

**Department of Health and Human Services
National Institutes of Health**

**National Center for Advancing Translational Sciences Advisory Council
and
Cures Acceleration Network Review Board**

**Minutes of Joint Meeting
May 10, 2018**

The National Center for Advancing Translational Sciences (NCATS) Advisory Council and the Cures Acceleration Network (CAN) Review Board held a joint meeting in open session on May 10, 2018, convening at 8:30 a.m. ET, in Conference Room 10, Building 31, on the National Institutes of Health (NIH) main campus. Christopher P. Austin, M.D., NCATS Advisory Council chair, and G. Lynn Marks, M.D., CAN Review Board chair, led the meeting. In accordance with Public Law 92-463, the session was open to the public.

Following the joint meeting, the NCATS Advisory Council met in closed session for the review and consideration of grant applications. The CAN RB and NCATS Advisory Council met in joint closed session to discuss internal operational issues.

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.	Valerie Montgomery Rice, M.D.
Daniel L. Hartman, M.D.	Megan O'Boyle
Katharine Ku, M.S.	Alan D. Palkowitz, Ph.D.
Geoffrey Shiu Fei Ling, M.D., Ph.D.	Harry P. Selker, M.D., M.S.P.H.
Brad Margus, M.B.A.	Anantha Shekhar, M.D., Ph.D.
G. Lynn Marks, M.D.	Stephen P. Spielberg, M.D., Ph.D.
Kalpana M. Merchant, Ph.D. (by telephone)	

Representative Members

None present

Guest Expert

Matthew Might, Ph.D., University of Utah

Ex Officio Members

Naomi Tomoyasu, Ph.D., Department of Veterans Affairs (representative for Rachel Ramoni,
DMD, ScD)

CAN REVIEW BOARD MEMBERS PRESENT

Chair

G. Lynn Marks, M.D., Senior R&D Advisor, Biomedical Advanced Research and Development Authority (BARDA), ASPR/HHS; and Chairperson, CAN Review Board

Vice Chair

Ronald J. Bartek, M.A., Co-Founder and Founding President, Friedreich's Ataxia Research Alliance

Executive Secretary

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

Board Members

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Representative Members

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Ex Officio Members

Naomi Tomoyasu, Ph.D., Department of Veterans Affairs (representative for Rachel Ramoni, DMD, ScD)

Frank F. Weichold, M.D., Ph.D., Food and Drug Administration (representative)

OTHERS PRESENT

Anne Berry, M.P.P., American Association of Medical Colleges

Karina Davidson, Ph.D., M.A.Sc., Columbia University

Rachel Levinson, M.A., Arizona State University

Joshua Smyth, Ph.D., Penn State University

NCATS leadership and staff

I. CALL TO ORDER, OPEN SESSION

Christopher P. Austin, M.D., and G. Lynn Marks, M.D., called the meeting to order. Dr. Austin welcomed members and guests to the 18th meeting of the NCATS Advisory Council and the 23rd meeting of the CAN Review Board. He reminded attendees that the open session was being videocast. Dr. Marks extended a welcome on behalf of the CAN Review Board, and Dr. Austin introduced the members of the Council and the Board and previewed the meeting agenda.

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

Anna L. Ramsey-Ewing, Ph.D., informed the group that the NCATS Advisory Council and CAN Review Board will hold joint meetings on September 27, 2018, and on January 10, May 16, and September 19 in

2019. The 2020 joint meetings will be convened on January 16, May 14, and September 17. The CAN Review Board will meet by teleconference on December 14, 2018; December 13, 2019; and December 11, 2020.

III. INTRODUCTION OF NEW STAFF

Christopher P. Austin, M.D., and other NCATS leaders introduced new NCATS staff members:

- Anne Pariser, M.D., previously served as the deputy director of the Office of Rare Diseases Research (ORDR) and is now leading the office as its director.
- Penny Burgoon, Ph.D., has been the acting director of the Office of Policy, Communications and Education. She has now taken on the role of director.
- Donald Lo, Ph.D., is now the chief of the Therapeutics Development Branch within the Division of Pre-Clinical Innovation (DPI).
- Clare Schmitt, Ph.D., is now the deputy director of NCATS' Division of Clinical Innovation (DCI).
- Erica Rosemond, Ph.D., now serves as the deputy director of the Clinical and Translational Science Awards (CTSA) Hub Program.
- Carol Lambert, Ph.D., has been the acting director of the Office of Scientific Review within the Office of Grants Management and Scientific Review. She is now the office director.
- Also new to the Office of Scientific Review is Jing Chen, Ph.D. has joined NCATS as a scientific review officer.

IV. DIRECTOR'S REPORT: Christopher P. Austin, M.D., Director, NCATS

Dr. Austin presented the main points of his report: a change in personnel, translational science highlights, and updates on NCATS' budget, policy and communications.

Personnel Change

Dr. Austin announced that Pamela McInnes, M.Sc., D.D.S., is retiring at the end of May 2018. She has made myriad contributions to NCATS as the deputy director of NCATS from 2013 to 2018. A national search is ongoing for her replacement. In the meantime, Danilo Tagle, Ph.D., M.S., will step in as acting deputy director.

Dr. Austin said that Dr. McInnes is considered one of the founders of this organization, as she joined during the very early days of NCATS. She has helped NCATS navigate and overcome many challenges, ensuring that NCATS became a place where very talented people from many disciplines work together.

Dr. Austin presented Dr. McInnes with a commemorative plaque in recognition of her service to NCATS, NIH and patients. Dr. McInnes thanked Dr. Austin and said that he is an extraordinary leader who has remained optimistic even under the most difficult circumstances. She also said that she has been with NIH—a place of extraordinary opportunities—for 28 years.

Addressing the NCATS Advisory Council, the CAN Review Board and NCATS staff, Dr. McInnes thanked her colleagues for their hard work and commitment. She said that NCATS is not fixed in place; it is strong and malleable, capable of thriving even in uncertain times. In closing, she said, "You will carry on and make your own road."

Translational Science Advances: Selected Highlights

- **Illuminating the Druggable Genome (IDG).** This Common Fund program is led by NCATS and the National Institute of Diabetes and Digestive and Kidney Diseases. As stated in a recent article in *Nature Reviews*, “The systematic collection and processing of a wide array of genomic, proteomic, chemical and disease-related resource data by the IDG Knowledge Management Center have enabled the development of evidence-based criteria for tracking the target development level of human proteins.” The IDG Knowledge Management Center, which is run by DPI, is a remarkable resource broadening the therapeutic landscape in evaluating novel targets, their role in disease, and the potential utility of new interventions, particularly biologics.
- **Tissue Chips 2.0.** The [Tissue Chips in Space](#) initiative is a partnership between NCATS and the Center for the Advancement of Science in Space (CASIS). The aim is to adapt and refine chips for on-flight experiments at the International Space Station. The goal of the [Tissue Chips for Disease Modeling and Efficacy Testing Projects](#) is to develop microphysiologic models to understand disease physiology, assess efficacy and toxicity of candidate therapies, and establish pre-clinical foundations for clinical trials. This milestone-driven program uses the UG3/UH3 mechanism. The program is slated to run from 2018 to 2023. Ten NIH Institutes and Centers (ICs) and Offices are now co-funding the program; NCATS is providing less than one-third of the total funding. Dr. Austin showcased the principal investigators and the 14 disease models they are working on.
- **NIH Common Fund Somatic Cell Genome Editing (SCGE) Program.** This program is designed to accelerate the translation of genome-editing technologies to the clinic for treatment of genetic diseases. Philip John (P.J.) Brooks, Ph.D., serves as the program coordinator. The SCGE program is soliciting applications to address needs for cell- and tissue-specific delivery systems, error-free editing machinery, standard assays for measuring off-target effects, and long-term cell tracking. Dr. Austin emphasized that the program is not just about CRISPR/Cas9 gene editing, but also zinc fingers and other technologies. This initiative applies to gene editing, both *in vivo* and *ex vivo*, as and gene transfer,. He announced that NCATS and the FDA Center for Biologics Evaluation and Research are co-sponsoring a workshop entitled [“The Growing Promise of Gene Therapy Approaches to Rare Diseases,”](#) slated for August 20–21, 2018, on the NIH campus.
- **CTSA Program.** Dr. Austin presented several program highlights. First, the Communications Working Group of the CTSA Program Steering Committee is improving bidirectional communication between CTSA Program investigators and NCATS as well as cross-consortium communication. Second, the annual CTSA Program meeting in April 2018 drew more than 300 scientists from around the country. Third, the CTSA Program is setting up the Clinical Data to Health (CD2H) initiative to accelerate innovative informatics to improve clinical care and enable the program to connect and collaborate more efficiently. Several new CD2H platforms are making informatics resources easily discoverable and accessible throughout the CTSA Program. These tools include Synapse, an innovation platform that allows for collaborative multimodal data analysis and workflows; Cielo for software interoperability and discovery platform for the CTSA Program hubs; and CTSAsearch for identifying skills and expertise across the CTSA Program Consortium and the broader biomedical research community to foster collaborative science.
- **Rare Diseases Clinical Research Network (RDCRN).** Two funding opportunity announcements (FOAs) will be reissued for [RDCRN consortia](#) and a [coordinating center](#). Dr. Austin explained that 10 ICs are supporting the RDCRN in addition to NCATS. Each consortium has at least one patient advocacy group as a partner.

Administrative, Policy and Budget Updates

- **Fiscal Year (FY) 2017 and 2018 Budgets.** Between October 1, 2017, and March 23, 2018, the federal government operated under five different continuing resolutions. Two brief shutdowns occurred during that period. The Consolidated Appropriations Act for FY 2018 provides a budget of \$742.4 million for NCATS, an increase of \$36.5 million over the 2017 budget. However, CAN received no increase. Dr. Austin pointed out that because of the way CAN fits into the budget, its relationship to the overall NIH budget may not be clear. NIH leaders are aware of this situation and will be focusing on this as they work on the budget.
- **FY 2019 Budget Request.** The NIH's request was \$35.5 billion, which would include moving three agencies to NIH: The National Institute for Research on Safety and Quality; the National Institute for Occupational Safety and Health; and the National Institute on Disability, Independent Living, and Rehabilitation Research. NCATS' request was for \$685.1 million. The request includes additional funding flexibility for CAN.
- **Highlights in NCATS Communications.** Dr. Austin wrote a commentary that was published in *Nature Reviews Drug Discovery*. Entitled "Translating Translation," the piece clarified the distinctions between translation, translational science and translational research. In addition, NCATS' communications team produced a video on the Stem Cell Translation Laboratory explaining how induced pluripotent stem cells can generate all human cell types to repair or replace cells or tissues.
- **Appointment of the NCATS Director as the NIH Liaison to the National Aeronautics and Space Administration (NASA).** Dr. Austin said that NIH and NASA have had a working relationship since 1998, established under a set of memoranda of understanding. In January 2018, Dr. Austin was appointed as the NIH liaison to NASA. NCATS' role has included stewardship of a trans-NIH working group to identify potential areas of programmatic overlap, participation in meetings with high-level leaders in the Department of Health and Human Services to develop an umbrella interagency agreement based on an NIH template, and an NIH portfolio analysis of funded and unfunded applications that might be relevant to NASA's mission.
- **New NIH Initiative to Address the Crisis of Opioids.** Helping to End Addiction Long-term (HEAL) is a new initiative supported by a total of \$1.1 billion for FY 2018 and FY 2019. Dr. Austin said that the HEAL priorities most relevant to NCATS include the development of new nonaddictive treatments for pain, establishment of a clinical trial network for chronic pain, improved therapeutic approaches to addiction, and evaluation of treatments and consequences of neonatal opioid withdrawal syndrome. The CTSA Program hubs are ready to engage in HEAL.

Discussion

Brad Margus asked when it might be possible to say that tissue chips accelerated development of a therapeutic or led to more rapid termination of a development program. What evidence could show that this initiative made a difference? Dr. Austin replied that the first tissue chips developed under this program are now in the validation stages and are being offloaded to the private sector for production. By collaborating with the pharmaceutical industry through the IQ Consortium, the transition from NIH to industry is already underway. Dr. Tagle said that the program will end in 2023, by which time the "commercial part" should be in the private sector, and the "science part" should be residing in other ICs. In terms of disease, sometime in the fall of 2018, data from tissue chip-based technology will be used for the first time in an approval process for a pre-clinical testing process. The Food and Drug Administration (FDA) has set up a core facility to understand the technology and its opportunities and limitations. The FDA has been a collaborator since the inception of the program. Frank Weichold, M.D.,

Ph.D., underscored the importance of informing the world that NCATS was the impetus behind the Tissue Chip program. The FDA is highly interested in observing how the tissue chips are adopted.

Dr. Austin suggested including a presentation on commercialization activity around the Tissue Chip program.

In reviewing the CD2H locations and investigators, Valerie Montgomery Rice, M.D., noted little diversity in the ethnic/racial composition of the CD2H teams and their geographic locations. Dr. Montgomery Rice emphasized the importance of intentionality when setting scoring standards to ensure that funded applications are inclusive and representative of the U.S. population. Those are key metrics that could lead to outcomes required to improve the nation's health. Dr. Austin said that the CD2H teams were selected on the basis of their application scores, and he said he appreciated Dr. Montgomery Rice's challenging words, and he underscored NCATS' commitment to doing things the right way.

Ronald Bartek, M.A., commented on a \$17 million [FDA program](#) supporting natural history studies of rare diseases. Some of the resources will go toward surveillance activities. Much effort will go toward developing new technologies to assess how well patients are feeling and functioning in the real world. The RDCRN and the FDA Center for Drug Evaluation and Research could form a powerful partnership.

Dr. Weichold and Dr. Pariser volunteered to learn more about the FDA's support of natural history studies of rare diseases and explore opportunities for RDCRN to partner with the FDA.

Dr. Marks asked about the degree of flexibility within the NCATS budget and about the possibility of enhancing CAN funding. Stephen Seidel, deputy director of the Policy Branch in the NCATS Office of Policy, Communications and Education, said that when CAN was authorized, the Congress stipulated that a specific amount has to be budgeted for CAN through a separate appropriation; NCATS cannot shift funds to CAN. Dr. Austin mentioned CAN's Other Transactional Authority, which could provide significant headway with challenging biomedical problems.

Mr. Margus spoke about a lack of progress with programs for developing new treatments for nicotine addiction. The science of nicotine addiction is compelling, but venture capitalists have little interest in development programs for addiction indications. Perhaps NCATS could forge a path for translational/clinical development of new treatments. Dr. Austin mentioned a program at the National Institute on Drug Abuse focused on pursuing new treatments for addiction.

Regarding the opioid crisis, Geoffrey Ling, M.D., Ph.D., said that this problem has been around for a long time, but it is more prominent because it has moved into new populations. However, the list of priorities is the same as ever. What could NCATS do that would be innovative? Dr. Austin said that NCATS is developing a variety of novel approaches, and one has been approved internally. NCATS is striving to familiarize leaders of other ICs with the CTSA Program to help them understand how the program could help jump-start clinical research to test new approaches to prevent and treat opioid addiction.

At the next joint meeting, Dr. Austin volunteered to present more information about NCATS' innovative proposals for tackling the opioid crisis.

Matthew Might, Ph.D., observed that many rare diseases involve increased or decreased sensitivity to pain; perhaps there would be some opportunities to apply knowledge from rare diseases research to help meet the need for more and better pain treatments.

Dr. Montgomery Rice asked about the barriers and challenges for addressing addiction. How could the NCATS Advisory Council build bridges to advance cutting-edge research? Dr. Austin said the challenges are threefold. First, some hesitation is likely due to the need for systems change. Second, many researchers and clinicians want fast answers, so they tend to rely on existing tools rather than

experiment with new approaches. Third, NIH is a siloed organization; each IC is used to operating in its own sphere, whereas the NCATS model relies on collaboration and sharing. Dr. Austin encouraged the Council members to engage with the categorical ICs and recommend partnering with NCATS.

V. NIH COMMON FUND UPDATE: SCIENCE OF BEHAVIOR CHANGE: Elaine Collier, M.D., Senior Advisor to Director, Immediate Office of Director, NCATS

Elaine Collier, M.D., introduced a new Common Fund program, the [Science of Behavior Change \(SOBC\)](#), which focuses on behavior change research—a systematic approach to behavior change. The SOBC team members come from almost all the NIH ICs.

Although behaviors are among the most important factors in determining whether people will live long, healthy lives, most people find it difficult to make positive lasting behavior changes. Researchers need to identify mechanisms that help make behavior change efforts successful to find out what works—and what does not.

A major focus of SOBC is on developing measures for putative targets (e.g., executive function). Assays and protocols are incorporated into SOBC-supported projects to build an evidence base. The community has been very enthusiastic about integrating experimental medicine approaches into behavior change research.

The SOBC program funded eight projects as well as a resource and coordinating center for outreach and dissemination of assays. The projects cover a range of targets and approaches.

Resources: NIH Science of Behavior Change Network: Karina Davidson, Ph.D., M.A.Sc., Vice Dean of Organizational Effectiveness, Executive Director of the Center for Behavioral and Cardiovascular Health, and Professor of Medicine and Psychiatry, Columbia University

Behavior change is actually the rubric under which biomedical interventions succeed or fail, according to Karina Davidson, Ph.D., M.A.Sc. Interventions may require changes in physician behavior or patient behavior or both. Behavior change is needed to integrate innovations into care.

Dr. Davidson spoke about the common methods used in the SOBC program for understanding behavior change. The validation process begins by identifying the mechanism, measuring the mechanism and influencing the mechanism, leading to mechanism change and ultimately behavior change. Self-regulation, for example, is a basic mechanism that underlies much of behavior change. Temporal discounting is the degree to which one favors small rewards now instead of larger rewards later. Temporal discounting can be measured using apps that present a computerized economic task to assess the degree to which the subject favors smaller rewards now versus larger rewards in the future. To influence temporal discounting, one can use episodic future thinking, which requires thinking about future events in specific and detailed ways. If an intervention mitigates discounting, then the researcher has identified a mechanism underlying successful behavior change.

Dr. Davidson presented background information on the SOBC Resource and Coordinating Center ([scienceofbehaviorchange.org](#)), which is a “digital destination” for scientists who want to understand the program, view the method framework, access assays and share insights. It also provides the general public with information about behavior science and behavioral change research. The [Measures Repository](#) also resides here.

The validation process uses one basic common pathway. For each target, a measure must be validated. SOBC is developing a repository of validated measures that serves as a resource for the scientific community. So far, 113 measures are in the repository. A researcher can select a domain and then click

on a button to access a measure. Links to the Open Science Framework reveal documentation on the domain. Then, the experiment can be launched as a computer test or as a Word document.

Dr. Davidson highlighted several recent outreach activities. Junior investigators in the field of behavior change participated in a workshop during which they adopted a measure or target and wrote a proposal or paper to study the putative mechanism in a new setting or a new population, or with a new health behavior. They could map their research question onto the SOBC method.

The SOBC Network aims to increase value and reduce waste in research. If upcoming scientists think about targets and validated measures, then we will start to have cumulative science in the SOBC field.

Discussion

Dr. Austin asked whether Dr. Davidson had considered identifying targets and validating measures to assess behavioral change *in scientists*. Dr. Davidson thought this would be possible. The immediate proximal target could be something along the lines of how many times SOBC is mentioned in proposals and publications before and after workshops, for example.

Anantha Shekhar, M.D., Ph.D., asked whether the SOBC initiative is directed toward changing behaviors only within a healthy spectrum. Would the standard method apply to behavior change in people with mental or behavioral disorders? Dr. Davidson said that the objective is to identify and validate universal targets that apply to all humans. Those with most disordered thinking will have the lowest scores, but the measures are validated in many populations.

Michael Kurilla, M.D., Ph.D., asked whether SOBC researchers have identified any long-standing presumptions in the field that have not been borne out in the research. Dr. Davidson said that they have not identified any yet. Target identification is new to the field, so it will be necessary to start measuring targets before testing long-held myths and prejudices.

Towards a Basic Stress Mechanism in Behavior: Joshua Smyth, Ph.D., Distinguished Professor of Biobehavioral Health and Medicine, Associate Director, Social Science Research Institute, and Director of the Stress, Health, and Daily Experiences Lab, Penn State University

Joshua Smyth, Ph.D., is a recipient of an SOBC initiative grant. He said that typical approaches to develop and apply stress measures (assays) yield a stress stratification framework that is very useful for identifying people at risk. However, Dr. Smyth is not doing this sort of research; rather, he is primarily interested in moments in time when a person is at risk for stress. By using repeated measures from daily life, an economic monetary assessment and daily diaries, his team is risk-stratifying moments and days within the individual.

Within-person stress response dynamics in everyday life shape health behaviors, which are the result of many micro-decisions within and across days; stress may impair those decisions. By understanding and influencing stress response targets, tailored to individual risk, it may be possible to enhance—at a momentary or a daily level—the probability of engaging in positive/desired health behaviors. Cumulatively, over time, these positive behaviors may translate into improved health.

Using the SOBC common method, Dr. Smyth identified stress response targets. Stress response indicators might include negative mood, rumination or reported stress. Stress reactivity is the most common metric in the field today; however, one could also target recovery magnitude or post-stressor elevation. The repetition of stress responses can result in stress pileup (reactivity plus recovery).

Measuring baseline stress is not simple. Baseline represents some average of nonevent measurements. Dr. Smyth applied a coordinated analysis approach based on measures of physical activity and sleep; both are important, and they exist on different temporal frames. His approach involved convergent

analysis of five independent data sets from diverse samples: three ecological momentary assessment (EMA) studies and two daily diary studies involving more than 5,000 participants.

Dr. Smyth reported that stress pileup leads to lower levels of physical activity. Linking stress response targets to daily sleep revealed that heightened reactions to stressors led to poor quality of sleep. He noted that the effect sizes were significant, but there was great heterogeneity, possibly indicating the presence of some unmeasured moderators.

Pileup is a new idea that has not been well studied. Pileup measures are confounded by time of day because stress can build up throughout the day. People who exercise at night will be more influenced by pileup than those who exercise in the morning, for example. Failure to recover from a stress response late in the day is strongly related to sleep quality. No relationship between sleep quality and morning failure to recover from stress was observed.

Dr. Smyth is planning to replicate these findings and then conduct some experiments to test just-in-time interventions at the risk moment to assess their ability to influence physical activity. He said that this method is transferable to new targets and health behavior outcomes. One could also assess heart rate variability or other physiologic indicators. The SOBC common method lends itself to personalized medicine because interventions could be dynamically tailored to address unique sets of risk. Stated otherwise, the right interventions could be delivered to the right person at the right time.

Discussion

Dr. Austin asked whether SOBC is an area in which NCATS should work to a greater extent, noting that implementation science is within NCATS' purview. SOBC appears to be a very useful scientific approach.

Dr. Montgomery Rice said that behavior change is understudied, and she encouraged NCATS to get involved in the SOBC initiative and make better use of community networks that have fostered milestone behavior changes in communities and individuals. She also recommended taking cultural influences into account to ensure that defined outcomes are relevant to communities.

Dr. Montgomery Rice noted that a person's past influences behavior risk today. How would SOBC address that question using the common method? Dr. Smyth acknowledged that people differ, and context varies. For his research project, by starting with each individual's baseline level of stress, he generated a moving estimate of what is normal for one person. Stress responses can be measured with wearable sensors, smartphone apps and brief microsurveys. The research team is providing an algorithm to link these parameters in a stress-response measure.

Alan D. Palkowitz, Ph.D., said that clinical trial design and disease settings could influence how data are gathered and understood. These factors could affect physiologic end points and other factors. He also inquired about baselines and tolerance to stress. Could the baseline drift over time, leading to a new normal level? Also, regarding rumination events, Dr. Palkowitz speculated that they could carry over from one day to the next. Could this phenomenon be isolated to learn about cumulative effects and perhaps find ways to help with recovery from stress? Dr. Smyth said that the notion of baseline turned out to be a central challenge. When establishing baselines, the study team tried to pull in as much family and medical history as possible. Questions about whether habituation and reactivity are associated with greater or lesser recovery would be important to explore.

Daniel L. Hartman, M.D., said that patient compliance is one of the biggest challenges in clinical trial outcomes. Self-reporting is a blunt instrument for assessing compliance. He recommended identifying objective measures, such as biomarkers, that could contribute to measurement.

Megan O’Boyle asked about the applicability of SOBC research to the limited-verbal or nonverbal autism community. Dr. Smyth said that assessments can be tailored to various populations based on parasympathetic arousal, for example.

Dr. Weichold said that the FDA needs to strengthen its response to several societal crises, including addiction, over-prescription and health economics. These all relate to human behaviors, which have been difficult to study, but now we have many new tools to analyze data sets as never before. Establishing SOBC as a science that affects public health and health outcomes is of critical importance.

Naomi Tomoyasu, Ph.D., asked how other NIH ICs are reacting to the challenge of standardizing SOBC with a common vernacular, metrics and measurements. Dr. Collier said that the key to adopting a common approach to SOBC is reliance upon an [Open Science Framework](#) with a high degree of transparency. Together, the ICs could move toward a common methodology and stimulate development of new assessments.

Dr. Tomoyasu mentioned behavioral economics, saying that behavior change is needed not only at the individual level but also at the provider and health-system levels.

Dr. Collier said that the SOBC Measures Repository is global. Scientists can disseminate their measures and allow others to use them in their research. The SOBC initiative has issued FOAs for integrating SOBC resources and measures into projects. Also, the SOBC Network has a “stealth intervention” for investigators to see how the resources are being used.

Dr. Marks recommended that NCATS get involved in SOBC. The time is right because the technology (e.g., personal wearable devices, artificial intelligence, machine learning) is ready. These technologies could become health decision support tools to improve outcomes. Dr. Shekhar also expressed enthusiasm for integrating SOBC into NCATS’ portfolio. Real-time psychological assessments of human behavior are critical. Behavior is paramount for preventing disease and improving outcomes. He suggested that NCATS could become the next “National Human Genome Research Institute” for behavior. Every behavior influenced could have small but cumulative effects on individual and public health—akin to genome-wide association studies in terms of data points.

VI. CTSA PROGRAM HIGHLIGHTS: Michael G. Kurilla, M.D., Ph.D., Director, Division of Clinical Innovation, NCATS

Michael Kurilla, M.D., Ph.D., has been the director of the Division of Clinical Innovation for nearly six months. He made the point that output does not equal outcome. Output is measured quantitatively in terms of publications and funding, but what really matters is outcomes, such as improved efficiency as exemplified by faster trial enrollment and higher throughput, novel methods and approaches. Outcomes from study or trial results include additional or alternative treatment options, enhanced clinical benefit and validated prevention strategies.

Beyond outcome is impact. Impact is all about “the delta” in terms of disease incidence, disease prevalence, morbidity and mortality, health care advice, health care delivery and health care costs. Impact is what Congress cares about. Dr. Kurilla emphasized the importance of recognizing and communicating to stakeholders that impacts occur over the long term, 10 to 15 years after an intervention or program.

CTSA Program KL2 Scholars in the News

Dr. Kurilla showcased the accomplishments of several KL2 scholars. All these highlights were featured in news items and received some publicity:

- [Putting the patient back into the health care equation.](#) Olayinka Shiyanbola, Ph.D., B.Pharm., at the University of Wisconsin-Madison, is working to improve health care outcomes through better patient adherence to prescribed treatment through a patient-centered approach. She organized focus groups and developed interventions for African-Americans with type 2 diabetes.
- [Doctors prescribe opioids at high rates to those at increased overdose risk, but trends improving, study finds.](#) John Mafi, M.D., Ph.D., at the University of California, Los Angeles, found that a rapid change in co-prescription rates suggests that a substantial portion of the initial opioid prescriptions were potentially avoidable. Death rates are sevenfold higher when opioids are combined with benzodiazepines.
- [You are when you eat.](#) Courtney M. Peterson, Ph.D., of the University of Alabama at Birmingham, conducted the first controlled feeding studies of early time-restricted feeding. The time window for food consumption affects metabolism.

Prosperous Pilot Studies

Dr. Kurilla reported that pilot studies conducted through the CTSA Program hubs have been very successful. Some host institutions now are starting their own institutional programs for running pilots.

- Fiza Singh, M.D., ran a pilot aimed at enhancing gamma band response in schizophrenia patients to improve working memory. (The gamma band is a type of brain wave associated with memory.) In schizophrenia patients, gamma bands tend to be very incoherent. The pilot used neurofeedback training via a computerized visual metaphor (a flying aircraft) to help patients bring gamma bands into coherence. The pilot led to a grant from the National Institute of Mental Health to test whether increasing gamma band coherence can improve working memory.
- Arash Kheradvar, M.D., Ph.D., reported in 2012 on the development of a self-expandable transcatheter aortic valve that does not crimp the leaflets during delivery. He has set up a company called FOLDAVALVE. Reduced crimping can help avoid damage to the aortic valve.

CTSA Program Scientific Highlights

- Evan Muse, M.D., is a KL2 scholar at the Scripps Research Institute. Along with co-author Eric Topol, M.D., the program hub's principal investigator, he validated a genetic risk score for atrial fibrillation in a prospective multicenter cohort study using ambulatory monitoring. People who had genetic risk scores in the top 20 percent had a three times greater risk of developing atrial fibrillation. This research was published in *PLOS Medicine*.
- CTSA Program researchers at the University of Pennsylvania reported on use of gene therapy in patients with transfusion-dependent β -thalassemia. Twelve of 22 patients with mild to moderate thalassemia were able to avoid transfusions for the 26-month follow-up period, and 9 of 22 needed fewer transfusions. The study was published in *The New England Journal of Medicine*.
- Another notable study was conducted by researchers at the University of California, Los Angeles. The cluster-randomized trial of blood pressure reduction in barbershops frequented by African-American men was published in *The New England Journal of Medicine*. Pharmacists were set up in barbershops where they provided care for clients' high blood pressure. More than 63 percent who accessed care through this innovative model lowered their blood pressure to healthy levels. Fewer than 12 percent who opted to see their doctors achieved similar reductions.

Clinical Research Forum's 2018 Top 10 Clinical Research Awards

These [awards](#) honor outstanding accomplishments in clinical research. Dr. Kurilla reported that 4 of the 10 awards were for CTSA Program activities.

CTSA Program Trial Innovation Network (TIN)

Dr. Kurilla explained that TIN consists of three components: Trial Innovation Centers (TICs), the Recruitment Innovation Center (RIC) and the CTSA Program institutions. The idea is to embed various tests within a clinical trial to assess how effective the trial design was and to test scientific and operational innovations. Study support comes from NIH ICs, industry and foundations. Dr. Kurilla offered some examples of TIN's accomplishments:

- Investigators running the Treatments Against Rheumatoid Arthritis and Effect on FDG/PET CT (TARGET) trial, sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, sought RIC support to enhance enrollment. RIC created simplified recruiting materials and a smartphone app for use by clinicians to check eligibility and provide site-specific contact information. Enrollment is starting to pick up.
- The pragmatic [Spironolactone Initiation Registry Randomized Trial in Heart Failure with Preserved Ejection Fraction](#) (SPIRRIT-HFpEF) will enroll 3,200 patients in the USA and Sweden. TIN is testing methods to maximize enrollment at the U.S. sites. RIC provided an electronic health record cohort assessment and a feasibility assessment.

Upcoming CTSA Program-Related Meetings

Dr. Kurilla presented a list of meetings demonstrating the broad range of CTSA Program activities.

Discussion

Dr. Montgomery Rice suggested partnering with insurers to find out whether they could identify people who meet eligibility criteria as a way to boost study enrollment. Training practitioners and study coordinators could lead to opportunities for providers to engage with patients in a familiar environment.

Dr. Montgomery Rice asked whether the patient gives informed consent prior to their health care provider checking their eligibility to participate in the TARGET trial. Neither Dr. Kurilla nor Dr. Austin had specific information, but it appears that none of the patient's information is entered in the app; the app just lists the eligibility criteria and provides contact information for the clinical trial. If the patient meets the criteria and is interested in the study, then a connection would be made between the researcher and the potential participant. Most likely, this change in recruitment strategy was approved by the IRB.

Mr. Bartek recommended that the RIC work with patient advocacy groups that have patient registries as a way of enhancing recruitment and retention. Dr. Kurilla said that the RIC responds to challenges that are brought to it. He said that SPIRRIT-HFpEF will gather some objective data on the value of using registries. Mr. Bartek thought it would be important to ensure that staff of the RIC and TICs are aware of the benefits provided by collaborating with patient advocacy groups.

Ms. O'Boyle commented on the new EU data standards expected to be issued this month. To what extent do CTSA Program studies enroll European patients? Dr. Austin said that NCATS and NIH are watching the situation closely. The new standards will affect U.S. research because of harmonization considerations. This is especially true for trials for rare diseases because they all are international studies. A major research exemption is being sought, but sometimes language has consequences that can impede research.

Dr. Montgomery Rice underscored the importance of appropriate disclosures for patients and subjects. Different local systems have limited connectivity, but insurers have great network capabilities. She recommended that consents for care be revised and standardized to allow patients to give their permission to be contacted as potential research subjects. Dr. Austin said that Dr. Ling facilitated a meeting with the Centers for Medicare & Medicaid Services (CMS), and Dr. Montgomery Rice arranged a meeting with an insurer. CMS only has Medicare under its purview, meaning that covered patients are mainly older than 65; therefore, the Medicare rolls would not be very helpful for rare diseases research. Dr. Tomoyasu said that sharing of Veterans Administration (VA) data is challenging due to limited funding for information technology. However, the VA has a wealth of longitudinal genomic and phenotypic data on 550,000 veterans.

Dr. Hartman said that it is challenging to think about scientific and operational innovation in clinical trials. Registries are not new, but apps are. Assessing NCATS' impact might require a control arm.

Regarding the Common Rule, Harry Selker, M.D., M.S.P.H., recommended that NCATS advocate for the integration of research into all clinical care. As a national resource, NCATS must take advantage of every opportunity to advance research.

VII. CLEARANCE OF CONCEPTS

Dr. Austin explained that NCATS is required to present ideas to this group for approval. Questions to consider include whether the concept addresses an important problem and whether it is an appropriate focus for NCATS.

CTSA Program Collaborative Projects Program: Philip John (P.J.) Brooks, Ph.D., Program Director, Division of Clinical Innovation, NCATS Discussion

Philip John (P.J.) Brooks, Ph.D., provided some background on various CTSA Program collaborative projects. The goal of this new program would be to support innovative and sustainable approaches to overcome roadblocks in translation by building upon strengths at individual CTSA hubs. This would support dissemination of successful methods and processes developed at individual hubs, thereby strengthening and enhancing the impact of the CTSA Program. Potentially, the program could have a sustainable and transformative impact on multiple domains of translational science.

Dr. Brooks said the program could help overcome challenges, such as the lack of underrepresented minorities participating in clinical trials, lack of natural language processing capacity in translational research, and variations in training opportunities across the CTSA Program.

Discussion

Dr. Selker and Dr. Montgomery Rice were the assigned discussants for this concept.

Dr. Selker said he favored this concept because it would support collaboration across institutions and partners, which is the hallmark of the CTSA Program. Dr. Montgomery Rice agreed, saying that this would be an excellent mechanism to spur interest in areas where requests for applications (RFAs) do not already exist. She recommended application criteria that would ensure inclusion of as many sites as possible. Dr. Shekhar asked about the optimal proportion of innovation funds to operational funds.

Dr. Hartman recommended using very specific criteria for evaluating success and demonstrating value of the program. Perhaps there should be some consideration of using forcing functions, such as requirements for the number of women and minorities to include in clinical trials.

The Advisory Council unanimously approved this concept.

Synthetic Technologies for Advancement of Research and Therapeutics (START): Dobrila Rudnicki, Ph.D., Program Officer, Office of Special Initiatives, Office of the Director, NCATS

Dobrila Rudnicki, Ph.D., reported that the cost of developing a new drug now exceeds \$1 billion. One factor exacerbating the situation is that libraries of compounds have exhausted the limits of structural diversity; it is increasingly difficult to find new compounds with chemical activity. Use of natural products for therapies has been limited due to low yields in their host organism, limited supply of some host organisms, the complexity of natural compounds' structures and the difficulty of modifying them. Synthetic biology can generate novel, biologically active compounds through advances in gene editing and synthesis, automation, metabolomics and so forth to enhance diversity of drug libraries.

The START program would formulate natural, biologically relevant pathways to engineer new and safer therapies; expand the current catalog of naturally occurring compounds and their analogues; identify, characterize and synthesize novel bioactive compounds; and enhance productivity and yield of biological systems that produce natural compounds. In terms of potential impact, Dr. Rudnicki said that the potential exists for catalyzing the field of synthetic biology for drug development.

Discussion

Dr. Palkowitz and Dr. Marks were the assigned discussants for this concept.

Dr. Palkowitz said that this is the time to make additional investments to catalyze natural products work. This area is still emerging; this program could spark further interest in natural products as potential new therapies. It is important to think about a "destination," however. NCATS should not aim to generate activity unless these products and tools could be adopted by industry with parallel investments. Dr. Palkowitz thought that this effort could make an impact in antibiotics research in particular. Exploiting synthetic biology to its full potential could help bring natural products back into the mainstream and enhance molecular libraries for developing new therapies.

Dr. Marks said that computational chemistry cannot do everything. Science is now circling back to natural products because of our improved ability to integrate responses and because different spaces in chemistry have opened up as new generations of drugs have been developed.

Kalpana Merchant, Ph.D., asked about doing a pilot focused on a major need, such as in the lipid area. Looking at a large group of new natural products might be less effective than working on something that is ready to go all the way through the pipeline by testing in existing systems. Dr. Rudnicki agreed that narrowing the focus sounds like a good idea. Pain medications might be a good starting point.

Others suggested collaborations with the National Institute of General Medical Sciences and the National Center for Complementary and Integrative Health. Dr. Rudnicki said that an NIH-wide working group has been assembled, so this group would be a way to involve other ICs in the program.

The Advisory Council unanimously approved this concept.

Universal Medium/Blood Mimetic for Use in Integrated Organs-on-Chips: Lucie Low, Ph.D., Scientific Program Manager, Office of Special Initiatives, Office of the Director, NCATS

Lucie Low, Ph.D., presented the next two concepts, which focus on the Tissue Chips program.

For the Tissue Chip program to be successful, organ chips will need to be integrated. This was a goal from the outset of this program. Integrating systems is challenging, however, due to the tissue chips' 3D structure, heterogeneity of cell types and fluid flow.

This project would develop a universal medium/blood mimetic that could be used in integrated systems and maintain cell viability and function for at least a month. Having a universal medium would make it

possible to link many new tissue types, expanding the utility of the chips, and make the technology more accessible to a wider community for commercialization and dissemination. Also, such a medium could be used in other systems across laboratories and help maintain phenotypes of iPSC-derived tissues.

Discussion

Dr. Palkowitz and Dr. Shekhar were the assigned discussants for this concept.

Dr. Palkowitz thought that having a universal medium would make sense in terms of providing some standardization. There will be a vulnerable period for this new technology; reducing variability and uncertainty will boost the field. Dr. Shekhar agreed, saying that a universal medium is an obvious and important need for the program.

Dr. Ling said that this concept was well written and included relevant milestones. He noted that this is a modest funding initiative, but he wondered if the amount of money would suffice. The second phase could go up to \$2 million, but even that would not be enough for achieving full commercialization.

Mr. Margus asked whether program staff have spoken with companies about the likelihood of creating such a medium. Dr. Low said that discussions have occurred throughout the program; indications are that it would be feasible to create a universal medium with the current capabilities in the field.

The Advisory Council unanimously approved this concept.

Non-Polydimethylsiloxane Biocompatible Alternatives for Organs-on-Chips: Lucie Low, Ph.D., Scientific Program Manager, Office of Special Initiatives, Office of the Director, NCATS

Dr. Low said that polydimethylsiloxane (PDMS) is a great material in many ways, but it can exhibit undesirable surface properties such as drug absorption, which can lead to drug/compound loss and/or cross-contamination of surrounding areas or tissues. What is needed is an alternative material in whole or in part for fabricating tissue chips.

Finding a material other than PDMS could translate into benefits for all sorts of microfluidics platforms. Some supplemental funds have been provided to tissue chip projects to test other materials, but this project would open up the challenge to a broader community.

Discussion

Katharine Ku, M.S., and Dr. Marks were the two assigned discussants for this concept.

Ms. Ku said that the negative properties of PDMS are well known. The materials science community can rise to challenges like this. Dr. Marks agreed and said that finding another material will be the key to the program and to the microfluidics field more broadly.

Dr. Ling suggested getting the National Science Foundation (NSF) involved in the quest. NSF is deeply involved with material engineers.

The Advisory Council unanimously approved this concept.

VIII. APPROVAL OF MINUTES

The minutes of the joint meeting held on January 11, 2018, were approved as written.

IX. ADJOURNMENT OF OPEN MEETING

Dr. McInnes, on behalf of Dr. Austin, thanked all participants for their input. She and Dr. Marks adjourned the open portion of the meeting at 3:04 p.m.

X. JOINT CLOSED SESSION OF NCATS ADVISORY COUNCIL/CAN Review Board

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 and CAN Review Board 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.

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

Dr. McInnes, on behalf of Dr. Austin, adjourned the closed session of the NCATS Advisory Council meeting at 3:50 p.m. ET.

CERTIFICATION

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

G. Lynn Marks, M.D.
Chair, Cures Acceleration Network Review Board
and
Senior R&D Advisor, Biomedical Advanced Research and Development Authority (BARDA), ASPR/HHS

Date