

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

**28th Meeting of the
Advisory Council**

**Minutes of Virtual Meeting
September 23–24, 2021**

The National Center for Advancing Translational Sciences (NCATS) Advisory Council held a meeting in open session on September 23, 2021, from 1:00 p.m. to 4:49 p.m. EDT, and on September 24, 2021, from 1:00 p.m. to 4:06 p.m. EDT via National Institutes of Health (NIH) Videocast. Joni L. Rutter, Ph.D., NCATS Advisory Council Chair, led the meeting. In accordance with Public Law 92-463, the session was open to the public.

Prior to the meeting, the NCATS Advisory Council met in closed session on September 23, 2021, from 10:30 a.m. to 12:30 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, Office of Grants Management and Scientific Review,
NCATS

Council Members

Paul A. Harris, Ph.D.
Theodore R. Holman, Ph.D.
Rebecca D. Jackson, M.D.
Annie M. Kennedy, B.S.
Matthias Kretzler, M.D.
Andrew W. Lo, Ph.D.

Kelly Marie McVearry, Ph.D., Ed.M.
Keith J. Mueller, Ph.D.
Rajesh Ranganathan, Ph.D.
Paula K. Shireman, M.D., M.B.A.
Marshall L. Summar, M.D.

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

Others Present

Frank F. Weichold, M.D., Ph.D., Director, Office of Critical Path and Regulatory Science Initiatives,
Office of Regulatory Science and Innovation, Office of the Chief Scientist, U.S. Food and Drug
Administration (FDA)
Michael Rosenblatt, M.D., Flagship Pioneering
Elizabeth Stoner, M.D., MPM Capital

NCATS leadership and staff

I. CLOSED SESSION OF THE NCATS ADVISORY COUNCIL

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

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

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

Joni L. Rutter, Ph.D., adjourned the closed session of the NCATS Advisory Council meeting on September 23, 2021, at 12:30 p.m. EDT.

SEPTEMBER 23, 2021

III. CALL TO ORDER, OPEN SESSION DAY 1

Dr. Rutter called the meeting to order and welcomed members and guests to the 28th meeting of the NCATS Advisory Council. She reminded attendees that the open session was being videocast, introduced the members of the Council and *ad hoc* members, and previewed the meeting agenda. Dr. Rutter noted that the meeting will span two days, September 23–24, 2021, with sessions held from 1:00 p.m. to 5:00 p.m. EDT both days.

IV. 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 June 2021 Council meeting.

V. CONFIRMATION OF DATES FOR FUTURE MEETINGS: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council

Anna L. Ramsey-Ewing, Ph.D., confirmed the schedule for the meetings of the NCATS Advisory Council for the remainder of 2021, 2022, and 2023:

- January 20–21, 2022
- May 19, 2022
- September 22, 2022
- January 26–27, 2023
- May 25, 2023
- September 28, 2023

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

Dr. Rutter began by welcoming new Council members: Rebecca Jackson, M.D.; Annie Kennedy, B.S.; Kelly McVeary, Ph.D., Ed.M.; and Rajesh Ranganathan, Ph.D. She also welcomed Gregory Jarosik, Ph.D., as the new deputy director of the NCATS Office of Grants Management and Scientific Review; and congratulated Philip John (PJ) Brooks, Ph.D., on his promotion to deputy director of the NCATS Office of Rare Diseases Research. Dr. Rutter took a moment to remember and recognize the work and life of

James E. Heubi, M.D., who was the director of the Center for Clinical and Translational Science and Training in Cincinnati but passed away in August 2021.

Dr. Rutter called attention to a thematic issue in the *Journal of the Clinical and Translational Sciences (JCTS): Re-engineering the Clinical Research Enterprise in Response to COVID-19: The Clinical and Translational Science Awards (CTSA) Experience*, which is a compendium of articles related to the CTSA response to the coronavirus disease 2019 (COVID-19). She thanked the 120 authors of the journal issue, who worked behind the scenes to support this compendium during the COVID-19 pandemic.

Dr. Rutter reported on the mission and approach of the Advanced Research Projects Agency for Health (ARPA-H), which is intended to benefit the health of all Americans by catalyzing health breakthroughs that cannot readily be accomplished through traditional research or commercial activity. The main goals of ARPA-H are to support transformative high-risk, high-reward research to achieve the following:

- Speed the application and implementation of health breakthroughs to serve all patients.
- Foster breakthroughs across various levels, from the molecular to the societal.
- Build capabilities and platforms to revolutionize the prevention of, treatment of, and cures for a range of diseases.
- Convert use-driven ideas into tangible solutions for patients more rapidly than previously believed possible.
- Overcome market failures through critical solutions or incentives.

The NIH and the White House's Office of Science and Technology Policy convened listening sessions on ARPA-H to garner feedback from patient advocacy groups, industry representatives, scientific and professional organizations, and other stakeholders. A small subcommittee of NIH Institute and Center (IC) directors meets regularly to determine how the NIH can best interface with ARPA-H once it is established.

Dr. Rutter described activities occurring at the leadership level by the NCATS Office of the Director (OD), emphasizing the NCATS response to COVID-19 and work of the Common Fund, the Helping to End Addiction Long-termSM Initiative or NIH HEAL InitiativeSM (HEAL), the Accelerating Medicines Partnership (AMP), and programs of the Foundation for the National Institutes of Health (FNIH). She reminded the Council that drug development is challenging, with an average drug development time lasting 10 to 15 years at a cost of \$2.6 billion. Moreover, the current drug discovery paradigm has a failure rate of 90 percent, pointing to the need for new technologies and better predictive tools. Only approximately 500 treatments exist for nearly 10,000 diseases, but NCATS is working to get more treatments to more people more quickly.

NIH HEAL Initiative

The NIH HEAL Initiative is a powerful effort to speed scientific solutions to the national opioid public health crisis. Twelve ICs are leading this effort, with NCATS participating by applying breakthrough approaches of translational science to advance new treatments for opioid misuse and challenges surrounding pain and addiction.

The preclinical side for the NCATS' HEAL program is led by Christine Colvis, Ph.D., and Steve Pittenger, Ph.D. Last year, all but two states were registering increased deaths from opioid overdoses, with an approximately 30 percent overall increase of fatal drug overdoses ending in October 2020. Jane C.

Atkinson, D.D.S., led efforts on the clinical side of the HEAL program, along with Yolanda F. Vallejo, Ph.D., both of whom focused on efforts to prevent and manage pain while reducing the risk of addiction.

NIH Common Fund

The NIH Common Fund addresses emerging scientific opportunities that no single IC could handle or address. The Common Fund functions like a venture capital space supporting high-risk, innovative endeavors with the potential for a large impact. NCATS leads three Common Fund Programs.

- **Extracellular RNA Communication.** This program began in 2013 and is coordinated by Danilo A. Tagle, Ph.D., M.S., with Christine Happel, Ph.D., serving as the Program Officer. This program explores the therapeutic and diagnostic potential of extracellular RNA.
- **Illuminating the Druggable Genome (IDG).** The IDG program began in 2014 and is coordinated by Dr. Colvis, with Karlie R. Sharma, Ph.D., serving as the Program Officer. This program identifies key signaling proteins that have been understudied but have the potential to be druggable or used to develop molecular probes, tools and assays, transgenic mice, recombinant cell lines, data, and digital resources for hundreds of understudied G-protein-coupled receptors, ion channels, and kinases.
- **Somatic Cell Genome Editing.** This program began in 2017, and the coordinator and Program Officer is Dr. Brooks. This project improves the efficacy, efficiency, and specificity of gene editing approaches for rare diseases; it also speeds the clinical development of gene-targeted approaches for diseases. Dr. Brooks also is leading the AMP Bespoke Gene Therapy Consortium (BGTC), which will be building capabilities by optimizing adeno-associated virus (AAV) vector generation and enhancing therapeutic gene expression within those vectors. These efforts can lead to reduced dosages and side effects for gene therapies, as well as standardized protocols for vector generation. This program is a large public-private partnership that is expected to launch next month.

Dr. Rutter explained that another NCATS program, A Specialized Platform for Innovative Research Exploration (ASPIRE), combines intramural and extramural programs. The program facilitates the joining of biology and chemistry with a focus on structural activity relationships related to drug activity and development. ASPIRE seeks to explore the chemical space to identify biological drug targets. The program is mostly built and is ready for testing. Multiple efforts have utilized and optimized the program.

NCATS recognizes the power of data science to drive translational science by increasing its efficiency and effectiveness. NCATS supports data science through the Common Fund via a vision built upon several main pillars, striving to do work that is impactfully innovative; sustainable; diverse, equitable, and inclusive; and transparent, open, and communicative. Currently, NCATS spends most of its time enabling data science, but future efforts will shift to a greater focus on inferring new knowledge using data science.

NCATS Response to COVID-19

NCATS supports multiple efforts focused on addressing the COVID-19 pandemic. The NCATS Tracking Resistance And Coronavirus Evolution (TRACE): Accelerating COVID-19 Therapeutic Interventions and

Vaccines (ACTIV) Variant Efforts (NCATS OpenData Portal Update) addresses how viral variants affect COVID-19 therapeutics and vaccines.

- **The Antiviral Program for Pandemics.** This program works to develop a portfolio of direct-acting, oral antiviral therapeutics for out-patient use against SARS-CoV-2 (the virus that causes COVID-19) and other viruses of pandemic potential, leading to Phase 2 trial-ready antivirals for rapid pandemic response. NCATS will build a platform to discover new antivirals using automated solutions.
- **National COVID Cohort Collaborative (N3C).** The N3C is driven by the CTSA, which joined with clinical and translational resources and health centers to leverage real-world electronic health record (EHR) data for COVID-19 research. The N3C is being used to help define the phenotype of “long COVID” and determine answers to research questions surrounding the phenomenon. N3C efforts are ongoing to establish privacy-preserving record linkage, a method to generate de-identified patient keys that retain privacy while enabling data linkability; and synthetic data, called MDClone, which allows algorithmically derived medical data. A recent Biomedical Advanced Research and Development Authority (BARDA)–sponsored N3C Data Challenge, the Pediatric COVID-19 Data Challenge, encourages the development of computational models to predict which children are most at risk for severe COVID-19 complications early in disease progression.

Training and Education

NCATS’ training and education efforts are intended to encourage sustainable translational research and build the careers of promising translational researchers.

- **Translational Science Interagency Fellowship (TSIF).** This 3-year NCATS joint postdoctoral fellowship with the U.S. Food and Drug Administration (FDA) provides combined translational science and regulatory science training through specific research projects of mutual interest. The TSIF welcomed its inaugural class of three fellows (Drs. Keyla Tumas, Elia Lopez, and Xinh-Xinh Nguyen) on September 13, 2021. The program currently is accepting applications for 2022.

NCATS also is offering several additional training courses: MEDI 501 (online translational science course); the Translational Science Training Program (TSTP); and TSTP proposal feedback and visit to NCATS.

NCATS 10-Year Anniversary

NCATS will be celebrating its 10-year anniversary at a virtual symposium, “NCATS at 10: Improving Health for All Through Translational Science,” on December 7, 2021, from 12:30 p.m. to 5:00 p.m. EST. Additional details can be found on the [NCATS Events webpage](#).

Discussion

Marshall L. Summar, M.D., asked about lessons learned from the NCATS COVID-19 projects. Dr. Rutter answered that NCATS learned how to harmonize disparate EHR data onto one data model. NCATS also learned that it must act more quickly and effectively when providing resources for academic health centers.

Referencing the AMP BGTC, which might be done in collaboration with Pfizer, Kelly Marie McVeary, Ph.D., Ed.M., asked what mechanisms and policies have been established by NCATS to ensure that repositories and resources developed in collaboration with pharmaceutical companies remain broadly available to the scientific community. Dr. Rutter responded that the AMP BGTC project is undertaken primarily through the FNIH, which can collect money from private partners, combine that private funding, and use the collective funds to build programs. The federal side of the program is managed by NIH ICs. The FNIH brokers these relationships and establishes clear expectations for collaborations that streamline collaborative processes and best practices. Dr. Rutter added that the ACTIV and TRACE efforts also are public–private partnerships with clear agreements in place.

Andrew W. Lo, Ph.D., commended NCATS for its NIH HEAL Initiative work and recommended that additional work in this area include collaborations with biopharmaceutical partners, which are typically reticent to focus on pain management and opioid addiction due to continued stigma. He added that NCATS could work to ensure that the remaining settlement money from opioid addiction lawsuits is funneled into efforts that will help the victims of opioid addiction directly.

Action Item: Dr. Lo, Council Member, recommended that NCATS consider collaborating with biopharmaceutical partners that have limited experience in studies in pain management and opioid addiction and working to ensure that settlement funds from opioid addiction lawsuits are parlayed into efforts that benefit the victims.

Dr. Lo noted that AAV vector work in gene-based therapies has resulted in occasional immunogenicity issues. He asked how NCATS can work more proactively on immunogenetic responses. Dr. Rutter responded that the FDA has held an advisory committee meeting specifically addressing the risks and safeties of AAV-based gene therapies, and NCATS held a similar meeting on immune responses to AAV. NCATS is conducting multiple activities in this area. Dr. Brooks added that, within the BGTC program, investigators are working to modulate the immune response to AAV treatments and optimize AAV trial efficiency. Dr. Lo asked whether it would be possible to develop an adaptive platform trial for gene-based therapies. Dr. Brooks stated that Phase 2 of the Somatic Cell Genome Editing program includes an initiative to support clinical trials of genome editors that address multiple diseases at a time. This effort will normalize clinical trials utilizing the platform capacity of such methods as gene therapy and genome editing. NCATS also supports two projects that are focused on basket trials of drugs with shared molecular etiology in multiple rare diseases.

Ms. Kennedy asked why the Centers for Medicare & Medicaid Services (CMS) has not been included in the early conversations for the BGTC. Dr. Brooks answered that CMS can be included in future conversations.

Action Item: Dr. Brooks will consider including CMS in future discussions about the BGTG.

Dr. Lo encouraged NCATS to provide incentives for nonclinical universities, noting that engineers, data scientists, and computer scientists will have much to contribute to drug discovery via data science. Paul A. Harris, Ph.D., asked whether the data science knowledge-accumulation phase will be done intramurally or extramurally. Dr. Rutter responded that most of the work in that area will occur intramurally. She added that the NIH has a variety of data-sharing guidelines, and new guidelines for 2023 mandate that data be deposited into repositories. The NIH is guided in this area by the FAIR (Findability, Accessibility, Interoperability, and Reusability) principles, but Dr. Rutter acknowledged that these principles might not emphasize impact sufficiently. She stated that guiding the development of data science best practices and guidelines with a focus on impact could be valuable.

Dr. Jackson asked how NCATS will drive efforts to incorporate large administrative data sets and public health data that can provide insight and increase the uptake and dissemination of new treatments. Dr. Rutter responded that this is one area of focus for the N3C, which includes environmental data and data on social determinants of health. She agreed, however, that applying this approach on a larger scale would be valuable, observing that N3C evaluates these factors only in relation to COVID-19.

Frank F. Weichold, M.D., Ph.D., emphasized the value of standardizing trial approaches that are used historically by single investigators in the CTSA network. He stated that many effective platforms exist in terms of data hubs and standardization of Institutional Review Boards (IRBs), which provide opportunities to standardize trial designs and conduct platform trials. He recommended that the CMS and FDA be invited as partners in NCATS-driven efforts for increasing clinical trial standardization.

Dr. Lo congratulated NCATS on its 10-year anniversary and recommended that it compile a compendium of its achievements to increase awareness of its value and accomplishments. Ms. Kennedy noted that many of the ARPA-H goals and objectives are parallel with NCATS' activities. She recommended that messaging regarding NCATS' accomplishments in areas of focus for ARPA-H be amplified.

Dr. Ranganathan asked how NCATS will be able to coexist with ARPA-H. Dr. Rutter responded that, at this stage, it is too early to know exactly how NCATS and ARPA-H will work together. NCATS supports many of the goals and objectives of ARPA-H, so Dr. Rutter is doing everything possible to align with ARPA-H and work as an arm of implementation to further existing NCATS efforts. Dr. McVearry asked what, if anything, Council members can do to support Dr. Rutter and NCATS. Dr. Rutter thanked Dr. McVearry and stated that she has been focused on emphasizing NCATS' abilities to ensure it can continue its work. Matthias Kretzler, M.D., recommended identifying synergisms between the two programs and avoiding overlap between NCATS and ARPA-H. Doing so could supercharge some of the NCATS efforts presented today.

Action Item: Council Members recommended that NCATS highlight the Center's accomplishments, as well as identify synergisms and avoid overlap between NCATS and ARPA-H.

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

14:22:13 From Matthias Kretzler to Everyone: also carefully consider alternative approaches including ASO and RNA-therapeutics and ability to deploy them as nimble platforms.

14:25:41 From Pj Brooks to Everyone: @Matthias, yes, I certainly agree. I think that one of the lessons of COVID is the scalability of mRNAs delivered by nanoparticles. Within the SCGE, we have several investigators developing nanoparticles to deliver genome editors.

14:27:22 From Pj Brooks to Everyone: ..and the discussions going on about ASOs as a platform at FDA may also be relevant to swapping different guide RNAs, which are also oligonucleotides, in the context of gene editing platform trials.

14:29:13 From Matthias Kretzler to Everyone: FAIR data for whom? Effort to define the user community and ways to respond to user cases can be very instructive in guiding path forward.

14:37:46 From Andrew Lo to Everyone: A related question is how BARDA relates to ARPA-H?

14:43:14 From Marshall Summar to Everyone: We have one of the BARDA BlueKnight facilities here at Children's and they do sound very similar to ARPA-H.

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

Michael G. Kurilla, M.D., Ph.D., provided an overview and updates regarding the DCI.

CTSA Consortium Activities

Dr. Kurilla presented a summary of staff updates, highlighting the recent retirements of Jane Atkinson, D.D.S., and Bernard Talbot, M.D., Ph.D., from DCI after 29 and 51 years, respectively. Newly hired staff include Mercedes Rubio, Ph.D., the new Chief of the Education and Training Section.

Currently, 61 CTSA Program Hubs exist throughout the United States. A suite of new CTSA funding opportunity announcements (FOAs) has been released. CTSA Collaborative Innovation Awards (CCIA) enable multiple CTSA to combine to address issues unable to be addressed by a single CTSA; four of these awards have been conferred in the past year. Dr. Kurilla highlighted one such project aiming to develop, implement, and evaluate the clinical utility of whole-genome sequencing (WGS) as a screening method in a diverse cohort of healthy infants.

Dr. Kurilla provided an overview of CTSA-funded principal investigators (PIs) and other researchers:

- 19 new CTSA Program PIs received awards between October 2020 and September 2021.
- Early-career researchers who received awards include—
 - Shanina C. Knighton, Ph.D., R.N., C.I.C., who is exploring the feasibility of tech-based hand hygiene among older adults.
 - LaPrincess Brewer, M.D., M.P.H., who is evaluating church-based partnerships to improve cardiovascular health outcomes in Black Americans.
 - Megan L. Srinivas, M.D., M.P.H., who is focusing on how the defunding of family planning health centers affects access to care in rural America.
 - Nathaniel W. Anderson, who is investigating the effects of pandemic school closures on children’s health.
 - Sarah Forrester, Ph.D., M.S., who is studying the effects of racism-related chronic stress on aging acceleration.
 - Rima Januszewicz, Ph.D., who is developing novel technology to print 3-D intravaginal rings for drug delivery.
- CTSA Program Diversity, Re-entry, and Reintegration Supplement awardees include—
 - Alexis Dunn-Amore, C.N.M., Ph.D., who is investigating high death rates due to pregnancy and childbirth complications among Black American women.
 - Roland Matsouaka, Ph.D., who is applying unique statistical approaches to analyze large registry data sets.
 - Carolina Velasquez, M.S., who is studying how body composition affects blood vessel health in young women from underrepresented groups.

Addressing COVID-19

Dr. Kurilla updated the council on DCI’s efforts in response to the COVID-19 pandemic.

- **N3C.** Launched in 2020, the N3C is a collaboration among NCATS information technology and informatics groups, CTSA Program Hubs, and the National Center for Data to Health. During the past year, the N3C Data Enclave—a secure national resource for EHR data from COVID-19–tested patients—has expanded from 50,000 patient records in September 2020 to more than 2.5 million records in September 2021. Multiple peer-reviewed manuscripts using N3C data are being published, including one of the first studies using synthetic epidemiological data.
- **NCATS-Managed Hospitalized Patient Convalescent Plasma Clinical Trials and Associated Projects.** CTSA programs supported the Convalescent Plasma to Limit COVID-19 Complications in Hospitalized Patients Trial (CONTAIN COVID-19) and its associated project, Rosetta Stone, which aims to standardize plasma assays. The Passive Immunity Trial for Our Nation for COVID-19 (PassItOn) also is being supported in concert with its associated project, Continuous Monitoring of Pooled International Trials of Convalescent Plasma for COVID-19 Hospitalized Patients (COMPILE), which aims to compile pooled data from convalescent plasma trials from around the world. Early results from these trials have indicated that convalescent plasma is not a magic bullet for COVID-19.
- **Other COVID-19 Randomized Control Trials.** ACTIV trials are public–private partnerships led by the FNIH and were established in 2020 to speed the development of COVID-19 therapeutics and vaccines. ACTIV Master Protocol 1 of Immune Modulators (ACTIV-1 IM), an inpatient trial investigating three immunomodulators of severe disease, has surpassed 75 percent enrollment. The Randomized Trial to Evaluate Efficacy of Repurposed Medications (ACTIV-6) is an outpatient trial looking to repurpose medications for the reduction of COVID-19 symptoms and prevention of hospitalization. This nationwide double-blind study—which includes such drugs as ivermectin, fluvoxamine, and fluticasone—has enrolled more than 300 participants after being initiated in June 2021. Additionally, Lenzilumab™, which was developed originally to treat cytokine storms associated with chimeric antigen receptor T-cell (CAR-T) cancer treatments, is currently in an ACTIV-5 trial to treat COVID-19.
- **Community Engagement Alliance (CEAL) Against COVID-19 Disparities.** CEAL is expanding to focus on urgent community-engaged COVID-19 awareness and education. Eight of the 11 CEAL research teams are located within CTSA programs; four additional CTSA Program Hubs will become CEAL sites.
- **The ABC Science Collaborative.** The ABC Science Collaborative, a CTSA-funded project established in July 2020, aims to connect researchers and physicians with school and community leaders to aid in the sharing and understanding of COVID-19 information. The effort was based primarily at Duke University in North Carolina but has since expanded to 14 other states.
- **Virtual Meetings.** An “un-meeting,” “Tackling the Digital Divide to Improve Telehealth,” was hosted by the Clinical and Translational Science Collaborative of Cleveland on March 26, 2021. Participants included clinicians, researchers, and representatives from industry and government agencies from 32 participating CTSA Program Hubs. Another un-meeting, “Exploring the Inclusion of Community Hospitals in Clinical Research,” was held on May 27, 2021, in response to difficulties in undertaking clinical trials when most COVID-19 patients are being treated at community hospitals.
- **JCTS Thematic Issue: *Re-engineering the Clinical Research Enterprise in Response to COVID-19: The CTSA Experience.*** A series of 14 articles by numerous CTSA Program institutions and

scholars was published in the June 2021 issue of *JCTS*. This issue described how the CTSA Program pivoted to address COVID-19's challenge to biomedical research and included lessons learned and best practices for future public health emergencies.

Non-COVID-19 Activities

Dr. Kurilla elaborated on DCI's mission-critical work.

- **CTSA-Supported Clinical Trials.** Time-limited palliative care trials published in *JAMA Internal Medicine* offered a new patient-centered approach, limiting intensive care stays for patients with advanced illnesses without affecting mortality. One study involving the modification of certain dietary fatty acids to reduce headaches was published in *The BMJ*. A longitudinal analysis of concussions and head injuries published in the *Journal of Neurosurgery: Pediatrics* studied head impact exposure in youth football players. A case study of a 5-week-old infant with encephalopathy and neurological symptoms—in which clinicians employed WGS analysis to diagnose thiamine metabolism dysfunction syndrome 2 (THMD2) within 13 hours and initiate treatment within 38 hours of admission—was published in the *New England Journal of Medicine*.

Discussion

Dr. Lo asked about ongoing research into messenger RNA (mRNA)–based *ex vivo* construction of antibodies because certain members of the public refuse vaccines but are willing to receive antibody-based therapies. He noted that it would be profitable for businesses to offer these treatments because these treatments are given continuously, rather than as a single- or double-dose vaccine. Dr. Lo also commented on a change in language for CTSA Program partnerships, which appears to restrict the budget to clinical research and asked about possible exceptions to this language for institutions that only contribute to clinical research. Dr. Kurilla noted that the monoclonal antibody idea has been raised and added that some current trials involve antibodies in immunocompromised populations; however, serious administrative barriers exist. He added that the question of whether mRNA-based technology can produce a sufficient antibody response remains unclear. With regards to the clinical research, Dr. Kurilla clarified that no restrictions exist on partnerships with institutions that do not perform clinical research; the clinical language merely speaks to the funding calculations for that CTSA Program award. As an option, Dr. Kurilla mentioned the RC2 funding mechanism for high-impact, interdisciplinary science in National Institute of Diabetes and Digestive and Kidney Diseases research areas, which has no required clinical trial components.

Dr. Ranganathan commented on the issues related to clinical trials in community-based health care centers in terms of the locations where clinical research can be performed relative to the locations where care is being provided. It is thus imperative to determine factors that will enable community-based health centers to perform these studies, which will save time and money, as well as allow these institutions to be more competitive for industry partnerships. Dr. Kurilla concurred and responded that a major lesson from the COVID-19 pandemic has been the importance of moving quickly to address issues at ground level. Community hospitals and rural clinics have both the patients and important questions that must be addressed; a shift in power from the academics to the clinicians must be made to accommodate these needs. Dr. Ranganathan added that a “spoke-and-hub” model for collaboration between academics and the community would be useful and that the community side needs more funding. Dr. Kurilla agreed that this arrangement would be beneficial for both sides and the entire medical field.

Dr. Ranganathan commented on the THMD2 diagnosis case study, pointing out that these cases can hit roadblocks, noting some of his experiences with such diagnosis. In terms of regulations and when dealing with insurance companies, approved tests are not identical to research tools. Dr. Kurilla agreed that this is an area where operational procedures do not always align well with the availability of new technologies.

Dr. Jackson encouraged an in-depth look at CTSA Program attributes that lead to training and career successes. In response, Dr. Kurilla highlighted the reorganization of the Division, including a new section focused on training and educational activities. This new section should enable the aggregation, evaluation, and tracking of successful program efforts, despite these programs' being separated within different hubs. Effects on multiple dimensions—such as scholars, institutions, individual fields, and public health in general—should be investigated. Dr. Jackson added that analyzing the intersection between individual researchers and training modalities could be more informative than looking only at individuals. The CTSA Program consortium has not always been data driven when thinking about new training opportunities, but an opportunity exists to advance this pedagogical science. Dr. Kurilla expressed his desire to have researchers funded by K and T programs contribute their institutional experience to this conversation.

Dr. Ranganathan asked about further discussion related to an open letter discussed at the June 2021 Council meeting, in which a subset of CTSA researchers raised concerns about changes being proposed by the consortium. Dr. Rutter noted that that letter had been received before the FOA was announced and that feedback related to the open letter was incorporated into the FOA. A technical assistance webinar for the FOA will be held soon, during which questions related to the FOA and the CTSA programs will be answered. Dr. Kurilla added that no further follow-up from the researchers has been received. Multiple conversations have been held internally with the CTSA Program steering committee, senior leadership of the clinical research forum, and academic clinical researchers.

Dr. Jackson noted that Dr. Harris had commented about the trainee tracking tool.

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

15:14:17 From Andrew Lo to Everyone: Could this also be used to address AAV9 immunogenicity?

15:27:16 From Annie Kennedy to Everyone: THIS is exactly what I was referring to when I was talking about the 10 year anniversary messaging. NCATS wasn't established to just populate academic journals. NCATS was established to change patient outcomes. And is doing exactly that. THANK YOU!

15:29:30 From Keith Mueller to Everyone: Outstanding researching the examples, with real-world, real-time impact. I was especially excited to the recognition of the benefits of research in different settings -- the medical deserts finding in NC, the recognition of needing to work with community hospitals, the work engaging Black churches. Thanks!

15:32:44 From Andrew Lo to Everyone: Agreed, it doesn't restrict collaboration, but it provides disincentives to work with partners that don't have a lot of clinical research funding.

15:33:31 From Marshall Summar to Everyone: Ironically what is crushing us in the Children's hospitals is RSV (we have 8 intubated patients in ER waiting for ICU beds for more than 2 days). Hoping NCATS can help lead from our COVID leadership to some of these other less publicized but big impact conditions.

15:33:37 From Paul Harris to Everyone: Great presentation Mike. I don't have an immediate question, but do want to add that there is a planned JAMIA special issue ('Best Practices in Research Patient Data Repositories' scheduled for publication in December 2021.) This one is heavily leveraging CTSA Informatics infrastructure and experts. The guest editor for this one is Les Lenert @ MUSC.

15:33:41 From Paul Harris to Everyone: <https://academic.oup.com/jamia/pages/call-for-papers>

15:48:13 From Paul Harris to Everyone: As an FYI - Kathie Hartmann @ VUMC has done a great deal of work formalizing trainee tracking + established / disseminated tooling in her FlightTracker platform. If you're planning to go deeper in planning this space, she'd be a great and key informant.

VIII. PROGRAM UPDATE: Drug Development Partnership Programs: Christine M. Colvis, Ph.D., Director, NCATS

Dr. Colvis provided an overview and updates regarding the Drug Development Partnership Programs (DDPP), listing the six DDPP programs. Dr. Colvis noted that each program corresponds to a different stage of the drug development pipeline. To familiarize new Council members with the Office, Dr. Colvis presented a historical overview of the DDPP programs and identified their associated program officers. Common themes of these programs include active program management, with frequent contact and milestones that must be met prior to continued funding, as well as collaborations between the DDPP staff and NCATS intramural research program.

Trans-NIH and NIH OD Programs

- **IDG Program.** This program for early-stage target discovery is a Common Fund program intended to support research that is transformative, catalytic, synergistic, crosscutting, and unique. It is managed by Dr. Sharma, and its goal is to improve understanding of protein families known to be drug-targetable that currently are not well studied. Almost one third of the human proteome falls under this "dark protein" category (i.e., with no associated publications or R01 support); these understudied proteins might be ideal targets for disease treatments or explain side effects of current drugs. The IDG program is focused on three targetable protein families: 63 ion channels, 116 G-protein coupled receptors, and 144 kinases. The IDG consortium is structured such that data from protein family-specific Data and Resource Generation Centers are fed into a Knowledge Management Center using an interface called Pharos, which was built by the NCATS intramural program and collects information about the entire proteome. Data also are sent to a Resource Dissemination Outreach Center that shares resources and reagents generated by the project. In a pilot project, the IDG program awarded several R03 grants to researchers outside the consortium. This R03 initiative has been successful, leading to four research grants, dozens of publications, many new collaborations, and the generation of new resources for the scientific community.
- **NIH HEAL Initiative.** Although the NIH HEAL Initiative incorporates both preclinical and clinical elements, DDPP is involved only in target discovery during the preclinical stage. Led by Dr. Pittenger, NCATS' two areas of focus are enhancing pain management and improving treatments for opioid misuse; both areas involve preclinical aspects. The NIH HEAL Initiative provides in-kind support in collaboration with intramural scientists. Researchers provide target compounds, subject-matter expertise, resources, and data. NCATS provides access to technology and resources, industry, expertise in drug development, and program management. Examples of preclinical HEAL resources include the intramural Division of Preclinical Innovation

components, such as the Induced Pluripotent Stem Cell (iPSC)–Derived Neurons for Pain and Reward Pathways, 3-D Bioprinted Tissue Models, ASPIRE Design Challenge Awards, and Developing of New Chemical Structures to Modulate Novel Targets. The extramural components include the ASPIRE Design Challenge Awards, Tissue Chip Models, and Identification of Novel Targets: HEAL Supplements to Explore IDG Targets

- **ACTIV Programs.** ACTIV is a public–private partnership co-led by NIH Director Francis S. Collins, M.D., Ph.D., and Paul Stoffels, M.D., that focuses on late-stage preclinical development of vaccines and treatments in response to the COVID-19 pandemic. It involves several working groups, including a preclinical working group, a therapeutics clinical working group, a clinical trial capacity working group, a vaccine working group, and a TRACE working group. The ACTIV preclinical working group was charged with providing guidance for the research community, as well as monitoring and disseminating resources, such as research animals and compounds. For example, the OpenData Portal was expanded to encompass information about animal models for COVID-19.

In-House Programs

- **New Therapeutic Uses (NTU) Program.** The NTU drug repurposing program, managed by Bobbie Ann Mount, Ph.D., is focused on late-stage preclinical and early clinical research. The NIH–Industry Partnerships program presented academic researchers with a chance to test drugs developed and discontinued by pharmaceutical companies that had reasonable safety profiles, with the main goal being Phase 2 clinical trials involving these repurposed drugs. NCATS was focused on specific process improvements, including template agreements to shorten the time to establish formal partnerships (from almost 1 year to around 3 months) and crowdsourcing to launch collaborations. Dr. Colvis noted recent research from this program. A drug originally developed by Sanofi is now being tested as a therapeutic for calcific aortic valve stenosis and will enter Phase 3 trials next year. NTU also supported a COVID-19 request for applications (RFA) in the past year. This RFA was designated urgent, allowing a more flexible and streamlined application process (e.g., no summary statements or Advisory Council meetings, a shortened internal staff review). Of the two awarded projects, one has advanced to Phase 3 with a commercial partner in less than 1 year. A workshop was held for repurposing off-patent drugs, which is a difficult process because investing in data collection for label updates when generic competitors are available is not profitable. Adding to the complexity, this problem cannot be fixed by a single government agency or biomedical sector. The workshop was focused on identifying research agendas, and a corresponding report has been published in *Nature Reviews Drug Discovery*.
- **LitCoin.** A new program led by Tyler Beck, Ph.D., LitCoin is a novel publication format that is citable and indexed by PubMed. The goals are to incentivize data sharing and build machine-readable, artificial intelligence–ready knowledge at the inception of traditional publications. The LitCoin format includes observations that might not fit into a narrative for a research article, which includes, but is not limited to, negative data. A workshop was held to receive input from researchers, publishers, and natural language processing (NLP) algorithm experts in the development of this format. A LitCoin NLP challenge—to create NLP systems that accurately capture the information denoted in free text and provide the output of this information through knowledge graphs—was announced and will commence on October 15, 2021.

- **Translator.** The goal of this program is to accelerate biomedical innovation by developing a biomedical “data translator.” This system for the computationally assisted exploration of knowledge will connect and analyze information from various sources that is not easily “mineable” and facilitate the construction of new hypotheses. Translator already has identified ketamine as a possible therapeutic for activity-dependent neuroprotective protein (ADNP) syndrome based on unrelated research into ketamine-associated toxicity. This finding led to the first drug trial for ADNP syndrome.

Discussion

Dr. Kretzler commented about the inclusion of biomedical information from several knowledge domains, including the Human BioMolecular Atlas Program (HuBMAP), the Human Cell Atlas, and several organ-specific networks. Dr. Kretzler mentioned that these networks include both transcriptional and protein activity information and that they are building tools anchored in ontology that are mappable and searchable. He offered to assist with the effort of integrating these tools into DDPP networks and programs. Dr. Kretzler noted that the Human Phenotype Ontology (HPO) network addresses questions that are similar to the case studies described by Dr. Colvis and that these efforts should be aligned. He added that finding a home for the ontology community would benefit all biomedical research. Dr. Colvis agreed and verified that DDPP communicates with the HPO network, although she was unsure about the status of the Human Cell Atlas. She noted that integrating temporal data into these networks will be the next big challenge and that help will be required for these efforts. Dr. Kretzler supported this assertion and added that he is encouraging the teams he is involved with to include time as a dimension in their data. These “4-D” models already are being published by himself and others.

Dr. Weichold thanked Dr. Colvis and the NCATS team for their in-house efforts and noted that few ontological activities have attempted to build synergistic efforts, which will be necessary for updating data in real time. He added that these activities cannot be achieved successfully by a single institution. Dr. Weichold highlighted the drug repurposing program, which would benefit from real-time data assessment’s being built into connected ontologies. The ability to quickly categorize assays, clinical information, and other outputs will be critical for supporting regulatory decisions and will conserve vital community resources. Dr. Weichold emphasized that data standardization will be essential for these efforts and offered his help in linking the data ecosystem. Dr. Colvis thanked Dr. Weichold and agreed, noting that 15 teams currently are working on the Translator project. This effort requires intensive management but was a deliberate choice because it is the only way to build a system that is useful to the entire community. Dr. Colvis expressed hope that these connections will be modularized with time and can be supported by multiple contributors beyond NCATS.

Dr. Harris asked for additional information about the number of cohorts in the drug repurposing program and other related metrics. Dr. Colvis replied that multiple rounds of funding opportunities have been launched since the initial awards in 2013. The drug used to treat calcific aortic valve stenosis came out of that first funding cohort; four more solicitations have been issued in collaboration with commercial partners. The program through which companies provide the assets has since been closed because industry partners depleted their supply of appropriate drugs to offer. Dr. Colvis noted that one positive outcome of this program has been companies’ offering repurposing opportunities to the research community of their own accord. Fourteen awards have emerged from these private–public partnerships. Other recent funding opportunities have included a solicitation for computational algorithms to identify drug indication pairs and two COVID-19 opportunities. In response to a follow-up

question from Dr. Harris on whether this program will be continued, Dr. Colvis noted that the research community has a lot of interest in drug repurposing. Although most discussions involve repurposing drugs on the market, space also exists for repurposing investigational drugs that are not yet commercially available. This process will be difficult, but this is the next frontier of drug repurposing.

Dr. Harris asked if the LitCoin stakeholder workshop resulted in any surprising feedback. Dr. Colvis responded that her group communicated with the stakeholders during the workshop development process; when the workshop was held, no major surprises emerged. She added that the community is excited and curious about this new concept, but also apprehensive. The ability to generate machine-readable pieces of information at the time of manuscript submission is achievable, and this will enable the essence of publications to be captured in a knowledge graph.

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

16:28:37 From Matthias Kretzler to Everyone: The cellular molecular landscape of human health and disease is remapped on the single cell level in HuBMAP, HCA and organ and disease specific networks. Linking to the emerging new ontology of organismal function and failure with NCATS molecular anchored program will help to close the dark matter and missing functional links for repositioning.

16:31:41 From Matthias Kretzler to Everyone: Please make sure your Translator team is connected to the robust effort active in the OBO foundry: <http://www.obofoundry.org/> Particularly the Human Phenotype ontology is working on solutions in this space also linking to HuBMAP emerging knowledge.

IX. ADJOURNMENT DAY 1: Clare K. Schmitt, Ph.D., Acting Deputy Director, NCATS OD

Dr. Schmitt adjourned Day 1 of the meeting at 4:49 p.m. EDT.

SEPTEMBER 24, 2021

X. CALL TO ORDER, OPEN SESSION DAY 2

Dr. Rutter called the meeting to order and welcomed Council members and guests to the second day of the 28th meeting of the NCATS Advisory Council. Dr. Rutter reminded attendees that the open session is being videocast and reviewed the agenda.

XI. CLEARANCE OF CONCEPTS

The Council and Board received presentations on six projects that NCATS is considering for funding. At the end of each presentation, the members discussed the proposal and voted on whether to approve of NCATS' moving forward with the concept.

Ethical Issues in Translational Science Research: Elaine Collier, M.D., Senior Advisor to the Director, Office of Translational Medicine

Elaine Collier, M.D., presented a renewal concept for support of the Ethical Issues in Translational Science Research program. This program seeks to address bioethical, legal, and social questions affecting ongoing and future research and its translation. The Ethical Issues in Translational Science Research program addresses ethical issues that impede the translation of new discoveries and technologies by developing data and evidence in relevant areas, such as synthetic biology chimeras;

gene editing; organoids; data collection, sharing, and privacy; machine learning and artificial intelligence; business models; citizen science; do-it-yourself science; and behavioral science. This program has garnered sustained interest from members of the translational science and ethics communities, and it has engaged stakeholders in ethical issues in translation.

Program renewal will continue development of data and evidence to inform ethical issues that affect the translation of new discoveries and technologies and approaches to their application to health. The renewal will expand interest areas to include ethical, legal, and societal challenges related to racial and health disparities in the translation of discoveries at individual, community, institution, and society levels. It also will encourage collaboration among bioethicists, legal scholars, social scientists, and translational scientists.

The renewal will extend the Ethical Issues in Translational Science Research program for an additional 5 years. The program will include two submission rounds per year, with only highly meritorious applications in translational science and bioethics research being selected for NCATS' support. The expected result of this concept renewal is to foster sustained focus for translational science and bioethics research; increase the knowledge base addressing ethical, legal, and societal implications of translation of discoveries' application to health; and recognize a professional community of experts.

Discussion

Dr. Harris expressed his support of the extension and expansion of this work, emphasizing the value of bioethics research at a time new resources and technology are abundant and must be introduced ethically and inclusively. He noted the need for more experts in this space, applauding the concept goal to build a professional community of experts in the ethical translation of research.

Ms. Kennedy expressed similar levels of enthusiasm for the concept. She stated that it will be important to determine carefully how equity is defined in this space. She called attention to guiding principles established during a recent series emphasizing that (1) all people have a right to access available, proven, cost-effective treatment; (2) early identification of disease and early treatment are cost effective; (3) individuals have a right to privacy regarding their health information; (4) the field of gene-targeted medicine is changing rapidly; (5) research and new knowledge are valuable to society; and (6) ongoing research can be of direct value to individuals.

Dr. Lo shared his enthusiasm for this initiative and his support of its continuation. He suggested that the number of grant applications could be increased by organizing workshops to which different communities, including policymakers, could be invited. These workshops would be centered on compelling topics, such as the ethics of gene editing and germline editing, the compassionate use of drug candidates, and biomedical privacy. Immediately following the workshops, an RFA can be presented, which could serve to encourage community members who had participated in the workshops to apply and form collaborations with other stakeholders. Dr. Rutter responded that the RFA associated with this program has garnered sufficient attention and attracted many applications; the number of grants awarded through this program is low due to budgetary constraints, not a lack of interest in the program. She added that NCATS leveraged the NIH OD Ethics Program to help support some of this work.

Action Item: Dr. Lo, Council Member, suggested that Dr. Collier and the Office of Translational Medicine explore ways to increase the number of grant applications in the Ethical Issues in Translational Science Research program to engage a broader range of communities.

Dr. McVeary commented on the ethical tension surrounding data donation and ownership, noting that this and similar ethical challenges have appeared rapidly alongside new scientific and technological advancements.

Dr. Summar took part in a Black women's health initiative, through which he found that participation in research is low among certain communities. He noted that participation can be increased if ethical concerns in these areas are addressed. Dr. Summar also recommended that participation in rare disease clinical networks be evaluated and improved where necessary.

Members unanimously approved the Ethical Issues in Translational Science Research renewal concept.

Action Item: Dr. Summar, Council Member, recommended that the Office of Translational Medicine establish a mechanism to ensure that participation in rare disease clinical networks is evaluated and improved as needed.

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

13:30:38 From Andrew Lo to Everyone: Please let us know how Council members can help get you more funding for this program!!

13:33:46 From Kelly Marie McVeary to Everyone: Potential follow up Action, If it is useful: Would it benefit Elaine Collier or Jane Kim to be introduced to the DoD AI Ethics leadership council that was stood up by the Joint Artificial Intelligence Center ("The JAIC")? This group has been convening international panels, working with the White House and the Pentagon, and healthcare innovation is one of JAIC's mission areas. I think they would love to meet Jane Kim and be aware of her project. Happy to make an introduction to the JAIC CTO.

13:37:23 From Marshall Summar to Everyone: For interest <https://www.rarediseasediversity.org/>

CCIA: Soju Chang, M.D., M.P.H., Medical Officer, DCI

The CCIA program was established to stimulate complementary collaborations that build on the strength of the CTSA consortium while generating innovative solutions benefiting translational science. These collaborations are centered on high-risk, high-impact projects that cannot be accomplished by any single CTSA Program Hub. NCATS has funded 47 CCIAs, comprising 16 R21 awards and 31 U01 awards. The awarded projects covered preclinical research, clinical research, clinical implementation, and public health.

One such project was the CCIA U01 Project: Training *Promotoras*/Community Health Workers using Culturally and Linguistically Appropriate Research Best Practices. This project sought to improve the research competency of community health workers by developing and disseminating an online course on research best practices. Increasing research competency enables community health workers to better connect academic researchers with communities, thereby facilitating the relevant, well-conducted research needed to assess and affect health in underserved communities.

The CCIA program, although already successful, can be improved by diversifying the CCIA portfolio across all stages of the translational science spectrum and by building on the collaborative nature of the

funding opportunity with other networks focused on translational science. NCATS proposes this concept to support synergistic activities that will improve the translational research process through collaboration and innovation.

The CCIA concept seeks to enhance collaboration with NIH ICs and other stakeholders, emphasize transformative and high-impact projects that address the missions and strategic goals of NCATS and NIH ICs, and support all phases of innovative and high-impact projects. The CCIA program will require the collaboration of at least three CTSA Program Hubs or at least two CTSA Program Hubs plus at least one other eligible organization.

The concept will emphasize work in late-stage translational science—such as clinical implementation and public health—and it seeks to change the funding mechanism to a performance-based approach driven by measurable milestones. The current R21 and U01 funding mechanisms will be replaced with UG3 and UH3 funding mechanisms, and awards will transition from UG3 to UH3 based on performance. UG3 awards will be for 2 years and focus on the development, demonstration, and feasibility assessment of innovative solutions that address scientific and operational barriers. UH3 awards will be for up to 3 years and focus on the dissemination, implementation, and evaluation of these innovative solutions.

The new CCIA concept will advance translational science through evidence-based approaches, enhance collaboration with NIH ICs and other stakeholders, leverage CTSA Program resources, and enhance the translational process so innovative interventions to improve health can be disseminated more efficiently. This concept is intended to support synergistic activities that improve the translational research process through collaboration and innovation while integrating the CTSA Program with NIH-funded translational research networks and activities that advance translational science.

Discussion

Dr. Lo stated that the CCIA program has been incredibly successful, and it should continue and grow. He mentioned that NCATS should strive to collaborate more frequently with clinicians, scientists, engineers, mathematicians, and other nonclinical innovators. The implementation of new technologies and innovative approaches in medicine results in valuable insights that originate in areas outside the traditional medical research community. Dr. Jackson added that she would like to extend the reach of this concept by targeting the private and government sectors to ensure that all major stakeholders are given an opportunity to guide and participate in the collaborative efforts supported by the CCIA program. Stakeholders from these sectors could be particularly valuable for providing insight and increasing the reach of the dissemination arm of projects. Dr. Chang added that the CCIA program includes processes for including stakeholders from broad areas—such as professional organizations, industry partners, and public health organizations—noting that the project is open to any eligible collaborator. Michael Rosenblatt, M.D., and Dr. Rutter confirmed that no restriction in this program exists that prevents the participation and collaboration of eligible institutions without a clinical component.

Paula K. Shireman, M.D., M.B.A., commented that further clarification around what constitutes an eligible institution for collaboration would be valuable. She also voiced concern about the use of milestones to determine award eligibility and project progression, reminding the Council that some of the research projects done under these award mechanisms do not have clear milestones and take considerable time to reach measurable milestones. Dr. Chang thanked Dr. Shireman for her recommendation and responded that the CCIA program will work with study teams to determine

reasonable and justifiable milestones. Dr. Rutter agreed that milestones can still be used, but with the opportunity for study teams to justify a lack of milestones in certain contexts.

Dr. Summar expressed a desire to increase the seamless free flow of collaboration and project components across CTSA Program sites. He acknowledged that legal agreements and traditional protocols can hinder the streamlining of multicenter projects. Dr. Summar drew attention to the value of extending studies seamlessly to medical centers that cannot conduct academic research but are better equipped to reach diverse patient populations. He noted the need for IRB approval presents difficulties for such an endeavor. Dr. Rosenblatt responded that the CTSA Program is working to circumvent IRB reliance concerns by using the [SMART IRB](#) program. He noted continuing difficulties in this area but indicated that the community has been improving at unifying projects, and he is eager for improvements to continue.

Dr. Weichold would like to encourage applicants to develop platform trials and registries, as well as build such capabilities as point-of-care and outpatient facilities. He recognizes the administrative difficulties inherent in such endeavors and encouraged the CTSA and CCIA programs to perform pilot work to provide examples and resources to facilitate this kind of work.

Dr. Harris asked whether applicants can target the UH3 funding mechanism without first going through the UG3 mechanism. Dr. Chang answered that the application phases must address both funding mechanisms. Dr. Harris recommended that the CCIA program provide clear guidance regarding the ideal number of collaborators for the different funding mechanisms.

Members unanimously approved the CCIA program concept.

Machine-Assisted Approaches to Shortening the Diagnostic Odyssey for Rare Diseases: Anne Pariser, M.D., Director, ORDR; Lili Portilla, M.P.A., Director, OSA

The years-long delay in diagnosis and frequent misdiagnosis of rare diseases (i.e., the diagnostic odyssey) can last decades. NCATS proposes in this concept, via the Small Business Innovation Research (SBIR) program, to accelerate and improve diagnoses for rare diseases using machine learning approaches that are readily usable in front-line clinical settings.

One objective of this concept is to develop machine-assisted approaches that accelerate and improve diagnoses for hard-to-diagnose patients and are applicable to a broad array of rare diseases. The strategies that are proposed or developed must be usable or adaptable to more than one health care setting, EHR, or database. The strategies also ideally would be usable and accessible by front-line clinicians and readily integrated into the clinical workflow of multiple care settings.

Concept coordinators strive to progress in the following key areas:

- Permit early identification and escalation of patients at high risk for a rare disease through data mining or via remote assessment in an office or home setting.
- Permit collection, integration, or assessment of data points from multiple sources.
- Permit more accurate assessment of the rare disease patient's overall medical utilization through new measures enabled through machine-assisted approaches.

NCATS promotes the idea that small businesses, via the SBIR program, can provide innovative solutions to the identification of patients who are at high risk of having a rare disease or who have been misdiagnosed or are undiagnosed. Success in this area would be achieved via the development of an

easy-to-use tool that is valuable to front-line clinicians and integrated into clinical practice, and for which accelerated diagnostic timelines can be shown.

Accelerating rare disease diagnosis using available data in EHR or health care system databases could shorten the diagnostic odyssey, save resources through targeted disease-specific care, limit irreversible complications of disease by enabling timely intervention, and change the research environment for rare diseases such that all patients with a rare disease have a chance for disease-modifying therapy.

Discussion

Ms. Lili Portilla noted that this concept proposes to utilize an SBIR grant funding announcement.

Ms. Kennedy voiced concern surrounding equitable representation in the statistics for diagnostic odysseys. She recommended careful thought surrounding the patient communities that will be identified and detected, keeping in mind the need to support those communities and properly educate and prepare providers who will be a part of this initiative. Ms. Kennedy also suggested that NCATS consider a new social contract addressing privacy, consent, data ownership, and care implementation that will correspond with diagnoses facilitated by this program.

Dr. Kretzler stated that the concept is compelling and supports the use of SBIR as an effective mechanism by which the concept goals can be achieved. He noted the potentially devastating consequences that can result from false-positive diagnoses, suggesting that any project that proposes to address many diseases simultaneously be tested extensively and in a wide range of different environments to avoid false positives. He added that SBIR awards rarely reach the intended audiences effectively because biotech and information technology communities rarely access NIH news releases that announce SBIR awards. These communities can be reached by professional organizations. Last, Dr. Kretzler recommended that the algorithms and platforms developed via this program be optimized to utilize NCATS resources.

Dr. Summar suggested that this effort be linked with existing efforts in the same area. He stated that collecting disease phenotypes and clinical courses of patients in a standardized way will be critical to the development of patient registries serving this effort.

Dr. Lo recommended building on energy in this area within the biomedical ecosystem. Diagnosing rare diseases more quickly and accurately will increase the market for biotech and pharmaceutical companies, which can align the goals of this effort with those of the private sector. Many stakeholders in this area would welcome an opportunity to collaborate with NCATS if a mechanism were in place for such collaborations. Collaborations with patient advocates could be similarly valuable. Dr. McVeary recommended reaching out to leading life sciences early-stage investors because they often are aware of life sciences technology long before members of the public. Ms. Portilla responded that the SBIR mechanism encourages the involvement of outside expertise; she noted that NCATS could highlight that component in the funding announcement and provide sources on where relevant expertise can be found.

Members unanimously approved the Machine-Assisted Approaches to Shortening the Diagnostic Odyssey for Rare Diseases concept.

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

14:23:26 From Marshall Summar to Everyone: Some of the work we have been doing.

14:23:30 From Marshall Summar to Everyone:

[https://www.thelancet.com/journals/landig/article/PIIS2589-7500\(21\)00137-0/fulltext](https://www.thelancet.com/journals/landig/article/PIIS2589-7500(21)00137-0/fulltext)

14:29:09 From Matthias Kretzler to Everyone: <https://amia.org/>

14:29:56 From Marshall Summar to Everyone:

<https://www.globalrareiseasecommission.com/AboutUs> for reducing diagnosis time.

14:37:33 From Andrew Lo to Everyone: globalgenes.org is another organization to consider

14:38:05 From Annie Kennedy to Everyone: As is EveryLife Foundation - I'd be remiss not to mention that www.EveryLife.org

NIH HEAL Trans-Agency Effort to Speed Scientific Solutions to Stem the National Opioid Public Health Crisis: Christine Colvis, Ph.D., Co-chair, HEAL Preclinical/Translational Research in Pain Management

The final three concepts that were presented focused on the NIH HEAL Initiative. These HEAL programs include different domain areas of research that are centered broadly on opioid use disorder, pain management, the development of nonaddictive therapies for pain management, and overdose.

The HEAL Initiative comprises more than 25 research programs, and the NIH receives approximately \$500 million per year of sustained research investment for the programs. The programs are governed via a trans-NIH governance structure, and partnerships across government, communities, and the private sector contribute to the NIH HEAL Initiative. Twelve NIH ICs are leading the studies, and 20 NIH ICs are collaborating on studies. NCATS plays a leadership role in three domains of the HEAL effort: preclinical and translational research in pain management, clinical research in pain management, and novel medications options.

Previously approved NIH HEAL Initiative programs include the HEAL Pain Management Effectiveness Research Network (ERN) and the Fiscal Year (FY) 2022 Concept for a Translational Training Opportunity that was presented during the May 2021 Council meeting. Additional FY 2022 concepts presented today are (1) HEAL & DDPP: Illuminating the Understudied Druggable Proteome, (2) HEAL New Innovator Awards, and (3) Trial Innovation Network (TIN) Infrastructure for the HEAL Pain Management Effectiveness Research Network (ERN).

Illuminating the Understudied Druggable Proteome: Karlie Sharma, Ph.D., Program Officer, DDPP

The Illuminating the Understudied Druggable Proteome concept will encourage research on understudied proteins within commonly drugged protein families to identify new targets for human disease. This will lay the groundwork for the exploration of these new targets for drug development by providing support for short-term projects that collect preliminary data on understudied proteins. This is a general concept for both NCATS and the NIH HEAL Initiative, and funding likely would come from both sources. The project will be disease agnostic, potentially covering all human diseases but focusing on NCATS and NIH HEAL Initiative priority areas, such as rare diseases and proteins associated with pain, addiction, and overdose.

Successes from the Common Fund IDG program have demonstrated that small research awards around understudied proteins stimulate more research on “new” proteins. The target landscape for drug

development would be larger, leading to the development of more treatments for more diseases. Success will be evaluated by monitoring the funding of new grants around targets studied under this initiative and by monitoring publications released around understudied targets.

NCATS proposes this concept to expand the target landscape for drug development by providing a needed opportunity for the collection of preliminary data around the role of understudied druggable proteins in human disease and biologic processes. Identifying new targets associated with human disease is a critical first step in the development of novel, more efficacious treatments.

Discussion

Theodore R. Holman, Ph.D., expressed enthusiasm for this initiative, noting that providing funding for the collection of preliminary data is valuable for initiating work in this area. He asked about the funding program of this concept. Dr. Sharma answered that the funding program utilized by IDG is an R03 mechanism, which provides \$100,000 for one year; she stated that a similar approach might be used for this concept's funding mechanism. Drs. Holman, Ranganathan, and Summar cautioned that \$100,000 might not be sufficient funding to enable significant progress in this area.

Dr. Ranganathan suggested that additional druggable protein families of interest could be identified via a request for information (RFI) to the community. Dr. Jackson stated that an additional RFI could be released to acquire approaches and information from the pain and addiction communities to better serve the objectives of the NIH HEAL Initiative.

Dr. Ranganathan asked how investigators are expected to connect proteins to diseases via work supported by this concept. Dr. Sharma responded that investigators could perform such work as developing mouse models or performing yeast screening assays to identify functions for particular proteins, which then could be connected to diseases using computational methods. Dr. Ranganathan asked whether proteins that already were associated with diseases would be eligible under this concept. Dr. Jackson added that restricting this work to proteins that are fully unconnected to diseases might be inappropriate for NIH HEAL Initiative work, which focuses on pain and addiction. Dr. Holman urged Dr. Sharma to remain flexible in terms of the protein families targeted by this work. Dr. Sharma answered that associated proteins could be eligible if they are classified as understudied.

Dr. Summar asked how some of the large databases around protein modeling will be incorporated into these efforts. He also asked how this work will build into a resource that others can use. Dr. Sharma responded that [Pharos](#) serves as such a database and has been incorporated into much of the work leading to this concept.

Members unanimously approved the Illuminating the Understudied Druggable Proteome concept.

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

15:29:32 From Matthias Kretzler to Everyone: Pharos is missing organismal context of model systems you are developing in NCATS with organ/trials on a chip. As these platform have been molecularly mapped or are being mapped projecting this information into pharos will allow to prioritize molecules for analysis.

15:32:34 From Karlie Sharma to Everyone: Thank you Matthias, that is a great point. I will make a point of speaking with the Pharos team to see how we can incorporate that data into Pharos.

15:34:16 From Matthias Kretzler to Everyone: you could even consider to provide incentives to Organ on a chip to submit molecular maps of the platforms (cell type specific transcriptomes / proteomes).

15:36:40 From Karlie Sharma to Everyone: Yes I think that would be something for us to consider, I am taking notes on this and will explore further with the Pharos team.

15:42:21 From Joni Rutter to Everyone: @Matthias - agree with Karlie —great ideas. We can circle up with Dan Tagle's team, too, to work on the organ on a chip angle.

HEAL New Innovator Awards: Christine Colvis, Ph.D., Director, DDPP

HEAL New Innovator Awards will support unusually creative early-career stage investigators from underrepresented backgrounds who propose innovative, high-impact research within the NIH HEAL Initiative domains of pain, addiction, or overdose. The emphasis of these awards is on the idea and the investigator, rather than the specific project. These awards could be applied to basic, translational, or clinical science.

The HEAL New Innovator Award already has been established at the NIH, but this application is the first time that it will be focused on the NIH HEAL Initiative and underrepresented groups. Applications for this award will not contain a detailed experimental plan or preliminary data. Instead, they will focus on the potential of both the innovative idea and individual investigator. The major components of the application will be the significance of the project and the problem that it seeks to address, the general approach that will be applied to address the problem in HEAL domains, an explanation of how the project is unusually innovative, and the qualities and experiences of the investigators that qualify them to pursue such research.

NCATS proposes this concept to foster original ideas from early-stage investigators in the HEAL fields and increase diversity within biomedical science. Success will be evaluated by monitoring the development of innovative approaches to treat pain, addiction, and overdose, as well as by examining the career trajectories of early-stage investigators from underrepresented groups who receive these awards.

Discussion

Dr. Jackson noted the increasing effects of the substance use epidemic occurring alongside the COVID-19 pandemic and recommended that this program address the growing need to curb substance misuse. She noted the larger effects of this epidemic on underrepresented groups and stated that building a workforce composed of underrepresented investigators who are addressing substance use disorder, pain management, and other HEAL domains is critical for increasing health equity. Keith J. Mueller, Ph.D., recommended that the research announcement and award description specifically include language encouraging investigators to focus on innovations serving underrepresented populations. Dr. Jackson added that the initiative could be improved by emphasizing that the clinical aspect of the project includes a call for creative new approaches to working at community and stakeholder levels.

Dr. Jackson recommended that the program include the establishment of investigator cohorts and components focused on career development to support the continued development of award recipients. Dr. Rutter agreed, noting that investigator cohorts could result in the cross dimensionality of

basic, translational, and clinical work among the different innovators. She also suggested that early-stage investigators could be contacted via different mechanisms, such as by reaching out to different associations to find innovators from underrepresented groups. Dr. Mueller added that early-stage investigators could be reached via different institutions and networks, such as the CTSA network.

Action Item: Dr. Jackson, Council Member, recommended establishing HEAL New Innovator Awards investigator cohorts and other program components focused on career development to support the continued growth of award recipients.

Dr. McVeary stated that this program is vitally important and the awards have the potential to be career-making for the recipients. She recommended including metrics for success beyond peer-reviewed publications to encourage recipients to focus on translational activities leading to commercial development, which can be more beneficial to communities than journal articles.

Dr. Summar noted that early-stage investigators will not have the means to access established and valuable resources, and he recommended that award recipients be provided training and vouchers to access resources.

Dr. Jackson recommended polysubstance use, rather than exclusively opioid use, be included in the focus of this concept. Dr. Rutter noted that the HEAL Initiative is considering polysubstance use in its efforts.

Members unanimously approved the HEAL New Innovator Awards concept.

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

15:55:22 From Kelly Marie McVeary to Everyone: Follow Up to the HEAL New Innovator Award Discussion: You asked about outreach. In addition to traditional outreach mechanisms, you might wish to reach out the newer “bio design” programs that are starting to mint a new kind of scientist-engineer. Some of the state universities are following the model established by Stanford’s wildly successful biodesign program, and I see a lot of diversity in the faculty and graduate students involved.

TIN Infrastructure for the HEAL Pain Management ERN: Yolanda Vallejo, Ph.D., Program Director, DCI

One way the NIH HEAL Initiative seeks to stem the opioid crisis is through a focused effort on understanding, managing, and treating pain. Using existing TIN infrastructure, the HEAL Initiative established the ERN to conduct clinical trials addressing pain management questions for multiple pain conditions in one network to confront a need for safe and nonaddictive treatments that alleviate pain. NCATS proposes this concept to continue support of TIN infrastructure through a dedicated FOA for ongoing and future trials in the HEAL ERN. Funding for this concept will be provided by the NIH HEAL Initiative.

The HEAL ERN has the following objectives:

- Compare the effectiveness of existing safe, nonaddictive therapies or ways to deliver current therapies.
- Strengthen and inform current guidelines for pharmacologic and nonpharmacologic treatments for acute and chronic pain.
- Provide patients and practitioners with a suite of effective strategies to alleviate pain and reduce reliance on opioids.

- Manage acute and chronic pain in people from diverse communities.
- Improve patients' quality of life.

The TIN facilitates the attainment of these objectives by providing infrastructure through three key components: Trial Innovation Centers, Recruitment Innovation Centers, and CTSA Program Hubs. The TIN provides many services to ensure the successful implementation and completion of ERN trials.

The ERN and TIN networks coalesce into a synergistic structure through which individual NIH HEAL Initiative awards support trial study teams and participant costs. Trials address pain management questions that are of interest to multiple NIH ICs. The NCATS TIN provides clinical support, biostatistical coordination, and recruitment and retention support. Trials are conducted within and outside of CTSA Program Hubs to allow the recruitment of diverse patients with multiple pain conditions.

The HEAL ERN currently is conducting five clinical trials:

- Effectiveness of an mHealth Psychosocial Intervention to Prevent Transitions from Acute to Chronic Postsurgical Pain in Adolescents
- Integrated Treatment for Veterans with Co-occurring Chronic Pain and Opioid Use Disorder
- Tailored Non-pharmacotherapy Services for Chronic Pain: Testing Scalable and Pragmatic Approaches
- A Sequenced Strategy for Improving Outcomes in Patients with Knee Osteoarthritic Pain
- Optimizing the Use of Ketamine to Reduce Chronic Postsurgical Pain

NCATS' TIN is providing clinical, data, recruitment and retention, and biostatistical support in all clinical trial phases. The trials span multiple demographics, pain conditions, and NIH ICs. Despite COVID-19 delays, all the trials have met their required milestones and have been approved to move forward.

Continued support of TIN infrastructure will enable HEAL ERN study teams to complete ongoing studies and facilitate future NIH HEAL Initiative studies by addressing critical roadblocks innovatively, leveraging the expertise and resources of the CTSA Program, and accelerating the translation of interventions into therapies in real-world settings. Trial results will advance NIH HEAL Initiative efforts to stem the opioid crisis by identifying safe, nonaddictive interventions and management strategies for pain; generating an evidence base to inform treatment guidelines for acute and chronic pain; and providing patients and practitioners with a suite of strategies to alleviate pain and reduce reliance on opioids.

The goal of this concept is to provide continued support of existing TIN infrastructure that is enabling ongoing and new trials in the HEAL ERN. Funding for this concept will be provided by the NIH HEAL Initiative.

Discussion

Dr. Jackson stated that she favors continued support for the TIN and highlighted that this concept is a practical extension of the program. She emphasized the component of this concept focused on translational science rather than translational research, noting that studying the process of translational science and evaluating the cost-effectiveness of these trials will be critical to the concept's success.

Dr. Mueller expressed enthusiasm for the concept in general and emphasized his approval of the potential for new trials to be included if the existing TIN infrastructure continues to receive support. He

also underscored that it will be critical to support trials that reach diverse communities and to understand how trials include people from diverse backgrounds and cultures.

Dr. Shireman mentioned that having an established network and TIN infrastructure will decrease the time and expense needed to perform NIH HEAL Initiative trials and other NIH trials of interest. She commended the TIN-supported trials that maintained progress despite the disruption of the COVID-19 pandemic and suggested that remote capabilities established in response to the COVID-19 pandemic can be helpful for recruiting participants in remote areas. She is eager to see which other trials will utilize the TIN network.

Dr. Summar asked whether any efforts are underway to establish standardized instruments and tools, especially digital tools, for pain trials and pain studies. Dr. Vallejo responded that, as part of the HEAL Initiative, efforts to establish standardized tools and terms are ongoing. For example, the HEAL Initiative encourages the use and testing of a digital overlapping pain tool that was developed recently.

Dr. Kretzler added that the FDA requires validation of such digital tools, which could facilitate remote trials and expand the reach of clinical trials. Dr. Weichold stated that small trials do not have sufficient participation to draw key conclusions, and a lack of validated and standardized tools prevents decision-making from a regulatory perspective. He recommended that these issues be addressed by NIH programs. Dr. Vallejo noted that the NIH HEAL Initiative actively is developing a data ecosystem that is centralized across the NIH HEAL Initiative to confront those concerns.

Members unanimously approved the TIN Infrastructure for the HEAL Pain Management Effectiveness Research Network ERN concept.

XII. PUBLIC COMMENTS

Comments from the public were accepted until October 9, 2021 and will be appended to the minutes.

XIII. ADJOURNMENT OF THE OPEN MEETING

Dr. Rutter thanked the participants for their input. The next meeting is scheduled for January 20–21, 2022. Dr. Rutter adjourned the meeting on September 24, 2021, at 4:06 p.m. EDT.

CERTIFICATIONS

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

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

Date

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

Date