems could benefit the ORDR by enabling technology-based applications for the rare diseases community. Applications include pain management and rehabilitation, remote monitoring and data capture for clinical trials, and diagnostic assistance for rare diseases with motor components.

NCATS will solicit SBIR applications to develop a virtual environment proof-of-concept system that incorporates dynamic audio, visual, full-body haptic and olfactory stimuli. The system should incorporate runtime logfile capabilities for remote patient monitoring and performance analytics and a human-in-the-loop system model that addresses patient personalization and biofeedback. The outcome will be a system that provides users a VR/AR pipeline to influence the accessibility, affordability and accuracy of therapeutic treatment and clinical use; design guidelines and efficacy considerations for existing VR/AR platforms; a multisensory tool or suite of tools for remote patient monitoring; and an AI-driven user behavioral model for adapting rehabilitation stimuli. The intent is that these remote-based systems would assist with clinical monitoring and rehabilitation efforts for patients with rare diseases, especially in cases where travel is impossible or difficult. The systems are intended to benefit the entire research community.

Discussion

Mr. Bartek commended NCATS for addressing the need for more improved technologies for virtual clinical monitoring and rehabilitation for patients with rare diseases. He inquired on plans to collaborate with the FDA on clinical trial design, collecting additional evidence on the patients' experiences using these systems in their own environment and accounting for the differences between the capabilities of patients. Mr. Michael called attention to the Federal Games Guild, which consists of representatives from across the NIH and FDA. He noted NCATS is having discussions with the FDA on incorporating gaming features in systems designed for the rare diseases community. The collection of additional data likely will depend on what is being monitored with the VR and the frequency of that monitoring. In addition, he explained that NCATS will rely on the applicants to address a broad range of rare diseases in a given design.

:: Lili Portilla posted in Chat to all participants:: We could also ask the offeror to engage with the FDA as part of the SOW.

Mr. Margus remarked on how the use of VR has increased in the rare diseases community, especially for ataxia telangiectasia patients. He suggested the SBIR awardees collaborate with both U.S. and foreign companies on new and emerging VR technologies. Ms. Portilla noted the SBIR program restrictions on collaborating with foreign entities, with an exception for unique technologies that are not available elsewhere.

Members unanimously approved the VR/AR systems for rehabilitation concept.

Platform for Rapidly Deployable Autonomous Laboratory: Samuel G. Michael, Chief, Information Technology Resources Branch, DPI, NCATS; Carleen Klumpp-Thomas, M.S., Research Services Core Lead, DPI, NCATS

Mr. Michael presented the SBIR contract concept on the topic of a platform for a rapidly deployable autonomous laboratory, which aligns with the NCATS ASPIRE initiative. The COVID-19 pandemic—and subsequent physical distancing and closing of research laboratories—has led to the postponement of critical experiments necessary for developing novel diagnostics and potential therapeutic interventions. The purpose of this SBIR contract concept is to develop next-generation distributed, AI-enabled, fully automated laboratories that are linked to a cloud-based virtual research organization (VRO) to acquire, harmonize, store, analyze and share data generated during experimentation.

The goals are to create a platform consisting of modular automated devices capable of performing laboratory tasks for both diagnostic and therapeutic discovery purposes. NCATS will solicit SBIR applications to develop the following: (1) a distributed, modular, autonomous lab instrumentation platform that focuses on such areas as HTS for drug discovery, next-generation sequencing, high content imaging, and polymerase chain reaction diagnostics and (2) a cloud-based VRO that connects each automated laboratory and AI methods that integrate the lab data into the VRO, allowing real-time data collection and analysis. NCATS will leverage its collaboration with Kebotix, Inc., on AI/machine learning models and HTS.

Carleen Klumpp-Thomas, M.S. described an example of use of the proposed platform. In collaboration with the National Institute of Biomedical Imaging and Bioengineering (NIBIB), one of its small laboratories without automated equipment was upgraded. The automation increased the laboratory's analysis capacity from 500 to 10,000 samples, and copious data were collected in real time and exported into a VRO.

Mr. Michael noted that the outcomes of the SBIR contract concept will be a system that provide users with (1) a platform that enables the on-demand initiation of physical experiments across laboratories, (2) a cloud-based VRO that houses data suited for analysis, and (3) a modular platform that can quickly add or scale up additional resources necessary for responding to public health emergencies. NCATS anticipates that using SBIR contract mechanisms will create opportunities for small businesses to facilitate an emergency commercialization for rapidly scalable instrumentation.

Discussion

Dr. Holman asked whether laboratories would need to supply all equipment, reagents, assay design and other materials to enable automation. Mr. Michael noted that ideally, the instrumentation would be in place during the assay optimization. Ms. Klumpp-Thomas added the NIBIB laboratory's ELISA assay was optimized rapidly based on a modified basic protocol.

Members unanimously approved the rapidly deployable autonomous laboratory concept.

XI. SPECIAL TOPIC PRESENTATION—Utilizing Artificial Intelligence, Machine Learning and Deep Learning to Enhance Preclinical Discovery: Samuel G. Michael, Chief Information Officer, Office of Administration Management, DPI, NCATS

Mr. Michael presented an overview of how AI, machine learning and deep learning (DL) can be used to enhance preclinical discovery. He emphasized that AI can be defined as any program that can take input and produce an output enabling such behaviors as reasoning, acting, adapting or reacting. Machine learning involves algorithms for which performance improves as they are exposed to more relevant data. DL can be defined as multilayered neural networks that learn from mathematical convolution of

vast amounts of data. Mr. Michael reminded the Council of the steps associated with the drug development process, starting with assay development and progressing through clinical development. He further explained that HTS requires extensive use of automation to run assays against large libraries of small molecules at different concentrations, yielding millions of data points during a single screening campaign.

Both machine learning and DL are subsets of AI. Although DL can automatically discover the features to be used for classification, machine learning requires these features to be input manually. Furthermore, in contrast to machine learning, DL needs high-end machines and considerably large amounts of training data to produce accurate results. Mr. Michael explained how neural networks work, using such inputs as tables of data, images, gene sequences, spectra and outputs that include classification and regression. He elaborated on the steps involved to train this process resulting in a model, which is then used on new data and checked for performance, with changes to the model structure incorporated until performance is satisfactory. This results in trillions of computations.

For more than 14 years, the DPI has generated millions of experimentally validated data points for compounds, biological assay results, high content imaging, medicinal chemistry, and other data types. These extensive data sets provide the opportunity to develop world-class, accurate machine learning/DL models that can be trained to conduct virtual experiments to help answer scientific questions more rapidly. Although current experimental approaches are accurate, they are limited by the number of samples that can be accommodated and are labor-intensive and time consuming. Current computational approaches are much faster, can accommodate a huge number of samples, but are not as accurate as biological experiments. Combining experimental and computational approaches can help each overcome its respective limitations. Mr. Michael described how NCATS is using a combination approach for compound libraries, noting that machine learning can predict noise in chemical library results.

Quantitative structure-activity relationship modeling coupled with five different machine learning approaches was used to develop a web-based tool that allows researchers to predict the likelihood of assay interference for any new chemical structure. In 2014, researchers developed roughly 50 million data points from 30 assays on 10,000 chemicals. Work was done to predict toxicity assay response based on chemical structure through the Toxicology in the 21st Century Data Challenge. Submissions were received from 18 different countries and predicted toxicity results of more than 100 compounds tested against 12 different assays that had been run previously. All displayed good predictive power, achieving greater than 80 percent accuracy, with several models exceeding 90 percent accuracy.

Mr. Michael described the application of AI and machine learning in the design of experiment optimization in collaboration with Kebotix to develop, test and implement an automated biological test platform with direct interface to informatics platforms. These efforts made use of a basic, stable Papain assay with selected variables to be modified in search of the optimal experimental conditions. Through a series of messaging queues, Kebotix sends messages to the NCATS robot, which executes the experiment and feeds the results back to Kebotix, which updates the model based on the results.

Mr. Michael highlighted the point in the process at which the virtual and physical meet: when the NCATS robot compiles the message received from Kebotix (that has been converted into a language the robot understands) and launches an assay. Using this approach, previous results are used to predict the next experiment to try to hit the optimal condition. Mr. Michael presented data showing five continuous days

of running completely autonomously. The team found that they could reach a 95 percent probability of reaching the optimal assay condition about five times faster than if using a brute force technique.

The conventional screening process is being improved upon by combining the physical and virtual, starting with development of an AI model at the outset of a pilot screen followed by a large virtual screen, validation, follow-up assays and medicinal chemistry from the start of the virtual screen. Results can be obtained virtually first, then validated physically, and the medicinal chemistry can be initiated sooner (saving experimental capacity for when it is needed). Shifting fully to this new paradigm will require better models; the more data that are experimentally validated and made available to the community, the better the models will become. Mr. Michaels described the NCATS Predictor tool, an AI-based, publicly available tool to predict biological activity that can predict more than 1,100 biological actives (available at https://predictor.ncats.io/). He pointed to the need to engage modelers from the academic community in these types of activities.

An exceedingly large number of molecules have never been included in the drug discovery process but might have significant drug development potential. NCATS has been focused on using models to find completely new chemotypes based on prior results. Mr. Michael described a collaboration with Eli Lilly using an automated chemical synthesis reactor—the Indigo Mobile Reactor, which can perform chemistry in an automated fashion—with the goal of identifying virtual compounds, finding a reaction path, and then creating that molecule and testing it. It is hoped that through a common platform—possibly a series of cloud-based platforms—the production of these compounds can be performed in a distributed manner. Mr. Michael described the data analysis process and pointed out that one of the challenges facing NCATS is the copious amounts of data being generated; a future Council meeting will feature a discussion on the complexity of analyzing these large amounts of data.

Mr. Michael commented that if it becomes possible to run high-throughput and virtual screens, analyze the data, and then identify chemicals to produce, automatically create those compounds, and feed them back into chemical libraries, the result would be an autonomous platform for drug discovery. NCATS has consistently shown that it is working across this space to introduce these techniques and demonstrate that elements of this process are already in place. Mr. Michael concluded that AI/machine learning/DL techniques are impacting the entire preclinical spectrum at DPI. Data generated by DPI and others are allowing more accurate models, which enable more research to be performed virtually and then experimentally tested for validation. He emphasized the significant benefit presented by autonomous laboratories and commented that DPI is at the forefront of connecting virtual platforms with physical systems to execute designs and test approaches in an autonomous fashion.

Discussion

Drs. Holman and Marks applauded these efforts and expressed enthusiasm for NCATS continuing to move forward in this area.

XII. PUBLIC COMMENT

A letter to Dr. Christopher Austin from the Physicians Committee for Responsible Medicine conveying strong support for the NCATS' response to COVID-19 to speed translational research was received on May 30, 2020.

XIII. ADJOURNMENT OF THE OPEN MEETING

Dr. Austin noted that the CAN Review Board update will be postponed until the September 17, 2020, Council meeting. He thanked all of the participants for their input and adjourned the open portion of the meeting at 5:01 p.m. ET.

CERTIFICATIONS

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

Christopher P. Austin, M.D.
Chair, NCATS Advisory Council
and
Director, National Center for Advancing Translational Sciences, NIH

Date

Anna L. Ramsey-Ewing, Ph.D.
Executive Secretary, NCATS Advisory Council
Executive Secretary, Cures Acceleration Network Review Board
and
Director, Office of Grants Management and Scientific Review, NCATS

Date