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
January 11, 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 January 11, 2018, convening at 8:30 a.m. ET, in Conference Room 6, 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.

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

Daniel L. Hartman, M.D.
Katharine Ku, M.S.
Brad Margus
G. Lynn Marks, M.D.
Kalpana M. Merchant, Ph.D.
Alan D. Palkowitz, Ph.D.
Valerie Montgomery Rice, M.D.
Harry P. Selker, M.D., M.S.P.H.
Anantha Shekhar, M.D., Ph.D.
Stephen P. Spielberg, M.D., Ph.D.

Representative Members

None present

Ad Hoc Members

Ronald J. Bartek, Friedreich's Ataxia Research Alliance
Geoffrey Shiu Fei Ling, M.D., Ph.D., Uniformed Services University of the Health Sciences
Matthew Might, Ph.D., University of Utah
Paul G. Yock, M.D., Stanford University (by telephone)

Ex Officio Members

David Atkins, M.D., M.P.H., Department of Veterans Affairs (representative)

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, 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

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Sharon F. Terry, M.A.

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Ex Officio Members

David Atkins, M.D., M.P.H., Department of Veterans Affairs (representative)
Frank F. Weichold, M.D., Ph.D., Food and Drug Administration (representative)

OTHERS PRESENT

Dane Christiansen, Health & Medicine Counsel of Washington
Murat Cirit, Ph.D., Department of Biological Engineering, Massachusetts Institute of Technology
Dale Dirks, Health & Medicine Counsel of Washington
Ki-Cha Flash, National Institute of Dental and Craniofacial Research
Ivan Rusyn, M.D., Ph.D., Interdisciplinary Faculty of Toxicology, Texas A&M University

NCATS leadership and staff

I. CALL TO ORDER

Christopher P. Austin, M.D., and G. Lynn Marks, M.D., called the meeting to order. Dr. Austin welcomed members and guests to the 17th meeting of the NCATS Advisory Council and the 22nd meeting of the CAN Review Board. He reminded attendees that the open session was being videocast.

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

The minutes of the joint meeting held on Sept. 7, 2017, were approved as written. The 2018 NCATS General Council Operating Procedures were approved as written.

Anna L. Ramsey-Ewing, Ph.D., informed the group that the NCATS Advisory Council and CAN Review Board will have joint meetings in 2018 on May 10 and September 27. The 2019 meetings will take place on January 10, May 16 and September 19. The CAN Review Board also will meet by teleconference on Dec. 14, 2018, and Dec. 13, 2019.

III. INTRODUCTION OF NEW STAFF

Christopher P. Austin, M.D., introduced Michael Kurilla, M.D., Ph.D., who recently joined NCATS as the director of the Division of Clinical Innovation (DCI). Dr. Kurilla remarked that in his 15 years with the National Institute of Allergy and Infectious Diseases, he worked on the full spectrum of translational research spanning prevention to diagnosis to response capabilities.

Valerie Montgomery Rice, M.D., underscored the importance of being as inclusive as possible in terms of the workforce for response capabilities, especially with regard to biosafety level (BSL) 3 and 4 facilities. She suggested fostering innovative collaborations and locating BSL 3 or 4 facilities to maximize access for researchers from a variety of institutions.

Other new staff were introduced, including:

- Jane Atkinson, D.D.S., is now the director of the Trial Innovation Network. For the National Institute of Dental and Craniofacial Research (NIDCR), she focused on oral mucosal diseases and salivary gland disease. She is still a staff dentist with NIDCR.
- Valerie Gordon, Ph.D., M.P.H., previously worked on trans-NIH initiatives focusing on clinical research and new policies regarding human subject protections. She will be taking on a role with the Trial Innovation Network as senior advisor for human subjects' protection.
- Pablo Cure, M.D., M.P.H., comes to NCATS from the National Heart, Lung, and Blood Institute where he managed a research portfolio. At NCATS, he will be overseeing two CTSA Program hubs and working on the coordinating center.
- Alina Predescsu, M.B.A., a Presidential Management Fellow, came to NCATS from Johns Hopkins University last September. At NCATS, she is working on pilot awards and metrics.
- Rashmi Gopal-Srivastava, Ph.D., M.Sc., previously with NCATS' Office of Rare Diseases Research (ORDR), is now providing programmatic oversight for four CTSA Program hubs and serving as lead on the national CTSA Program Lifespan Domain Task Force.
- Alice Chen, M.D., spent several years at the Food and Drug Administration (FDA). At NCATS in ORDR, she working on the Rare Diseases Registry (RaDaR) Program.
- Eric Sitt, M.D., M.H.A., also a Presidential Management Fellow, is interested in population health management and health disparities. At ORDR, his focus is on RaDaR and the Genetic and Rare Diseases Information Center.
- Tiina Urv, Ph.D., has been working with the CTSA Program for a few years. She is now the new program director for the Rare Diseases Clinical Research Network (RDCRN) program.

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

Dr. Austin announced that members of the Advisory Council and CAN Review Board received thumb drives with information about NCATS activities that occurred since the last meeting.

Administrative, Policy and Budget Updates

- **Fiscal Year (FY) 2018 and 2019 Budgets.** The President's proposed FY2018 budget of $25.9 billion for NIH represented a $5.8 billion (20 percent) reduction, but appropriations bills were not voted on by the full chamber. NIH has been operating under a series of continuing resolutions, which creates major challenges for planning and management. At this point, NIH is nearly halfway through the fiscal year, and it is possible that the entire budget has already been consumed. The out-years of grants are always funded at the 90 percent level, meaning that

moving forward in terms of new obligations and new grants has to be done judiciously. The President's FY2019 budget is expected in early February 2018.

- **Visits from Congressional Representatives.** Senator Roy Blunt (R-Missouri) and Congressman Tom Cole (R-Oklahoma) visited NIH in December 2017. Blunt serves as the chair of a Senate Appropriations subcommittee and has been a booster of NIH and biomedical research. They both have championed NIH budget increases in recent years.
- **Looking back at FY2017.** With its $706 million budget for FY2017, NCATS was about at the median of funded Institutes and Centers (ICs). The trend in NCATS' annual budgets mirrors that of the rest of NIH. About 70 percent of NCATS' FY2017 budget supported DCI. Having such a large proportion of the budget dedicated to one line item can lead to some managerial challenges. Over the past several years, Congress has said it is excited about biomedical research, but the emphasis is on results. ICs that do not have a disease-centered program such as the Cancer Moonshot or the Precision Medicine Initiative are at a disadvantage. It is important to realize that many people have translational "disease" in that they cannot be diagnosed properly due to the lack of adequate technologies.

DCI Highlights

- **CTSA Program Meetings.** Dr. Austin remarked on the CTSA Program meetings held in Washington, D.C., on Oct. 25–27, 2017. The Program Steering Committee met on the first day to discuss the state of the CTSA Program. The Steering Committee will revisit and streamline communications to increase transparency and decide on the best ways to collaboratively address translational science bottlenecks and barriers. More than 300 CTSA Program colleagues met on the second day. The final day was dedicated to reviewing the progress of the Trial Innovation Network and setting milestones for next year.
- **CTSA Program Collaborative Innovation Awards (CCIA).** This U01 award mechanism supports three or more CTSA Program hubs working together to disseminate innovative approaches to other institutions for overcoming translational science roadblocks. The partners may take on intractable problems that no single CTSA Program hub could solve. Dr. Austin highlighted two CCIA projects: the National IPS Cell Network with Deep Phenotyping for Translational Research, and the Strengthening Translational Research In Diverse Enrollment (STRIDE).
- **Visits to CTSA Program Hubs.** Since the last meeting of the Advisory Council and CAN Review Board, Dr. Austin has visited three hubs: Washington University in St. Louis; University of California, Davis; and the University of Alabama at Birmingham.
- **CTSA Program Funding Opportunity.** PAR-18-464 was reissued.
- **Opioid Crisis:** According to Dr. Austin, the CTSA Program has the opportunity and obligation to take on the challenge of the opioid crisis. Prescriptions are decreasing, but fatalities continue to increase. In 2016, the number of overdose deaths increased by 20 percent, and the number of deaths due to synthetic opioids surpassed the number caused by heroin or prescription opioids in 2016. Research is needed in all areas of translation, including better pain management, opioid addiction treatment and overdose reversal. Redonna Chandler, Ph.D., former DCI deputy director, has moved to the National Institute on Drug Abuse (NIDA); she will coordinate a collaboration between NIDA and NCATS.

ORDR Highlights

- **RDCRN Gene-Editing Clinical Trial for a Lysosomal Disease.** Dr. Austin described a trial being conducted by researchers in the Lysosomal Disease Network. A patient with mucopolysaccharidosis II participated in a first-in-human gene editing trial in November 2017.

The hope is that the patient will not require any enzyme infusions in the future. The plan is to figure out a platform that could apply to other rare diseases by addressing issues related to technology, safety and heterogeneity (different mutations). ORDR staff are planning a workshop to be jointly convened by NCATS and the FDA during the spring of 2018 on the growing promise of gene therapy approaches.

- **RaDaR.** Dr. Austin explained that a data repository was established as a pilot program with registries from 12 patient advocacy groups. Efforts for Phase 1 of the Global Rare Diseases Patient Registry Data Repository (GRDR) focused on development of common data elements and the pooling of data from different sources. The work was successful, but mapping data post hoc proved to be highly challenging and unscalable. For Phase 2, a group at Harvard University mapped GRDR data to available standards, showing that it was possible to generate a unified database based on common data elements. The data will be available via RaDaR.
- **Toolkit for Patient-Focused Therapy Development.** The toolkit is a repository of tools to help patients and advocacy groups engage in therapy development at every stage. The website went live in September 2017.
- **Drug Discovery, Development and Deployment Map (4DM).** Dr. Austin said that the most common schemata (e.g., pipeline, chevron diagram) for depicting the drug development process are inaccurate and do not reflect the process's complexity. Nevertheless, many stakeholders operate on these bases. The Action Collaborative of the NASEM Forum on Drug Development and Deployment used crowd sourcing to come up with a dynamic map representing therapeutic development. Now published in two journals, 4DM is available free under a Creative Commons license at ncats.nih.gov/translation/maps.

Discussion

Regarding the 4DM map, Alan D. Palkowitz, Ph.D., spoke about distinguishing different paths for different diseases, because drug development is not "one size fits all." He suggested that cross-learning could occur if 4DM were more platform based. Dr. Austin said that the complexity in drug development arises from a lack of innovative solutions; having new tools such as tissue chips could contribute to a transformation strategy.

Kalpana M. Merchant, Ph.D., suggested peppering 4DM with some real-life examples. Also, because this model is for academic research, clinical research organizations (CROs) could be considered a resource.

Dr. Montgomery Rice commented on STRIDE and suggested that other collaborators would be useful in this space, namely insurers, the Centers for Medicare & Medicaid Services and providers. Insurers have access to data, and trusted providers could remove many barriers to research participation. Major insurers have data on 140 million people and know when visits are scheduled. They would probably be receptive to working with CTSA Program hubs and providing some analytics.

Dr. Montgomery Rice asked about the backgrounds of the STRIDE staff who are involved in community engagement. Dr. Austin said that the staff are trusted in the community and have similar backgrounds to the community members.

Ronald J. Bartek emphasized the role of patient advocacy organizations because of their success in recruiting patient-participants for clinical trials.

Sharon F. Terry, M.A., said that the opioid crisis is more extreme than the AIDS crisis was. Bold action is needed, but the opioid crisis does not have any activists to press for change. Detoxification facilities, treatment facilities and medical centers should share data.

Geoffrey Shiu Fei Ling, M.D., Ph.D., said that the opioid crisis is an opportunity for NCATS, but the first step should be identifying what is different about this crisis. NIDA has been working on opioid addiction for decades. Frank F. Weichold, M.D., Ph.D., pointed out that one new thing is the FDA's emphasis on responsible prescribing practices for pain management. Dr. Austin said he is optimistic because NIDA has approached NCATS, seeking to establish a partnership. The limitation on this partnership is funding because it would be costly to conduct clinical and outcomes research.

V. UPDATE FROM THE TISSUE CHIP VALIDATION CENTERS: Danilo A. Tagle, Ph.D., Associate Director for Special Initiatives, Office of the Director, NCATS

Danilo A. Tagle, Ph.D., briefly reviewed the history of the Microphysiological Systems (MPS)/Tissue Chips for Drug Screening program that has supported development of tissue chips. This was the first initiative undertaken by CAN. The effort was also supported by the Defense Advanced Research Projects Agency (DARPA), which provided funding, and the FDA, which provided insight and expertise. Dr. Tagle said that as of October 2017, more than 500 articles on the program had been cited more than 5,600 times.

The goal was to develop 10 human tissue chips. The first five years of the program was dedicated to platform development. The investigators came up with organ-systems-on-chips that were physiologically relevant, genetically diverse and pathologically meaningful. The chips were required to maintain viability for a minimum of 28 days and be modular to allow linkage to other tissue chips. Recently, the focus of work has been on functional validation, development of a training set of compounds and multi-organ integration. Training sets of biomarkers and assays have been created in collaboration with the IQ Consortium.

Principles of validation were adapted from a guidance document published by the Organisation for Economic Co-operation and Development (OECD). The validation framework comprises three levels:

- Physiological validation by tissue chip developers focusing on organ structure and function with use of training set of compounds
- Analytical validation by independent Tissue Chip Testing Centers (TCTCs) using a validation set of compounds
- Industrial validation by industry and regulatory agencies using a proprietary set of compounds in a CRO-type environment.

The TCTCs have been operating for a year with U24 support. Funding is being renewed for another two years with the goal of making the testing centers self-sustaining after NCATS support.

Murat Cirit, Ph.D., Director, Translational Center of Tissue Chip Technologies (TC^2T) and Head of Translational Systems Pharmacology, MIT

Murat Cirit, Ph.D., spoke about the potential applications of the tissue chips in pharmacokinetic studies; disease models; pharmacodynamics studies for small molecules, biologics and nano-therapeutics; ecotoxicology; and personalized medicine. For pharmaceutical companies and regulatory agencies, the tissue chips could be useful for target validation; efficacy and toxicity screens; studies of absorption, distribution, metabolism and excretion (ADME) properties; studies of mechanism of action; and biomarker discovery.

TC^2T applies a systematic and quantitative workflow that uses a combined experimental and computational paradigm for translation of organ-on-chip data to clinical outcomes. The first validation

strategy focuses on technology transfer to ensure that the platform is working properly in the tissue chip testing center. Dr. Cirit emphasized the importance of eliminating nonspecific binding and using serum-free medium in the chips. TC^2T is focusing mainly on clinical markers for a given organ system.

Validation of the kidney, blood-brain barrier and brain models is complete.

Dr. Cirit discussed the kidney MPS validation. The University of Washington and Nortis developed the MPS, which recapitulates the kidney's proximal tubule. The technology was successfully transferred to the testing center and the system is highly robust. The cells in a 2-D system did very poorly, whereas the 3-D system kept them healthy. Testing with four drugs at four doses revealed that the KIM-1 responses (a marker of acute tissue injury) in the tissue chip were similar to those of human tissue *in vivo.*

The brain MPS (Thomson Model) also underwent testing at TC^2T. The validation team compared the characteristics of a neuronal monoculture with a differentiated neuronal cell population (neurons [GABAergic and glutamatergic], neuroglia and neural progenitor cells). The neuronal monoculture was not able to distinguish between neurotoxic and non-neurotoxic compounds.

For the liver MPS, TC^2T carried out a quantitative assessment of donor-to-donor variability and translation to clinical data.

In a multi-MPS platform (gut-liver integration), pharmacokinetic studies revealed the importance of organ chip integration as drug metabolism in the liver was key.

Dr. Cirit also spoke about the importance of data management and sharing. The validation data from the tissue chip testing centers, along with data from the developers, are sent to the Pittsburgh database where they are combined with clinical and chemical data and made available to the collaborators and the public.

Major challenges remain in terms of building broad biology/physiology knowledge, multidisciplinary infrastructure, cell sourcing, biomaterials, tissue chip medium, assay development and validation, platform materials, throughput and automation, and *in vitro* to *in vivo* translation.

Ivan Rusyn, M.D., Ph.D., Professor and Chair, Interdisciplinary Faculty of Toxicology, Texas A&M University

Ivan Rusyn, M.D., Ph.D., said that TEX-VAL is the tissue chip testing center at Texas A&M University. Tissue chips are considered a device, and the FDA qualification program would be relevant. Validation is specifically prescribed in OECD guideline 34. Regulators are interested in fit-for-purpose validation with clearly defined comparators and gold standards. The 2017 National Academies of Science report *Using 21st Century Science to Improve Risk-Related Evaluations* defined how test results should be interpreted in terms of a positive or negative response. Regulators want to see performance standards for devices.

The deliverables for TEX-VAL included publications and reports on the outcomes of testing and comparison of 3-D and 2-D systems, detailed technology transfer and experimental protocols, phenotypic endpoint descriptions and guidance for interpretation, lists of necessary equipment (e.g., syringe pumps), and costs. The tissue chip systems are more expensive than animals.

The TCTCs possess broad relevant technical and scientific expertise, and they are experienced in using alternative methods in regulator applications. They are independent from the NCATS-funded tissue chip developers.

TEX-VAL tested Vanderbilt University's neurovascular unit (blood-brain barrier model). It consists of two separate chambers and four different cell types. It takes three weeks to establish the blood-brain barrier. Four of nine chips developed a sufficient blood-brain barrier by 21 days. Comparison of performance was challenging due to a lack of replicability. In Dr. Rusyn's view, the neurovascular unit is a very good system when it works, but it would be impossible to onboard it at every laboratory.

The University of Washington's proximal kidney tubule module is very physiologically relevant, according to Dr. Rusyn. Ten chips with HIM-31 cells and 38 chips with Lonza cells were tested. The chips were viable for at least 28 days.

The bone/tumor model developed at Columbia University consists of de-cellularized bovine trabecular bone with human osteoblasts or Ewing's sarcoma cells. There is no flow in the MPS. It demonstrated clear dose responses.

Testing is still under way for the Johns Hopkins University intestinal (jejunum) enteroid model and the cardiac chip developed by the University of California, Berkeley.

Dr. Rusyn concluded his presentation with a discussion about potential use of tissue chips in decision making from a customer's perspective:

- This technology is very useful and promising. Bioengineering research and development need support.
- The applications of tissue chips will be highly fit for purpose, and tissue chips are not likely to replace animal or *in vitro* studies (for efficacy and safety).
- Developers need to appreciate the need for portability, ease of use and cost of devices.
- The end-users (companies) need to be ready for this technology in terms of workforce expertise and versatility.
- Decision-makers (inside and outside of government) need to be educated on what constitutes the state-of-the-art. The FDA's response to onboarded tissue chips has been mixed so far.

Validation is neither cheap nor quick under the OECD GD 34 guidance document on validation and international acceptance. Dr. Rusyn mentioned the European Union (EU) Network of Laboratories for the Validation of Alternative Methods (37 EU-NETVAL) as an example of a safe harbor consortium for fit-for-purpose validation.

The tissue chip technology is still immature and rapidly developing. Dr. Rusyn said that the potential tissue chip market is highly fragmented, making it difficult to establish strategic partnerships.

Discussion

Mr. Bartek asked about the cell types included in the brain chip. Could the MPS be adapted if a particular user wanted to test a different sort of neuron? Dr. Cirit said that the chip he mentioned used embryonic brain cells, neuroprogenitor cells and astrocytes. Dr. Rusyn said the MPS is not really a brain on a chip.

Brad Margus said that the tissue chips are supposed to accelerate the drug development process. When will one of these devices be adopted by the global pharmaceutical industry? Will companies be willing to kill a potential drug based on negative tissue chip results? Is the technology still in the early stages? Is some of this work highly translatable, for example, could a tissue chip better predict human dosage than animals? Dr. Tagle said that pharmaceutical companies and the FDA have been working with the

technology; some companies have imported it into their own research and development laboratories. Some companies have set up their own programs. Dr. Tagle could not say when an investigational new drug (IND) application based on chip data might be submitted. The FDA would probably consider chip data in comparison to data collected in traditional ways, depending on the context of use.

Dr. Rusyn said that the reality is that tissue chip technology will continue to grow organically, but the pharmaceutical industry should be at the table driving the discussion. Dr. Tagle added that NCATS has fostered a collaborative climate with the pharmaceutical industry, DARPA, the FDA and manufacturers. The technology is still evolving and can be improved in terms of miniaturization. NCATS is also working with the National Aeronautics and Space Administration on including tissue chips in payloads.

Dr. Marks had concerns about clinging to old systems despite their lack of predictability of safety and efficacy in humans and irreproducibility of animal models. The opportunity to move forward with this system could accelerate the field.

Anantha Shekhar, M.D., Ph.D., asked whether toxicity is the right target for this technology. Drug toxicity usually shows up two years after marketing when thousands of people start taking a drug. Perhaps a better use of the tissue chips would be testing for efficacy and proof of concept, for which no good models currently exist. More drugs fail because of efficacy than safety. Tissue chip testing could help with go/no-go decisions. Dr. Tagle said that Tissue Chip 2.0 is an attempt to address efficacy testing. Thirteen investigators were funded, including several working in rare diseases. This new program is validating disease models. The next step will involve testing of proprietary compounds.

Stephen P. Spielberg, M.D., Ph.D., inquired about impediments in drug development that could be solved with this technology, which does not appear to be a viable model for detecting idiosyncratic human toxicity. Animal models do not predict fetal abnormalities (teratology) or generalized toxicology. He recommended striving for more granularity in terms of the questions that could be answered with tissue chips. Furthermore, he said that the pharmaceutical industry needs to drive that discussion.

Daniel L. Hartman, M.D., agreed about defining the problem to be solved with MPS technology, but cost has to be a consideration. What is the target product profile from a cost and time perspective?

Dr. Spielberg underscored the importance of developing a model capable of predicting efficacy or toxicology. Could a company use MPS to sort through drug candidates and figure out which one to pursue? He also mentioned the idea of combining MPS with high-throughput screening. He advocated thinking strategically to focus on validating pathways that would be easiest for both individuals and agencies to use and ultimately accelerate the quest for molecules that are effective and safe.

Dr. Austin said that the IQ Consortium has a toxicology orientation. Is there a pharmaceutical group devoted to efficacy? Dr. Palkowitz said that the industry is not organized that way, and he suggested involving computational scientists and medicinal chemists.

Dr. Palkowitz said that that toxicology might be the most proximal application of MPS, but it is really a tool for discovery and isolating complexity. The result could be an assay system to iterate a problem with molecular modifications. He recommended greater involvement of practitioners to obtain firsthand information on use cases.

The usual path for industry, according to Dr. Palkowitz, has been through animal models, not humans. Developing animal tissue chips could build predictive value.

Dr. Palkowitz added that a key challenge in dealing with the opioid crisis is the lack of pain models for developing new pain drugs. Pain systems could be an opportunity for MPS. He recommended including this opportunity in future planning.

Dr. Shekhar said that the CTSA Program hubs have excellent scientists working on many diseases, including rare diseases. The hubs might be well positioned for advancing use of tissue chips in efficacy and toxicology testing.

VI. CURES ACCELERATION NETWORK REVIEW BOARD UPDATE: G. Lynn Marks, M.D., Senior R&D Advisor, Biomedical Advanced Research and Development Authority (BARDA), ASPR/HHS; and Chairperson, CAN Review Board

Dr. Marks reviewed the agenda of the 21st CAN Review Board meeting held on Dec. 15, 2017. He spoke about the great challenge of operating under continuing resolutions because of the lack of predictability in the budget. Continually preparing for orderly shutdowns results in enormous waste of time and money.

During the December meeting, Dr. Marks reviewed the history of the CAN Review Board and commented on the importance of its mission to address gaps and barriers to accelerate cures across a range of disease areas. He said that the 21st Century Cures Act now allows NCATS to support clinical trials through phase 2B; this change is likely to have a major impact.

Speakers covered the status of current CAN programs and presented two concepts for clearance: the Biomedical Data Translator and NCATS Collaborative Rare Disease Platform Vector Gene Therapy Trials. Both concepts were approved unanimously.

Dr. Marks, Mr. Bartek and Dr. Austin led a brainstorming session during the December meeting. The discussion focused on the major obstacles to clinical progress. The CAN Review Board identified needs for biomarkers, compounds against suitable targets, target identification (from the perspective of the pharmaceutical industry) and better outcome measures. Regarding outcome measures, FDA colleagues said that not only is there a need for clinical endpoints, but there is also a need for collecting evidence to show that patients are feeling or functioning better or demonstrating incremental improvements in medical conditions. FDA representatives said that even evidence of mild signals would be helpful. The endpoints could be completely exploratory and would not necessarily need to be compared to a validated outcome measure. Dr. Marks also reported that the meeting participants identified the need for high-quality natural history studies. Imprecision in understanding the natural history of disease has led to failure of many clinical trials in many diseases.

Dr. Marks spoke about the importance of advocating for additional funding, but he suggested taking action while waiting for additional resources. For example, CAN could connect with other groups working on the opioid epidemic, focus on data collection via wearable devices and leverage resources from other ICs and other groups.

In summary, Dr. Marks said that the meeting was very exciting and could portend a shift in the CAN Review Board and how it works. Dr. Austin thanked Dr. Marks and Mr. Bartek for running a successful CAN Review Board meeting.

VII. CLEARANCE OF CONCEPT

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

Clinical Trial Readiness for Rare Diseases: **Petra Kaufmann, M.D., M.Sc., FAAN, Director, Office of Rare Diseases Research, NCATS**

Petra Kaufmann, M.D., M.Sc., stated that more than 7,000 rare diseases exist, but less than five percent have an effective treatment. NIH's investments in rare diseases research has led to unprecedented opportunities to translate scientific advances into treatment. Sustainable business models for rare diseases and product development are challenging; de-risking is needed to attract private sector investment. To evaluate transformative treatments such as gene therapy, high-quality, recent natural history data are required in addition to biological and clinical outcome measures that are fit for the intended purpose.

Patient groups are seeking to contribute to trial readiness through natural history studies, and NCATS has partnered with the FDA in support of its natural history initiative. High-quality natural history data sets are critical to de-risking because they provide an understanding of disease presentation and course.

This initiative would aim to support studies that focus on specific gaps in natural history data and outcome measures. Initially, the focus will be on a subset of studies in disease indications for which there are credible clinical development candidates and for which there is no effective treatment currently. Higher priority would be given to studies that include partnerships with patient advocacy groups.

Studies could be standalone or ancillary to ongoing studies or networks. This funding opportunity announcement (FOA) is not intended to establish information technology platforms or help with biomarker discovery, assay characterization and so forth. NCATS, possibly in partnership with other NIH ICs, patient groups or private-sector stakeholders, would solicit applications for studies supporting clinical trial readiness. Criteria for evaluating success would be in terms of numbers of natural history datasets, biomarkers, clinical outcome measures, refinement of population samples and clinical trials launched.

Dr. Kaufmann also provided an overview of other ongoing research and activity in this area, which could provide opportunities for synergistic collaboration. The proposed initiative would help prepare research groups to take advantage of Trial Innovation Network resources.

Discussion

Mr. Bartek and Dr. Spielberg were the two assigned discussants for this concept.

Mr. Bartek expressed his enthusiasm for the concept, which addresses some key obstacles and could lead to a platform for many diseases. Working in collaboration with other ICs, patient advocacy groups, industry groups and the FDA is a good idea. He was also impressed with proposed use of CTSA Program assets (e.g., Trial innovation Network). He asked about interfaces with other grant programs and whether receiving a grant under this FOA would reduce other research resources. Dr. Kaufmann said that, for NIH grants, the result would be a synergy: a small additional investment on top of an existing program could help provide tools or natural history data to prepare for a clinical trial. NCATS would work from a stewardship perspective to ensure that funding would be synergistic.

Dr. Spielberg said many clinical trials fail not because the compounds do not work but because the natural history of the disease is not understood. Understanding rare genetic diseases provides insights into the whole of human biology. Dr. Spielberg pointed out that even common diseases are rarely described adequately. He recommended including some pathways for patients and physicians to help them collect data in standard formats. Electronic health records could become effective research tools.

Dr. Spielberg observed that disease progress varies by age. The FDA struggles to extrapolate efficacy across age groups (i.e., adult disease vs. pediatric disease vs. teenage disease). This caveat applies to both common and rare diseases. By looking at the rare disease population, it should be possible to learn more about common diseases and develop platforms that can be applied broadly.

Ms. Terry noted that if an advocacy group collects data through wearable devices, the term "study site" has no meaning.

Dr. Montgomery Rice suggested that insurers could be a source of natural history data from insurance records and electronic health records.

The Advisory Council unanimously approved this concept.

VIII. NCATS DIVISION OF PRE-CLINICAL INNOVATION UPDATE: Anton Simeonov, Ph.D., Scientific Director and Director, Division of Pre-Clinical Innovation, NCATS

Dr. Austin said that five years have elapsed since the last full presentation on the Division of Pre-Clinical Innovation (DPI). Not all pre-clinical programs reside in DPI. For DPI, the focus is on predictive toxicology, predictive efficacy, and de-risking of undrugged targets and untreatable diseases (potential intervention points).

Dr. Austin reviewed NCATS' 3-D paradigm: develop, demonstrate, disseminate. Within this paradigm, DPI focuses primarily on the demonstration of external projects via collaboration and the dissemination of approaches that work. Dr. Austin also presented a traditional model depicting the **"**valley of death" in drug development. The valley represents the space that NCATS occupies, where research is "too applied for NIH and too risky for industry." DPI works on transforming the scientific ecosystem by turning potential into proof of concept.

Anton Simeonov, Ph.D., the Scientific Director and Director of DPI reviewed the Division's role and characteristics. DPI is addressing the shortcoming of the process that takes basic research discoveries to first-in-human testing. DPI staff represent many disciplines and subdisciplines. Unlike the rest of NIH, there is no tenure or tenure track at DPI, which allows staff to fearlessly pursue translational bottlenecks. The incentive system of traditional tenure is poorly aligned with what is needed in translational space. This model has served DPI well because people can change gears rapidly to respond to public health crises and other critical research needs. People develop expertise in different fields. DPI teams are also highly collaborative, working with outside experts, the rest of NCATS, other ICs and other federal agencies.

At DPI, project management plays a strong role, especially in late-stage projects approaching the IND application step. DPI research focuses on deliverables, be they molecule tools, drug candidates or databases, to help others conduct translation more readily.

Predictive Toxicology

According to Dr. Simeonov, the Toxicology in the 21st Century (Tox21) program is marking its 10th

anniversary this year. Initiated in partnership with National Institute of Environmental Health Sciences, the Environmental Protection Agency (EPA), the FDA and other agencies, the Tox21 program is designed to develop *in vitro* assays to (a) predict what will happen *in vivo* with exposure to drug candidates or environmental chemicals, and (b) prioritize chemical or toxicological interventions.

Tox21 collaborators are assembling a collection of 10,000 diverse chemicals (e.g., drugs, failed drugs, industrial chemicals, pesticides). About a third are drugs or drug-like chemicals. Initial efforts focused on developing new analytical methods and building predictive models. The result is the largest-ever toxicology data set (more than 90 million data points) in the public domain.

The Tox21 program also taps into a worldwide audience to build knowledge models. Sometimes prizes are awarded. Some predictive models had up to 90 percent accuracy, and some came from small countries and small businesses.

EPA is using an estrogen receptor assay data developed by the Tox21 program for regulatory purposes. Also, the EU's Innovative Medicines Initiative is using Tox21 data to rank compounds.

Dr. Simeonov reported that Tox21 program scientists responded rapidly to the Deepwater Horizon oil spill in the Gulf of Mexico. British Petroleum was ready to apply millions of gallons of oil dispersant into the Gulf without testing. Tox21 stepped in to test the dispersant for androgen and estrogen receptor activity. The tests were negative, and the dispersant was then applied.

DPI researchers also build models to predict whether a new drug will be metabolized rapidly or slowly or be cross-reactive with other therapeutic candidates. Such efforts have been historically challenging for competitive reasons. Dr. Simeonov said that DPI staff built a public portal for collaborative improvement of predictive models. They use machine learning and algorithms to use everyone's data without reviewing proprietary structures.

Predictive Efficacy

Dr. Simeonov said that tremendous progress has been made in the past 20 years in predictive efficacy. Predictive efficacy testing has moved from single tests in petri dishes to fully automated robotic screening of about 1 million tests per day. Yet challenges remain.

Aided by extreme miniaturization and advances in informatics data processing, DPI researchers developed a process for testing drug candidates at multiple doses. Output consists of rich pharmacological data sets with improved reliability and accuracy rates. With this powerful platform, DPI teams are profiling large chemical collections for undesirable properties.

Other DPI efforts aim to improve drug testing models to better predict effects in humans. Examples include 3-D tissue bioprinting to create arrays of tissues. A skin array was the first available for community use.

DPI is also using the power of induced pluripotent stem cells (iPSCs) for potential use in personalized medicine. Present methods for producing cells are expensive and not standardized or scalable. DPI staff set up a Stem Cell Translation Laboratory that applies cutting-edge technologies (single-cell proteomics, next-generation sequencing, and screening technologies) to establish quality control standards and improve methods for cell production by reducing cost; increasing efficiency; and demonstrating scalability, reproducibility and transferability.

Derisking Undruggable Targets, Untreatable Diseases (Medicinal Chemistry)

Dr. Simeonov said that DPI researchers strive to improve molecules that come through high through-put screens using multiparameter optimization (i.e., potency, solubility, metabolic stability). DPI staff also developed about 200 high-quality small molecules to use as target probes. A paper on small molecule probes for studying cancer metabolism was published in *Science.* This was a fledgling field just a few years ago, but DPI has made meaningful progress. Some compounds are in development as therapies.

Drug repurposing is very important to DPI, and initial efforts have focused on collecting compounds and reconciling chemical structures, stereoisomers and misspelled names. Each compound had to be synthesized or procured. DPI's collection has been used in public health emergencies. For Zika virus, DPI researchers scrambled to build screening methods from iPSC lines, set up screens and conduct some validation studies. The compounds are now available for further validation by the community.

DPI staff are working on rapid discovery of drug combinations for untreatable diseases. One paper on an oncology example was published in the *Proceedings of the National Academy of Science,* and the source code was also made available so others could replicate the process.

Dr. Simeonov said that DPI and NIH Clinical Center scientists collaborated to discover drug combinations to combat resistance to anti-infective drugs. They identified several three drug cocktails that were effective against 10 common multidrug-resistant isolates. Efforts are under way to develop rapid screens to guide clinicians about antimicrobial combinations for treating patients.

DPI provides scientific expertise and contract resources to support the Therapeutics for Rare and Neglected Diseases (TRND) and Bridging Interventional Development Gaps programs. The goal is to move these projects toward first-in-human testing and attract private investment. DPI has in-house capabilities for pharmacokinetics, ADME and IND-directed toxicology studies.

In terms of therapeutic development outcome measures, Dr. Simeonov reported that, as of November 2017, DPI received more than 600 proposals and accepted 70 projects. The 29 active projects led to 34 clinical trials, four natural history studies and 32 INDs. Five startup companies formed with TRND de-risked assets. Twenty-two agents have been licensed, acquired or raised funding after NCATS de-risking.

Dr. Simeonov gave an example of how DPI researchers used a partnership network to develop a new treatment for pulmonary alveolar proteinosis (PAP). Current treatment is whole-lung lavage under general anesthesia. Intravenous granulocyte-macrophage colony-stimulating factor (GM-CSF) is approved for myeloid reconstitution after bone marrow transplant. It is required for development of alveolar macrophages in the lung. TRND worked on toxicology for a new route of administration and then partnered with DCI to run a clinical trial that started last year in CTSA Program hubs.

Sharing Know-How

DPI's *Assay Guidance Manual* is published as an e-book to facilitate rapid updates. DPI staff disseminate the manual to end users through lectures and workshops attended by diverse audiences, thereby fulfilling the educational mission of NCATS.

Looking Ahead

Dr. Simeonov reported that his team is preparing a formal DPI strategic plan. NCATS leadership will be briefed when the implementation plans are ready, and the Advisory Council and CAN Review Board will be updated soon thereafter.

Discussion

Mr. Margus asked about the iPSC screens and how it is possible to figure out what goal was achieved. The chemistry after a screening hit is a major barrier. Dr. Simeonov said that, for many rare disease screens, libraries of approved drugs are used.

Dr. Merchant asked about the predictive efficacy module. How is DPI increasing predictive validity of systems? Are there certain indications or phenotypes for which models are more predictive? Dr. Simeonov said that for many genetic diseases, DPI staff can develop assays that report on the particular gene or gene product. Those assays do not rely on phenotypic screens. DPI scientists have worked hard to develop better reporter systems. To reduce false positives, DPI staff use two reporters; only if a positive signal is detected from both reporters, does DPI have confidence in the results. If only one is positive, then reporter interference is suspected.

Dr. Merchant asked about the iPSC system, and Dr. Simeonov described efforts to increase sophistication of iPSC technologies. The Zika screen, for example, was developed using astrocytes derived from iPSCs.

Dr. Merchant asked about the role of bioprinting. Dr. Simeonov said that bioprinting could fill the gap between tissue chips and single-well tests.

Dr. Palkowitz asked about collaborative science and new technologies and whether DPI is raising the floor of the valley of death or filling it in. How do these activities fit together to help the wider community? He suggested thinking more deeply about how tools, such as biophysical science tools for defining druggable surfaces and structure-guided approaches, can be used in tandem or as part of an extended process to help bridge the gap and be transformative. Dr. Palkowitz suggested that a future meeting could include a presentation on this forward-thinking strategy using an example, such as Niemann-Pick disease and cyclodextrin, now in phase 3 trials. NCATS could continue to evaluate cyclodextrin for related diseases, now that it has this platform.

Dr. Shekhar asked about tracking cost. Can DPI shortcuts reduce the astronomical cost of drug development? Dr. Simeonov said that there are data on high-throughput screening to show that it saves money. With the compound library, very high-quality data help reduce the number of hits lost in confirmation. Also, DPI researchers are testing machine learning as a means of predicting novel molecules that are not part of the library. Dr. Austin pointed out that both unit cost and failure rate contribute to costs. NCATS is working on both, but the main emphasis is on the failure rate because that is a multiplier. A small, retrospective analysis of the rare disease portfolio done by a finance professor at MIT, showed that the success rate of NCATS programs was twice that of the industry average at half the cost.

Dr. Austin further noted that the development of GM-CSF for PAP was a collaboration with the CTSA Program. That way, paperwork and various agreements were streamlined, netting major cost savings for NCATS, but those savings might not translate to academic centers or pharmaceutical companies.

IX. ADJOURNMENT OF OPEN MEETING

Dr. Austin thanked all participants for their input. He and Dr. Marks adjourned the open portion of the meeting at 3:04 p.m.

X. CLOSED SESSION OF 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.

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

Dr. Austin adjourned the closed session of the NCATS Advisory Council meeting at 4:03 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