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

## Ninth Meeting of the
## Cures Acceleration Network Review Board

## Minutes of Meeting

**December 12, 2014**

The Cures Acceleration Network (CAN) Review Board convened a meeting by teleconference, in open session, at 11:00 a.m. ET on December 12, 2014. Freda C. Lewis-Hall, M.D., CAN Review Board chair, led the meeting. In accordance with Public Law 92-463, the session was open to the public.

**CAN REVIEW BOARD MEMBERS PRESENT**

***Chair***

Freda C. Lewis-Hall, M.D., Executive Vice President and Chief Medical Officer, Pfizer

***Vice Chair***

Geoffrey S. Ginsburg, M.D., Ph.D., Director, Center for Applied Genomics & Precision Medicine; and Professor of Medicine, Pathology and Biomedical Engineering, Duke University Medical Center

***Executive Secretary***

Danilo A. Tagle, Ph.D., M.S., Associate Director for Special Initiatives, NCATS

***Board Members***

Robert J. Beall, Ph.D.
Jorge L. Contreras, J.D.
Pamela B. Davis, M.D., Ph.D.
Louis J. DeGennaro, Ph.D.
Frank L. Douglas, Ph.D., M.D.
Eric D. Kodish, M.D.
Bernard H. Munos, M.B.A.
Lawrence A. Soler, J.D.
Scott J. Weir, Pharm.D., Ph.D.

***Ad Hoc Members***

Harry P. Selker, M.D.
Anantha Shekhar, M.D., Ph.D.

**INVITED PRESENTER**

Christopher P. Austin, M.D., Director, National Center for Advancing Translational Sciences (NCATS)

**OTHERS PRESENT**

Julie Babyar
Rebecca M. Farkas, Ph.D.
Caren Howard
NCATS leadership and staff
Mei-Chun Lai
Kim Ng
Sara Siegler

## I. CALL TO ORDER AND OPENING REMARKS: Freda C. Lewis-Hall, M.D., Executive Vice President and Chief Medical Officer, Pfizer; Chair, CAN Review Board

Freda C. Lewis-Hall, M.D., welcomed the participants to the ninth meeting of the CAN Review Board on behalf of herself and Geoffrey S. Ginsburg, M.D., Ph.D., vice chair of the CAN Review Board. Dr. Lewis-Hall said that no discussion points or questions had been submitted in advance of the meeting.

## II. CONFIRMATION OF DATES FOR FUTURE MEETINGS OF THE NCATS ADVISORY COUNCIL AND CAN REVIEW BOARD: Danilo A. Tagle, Ph.D., M.S., Associate Director for Special Initiatives, NCATS; Executive Secretary, CAN Review Board

Danilo A. Tagle, Ph.D., M.S., reviewed the 2015 meeting schedule for the CAN Review Board and the NCATS Advisory Council:

January 15: Joint Meeting
June 17–18: Joint Meeting
September 3–4: Joint Meeting
December 11: CAN Review Board only (teleconference)

## III. UPDATE ON NCATS: Christopher P. Austin, M.D., Director, NCATS

Christopher P. Austin, M.D., welcomed members and guests to the ninth meeting of the CAN Review Board.

Regarding the U.S. federal budget, Dr. Austin noted that the House of Representatives passed a $1 trillion-plus funding bill, the so-called CRomnibus (a portmanteau of "Continuing Resolution" and "omnibus"). The Senate has passed a two-day Continuing Resolution, with a vote expected on the funding bill in a few days. The line item for the U.S. Department of Health and Human Services includes a full year's appropriations.

Assuming that the CRomnibus passes in its present form, Austin projected that CAN funding would remain unchanged. He said that NCATS staff already are working on the fiscal year 2016 budget request.

Austin acknowledged the hard work of the CAN Review Board on the concept clearances presented at the joint meeting in September, saying that Board members' input has

been incorporated into the concepts. Since the concepts have been cleared, the NCATS staff are planning to develop initiatives and issue funding opportunity announcements, taking into account budgetary considerations and program priorities. Because of budget constraints, NCATS may not be able to embark on new CAN initiatives right away, but when additional funds are available, NCATS can act quickly. It takes time to issue funding announcements, and so the lag time will be well spent.

Austin also announced that NIH will become the latest partner in Pfizer's Centers for Therapeutic Innovation (CTI) initiative. In addition to NIH, the CTI network includes 25 academic and patient foundation partners that collaborate with Pfizer. The NIH collaborative agreement will bring together NIH intramural and Pfizer scientific leaders working on targets amenable to intervention with biologics (e.g., antibodies, peptides, conjugated antibodies) via joint project teams aimed at developing proof-of-concept probes and then clinical probes. CTI has a particular emphasis on accelerating innovative discoveries from bench to bedside, which is a point of synergy with NCATS. Austin anticipates that this novel collaboration will help advance NCATS' mission to get more treatments to more patients more quickly.

## IV. TISSUE CHIP FOR DRUG SCREENING PROGRAM — PHASE II: Danilo A. Tagle, Ph.D., M.S., Associate Director for Special Initiatives, NCATS; Executive Secretary, CAN Review Board

Danilo A. Tagle, Ph.D., M.S., provided an update on NCATS' Tissue Chip for Drug Screening program, also referred to as the Microphysiological Systems (MPS) program. The program goal is to develop an in vitro platform using human tissues to evaluate the efficacy and toxicity of promising therapies. The effort is being funded by NCATS through the CAN budget, the NIH Common Fund, and several other NIH Institutes and Centers (ICs). The Defense Advanced Research Projects Agency is carrying out a parallel, complementary program, and the U.S. Food and Drug Administration (FDA) is providing regulatory science guidance for the projects.

According to Dr. Tagle, all 10 human physiologic systems will be functionally represented by human tissue constructs on bioengineered platforms (tissue chips), resulting in an integrated experimental system that is physiologically relevant, genetically diverse and pathologically meaningful. The system will be modular and reconfigurable. Tissues need to be viable for at least four weeks to accommodate the need for repeated testing. After five years, the technology will be made available to the research community.

The Tissue Chip program is being conducted in two phases, the first of which was directed at developing cell sources and platform; that phase concluded in July 2014. During Phase II, the individual tissue chips will be integrated into a human body on a chip — a system that can mimic the complex functions of the human body.

The performance measures used to evaluate transition from Phase I to Phase II included a scoring metric based on criteria compiled from recommendations of the CAN Review Board and a trans-NIH working group, as well as program goals and deliverables. The criteria included:

- Achievement of milestones;
- Validation;
- Reproducibility;
- Performance with a training set of compounds;
- Publications, patents and awards; and
- Other criteria, such collaborative efforts with other Tissue Chip awardees.

Tagle explained that MPS consortium members completed the majority of milestones for bioengineered platforms for the major organ systems. The members also developed a set of tools useful across the MPS consortium, among them sources and procedures for human induced pluripotent stem cells (hiPSCs); a training set of test compounds; miniature pumps, microanalyzers and biosensors; and improved biocompatible scaffolds to support three-dimensional (3-D) organ systems.

Tagle highlighted the progress made by the consortium members:

- **Liver:** Collaborators at the University of Pittsburgh developed a 3-D biomimetic liver sinusoid construct for predicting physiology and toxicity. The construct consists of four different cell subtypes (i.e., hepatocytes, stellate cells, Kupffer cells and endothelial cells). The liver on a chip generates biochemical and metabolic readouts and exhibits stable function, as evidenced by albumin secretion and enzymatic activity for up to four weeks. Optogenetic biosensors transduced into cells using lentiviral-based vectors are being used as readouts to show appropriate responses to test compounds.

- **Heart:** Researchers at the University of California, Berkeley, have integrated wild-type hiPSC-differentiated cardiomyocytes in dynamic cultures; the cardiomyocytes are capable of "beating." In systems created with hiPSCs from a patient with long-QT syndrome, the "heart rate" is slower than in systems derived from wild-type hiPSCs. When exposed to isoproterenol, the rate of beating increases, as would be expected of a beta-andrenergic agonist used for treating slow heart rate.

  In addition, researchers at Harvard University's Wyss Institute are linking cardiomyocytes and lung tissue on a chip to mimic the cardiopulmonary system. When the cardiomyocytes are stimulated, they "beat" uniformly. When hiPSC-derived myocytes from patients with Barth syndrome are used in the device, cardiac myopathy is evident, along with a weakened "heartbeat" compared with

a normal control. The disease is caused by a mutation in the *TAZ* gene that affects mitochondrial function, with cardiac damage resulting from the action of reactive oxygen species. The phenotype of the cardiomyocyte Barth syndrome on chip can be rescued by adding *TAZ* cDNA, which in turn produces the TAZ protein that restores the sarcomere structure. The search is under way for appropriate drug candidates.

- **Brain (neurodevelopment):** An investigator at the Morgridge Institute for Research in Wisconsin incorporated either hiPSCs or embryonic stem cells into a platform that could be used for predicting neural toxicity and teratogenicity. The stem cells differentiate into neuronal and glial subtypes. These cells self-aggregate and form a laminar structure, complete with neurons, glia and vasculature.

- **Skeletal muscle:** Duke University researchers are developing a bioengineered chip that consists of human muscle bundles capable of contraction and calcium efflux when exposed to electrical stimulation.

- **Kidney:** Investigators at the University of Washington currently are conducting research using a tissue-engineered 3-D kidney on a chip. The MPS platform supports self-assembly of renal tubules from primary renal tubule epithelial cells, and it recapitulates normal kidney expression of markers such as SGLT2 and KIM-1. The bioengineered microvasculature in the model recapitulates the operation of kidneys in terms of platelet adhesion and coagulation of red blood cells in the presence of cyclosporine A.

- **Microvasculature:** The team at Washington University in St. Louis is working on combining tumor spheroids and cardiac tissue, resulting in an MPS model of microvasculature. Using 1-micrometer beads, the scientists have demonstrated the formation of microchannels from hiPSCs and perfusion of the tissue, as well as the angiogenic effects in tumor spheroids.

- **Gut:** Investigators at the Cincinnati Children's Hospital are combining hiPSC-derived gut and nerve tissue to create gut enteroids — 3-D multicellular "mini-guts" with innervated structures. This bioengineered device will be tested soon for peristaltic activity; if successful, the chip could support studies of the intestinal microbiome.

Tagle presented graphical representations of two systems envisioned for Phase II of the program. One group of investigators within the MPS consortium is planning to integrate the liver, kidney and gastrointestinal systems. This highly collaborative effort is intended to link the individual tissue chips in a largely engineering-driven initiative by looking at issues of organ scaling and perfusion by using miniature pumps and valves. Another integration plan by another group of investigators is driven more by biology in order to

connect MPS models of the liver, heart, microvasculature and brain. This effort is more about developing organs on chips using the same hiPSC line and the identical engineering platform.

Organs on chips generated from hiPSCs could in the future be used to study the human microbiome, toxins, infectious diseases and countermeasures against bioweapons. Also, they might serve as tools for clinical trials. The human body on a chip could be extended to develop personalized chips to predict drug response in individuals and support individualized medicine. The technology could enable studies in many different genotypes and populations and could further research in rare diseases and therapeutics development while serving to expedite studies of drug efficacy as well as screening for toxicity.

More information is available at www.ncats.nih.gov/tissue-chip.html.

***Discussion***

Geoffrey S. Ginsburg, M.D., Ph.D., inquired about the regulatory path to apply the tissue chip technology in various clinical development settings, the commercialization pathway, and related considerations. He underscored the importance of ensuring that this technology will be useful to a variety of stakeholders. Tagle responded that partners in the biotechnology and pharmaceutical sectors have been interested in this technology; some are already collaborating with the academic investigators on development of the platforms, for example. Also, some of the academic institutions are setting up companies for investment and commercialization. Insofar as the human body on a chip is concerned, Tagle said that several models could be exploited to commercialize the concept. For example, the business model of contract research organizations already exists. NCATS has issued a request for information (RFI) to probe commercial interest in the technology; the responses are being synthesized now. Academic investigators might be interested in forming partnerships with the companies that responded to the RFI.

To ensure that the technology could be used in the regulatory process, the FDA has been involved since the start of the MPS program, Tagle explained. Meetings with investigators occur regularly, and the FDA hosted a meeting this past summer to introduce regulators to the technology. An ongoing conversation between NCATS and the FDA will help ensure that drug developers understand what kinds of data sets would have to be generated to compare with the current paradigms for toxicity testing in the support of a regulatory application.

Frank L. Douglas, Ph.D., M.D., asked about potentially using the tissue chip devices as surrogates for animal toxicity studies and whether they would be amenable for high-throughput analysis for prioritizing compounds for further development. Tagle clarified that the major goal is for the chips to supplant animal toxicity studies; they are not

envisioned as a potential high-throughput tool. He speculated that some candidate drugs coming out of screening could be prioritized and then tested in chips as a supplement or substitute for animal testing.

Scott J. Weir, Pharm.D., Ph.D., inquired about the possibility of other NIH ICs leveraging CAN funding for the MPS program. Tagle pointed out that CAN funds are supporting only a portion of the project; monies from other ICs and the NIH Common Fund are already offsetting some of the total program costs. The National Institute of Biomedical Imaging and Bioengineering, National Cancer Institute, National Institute of Environmental Health Sciences, Office for Research on Women's Health, and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, for example, have contributed funding for certain projects. The goal is to leverage the program's initial successes and encourage other stakeholders to invest in the next phase of the program.

## V. CAN REVIEW BOARD DISCUSSION

**Freda C. Lewis-Hall, M.D., Executive Vice President and Chief Medical Officer, Pfizer; Chair, CAN Review Board; and Geoffrey S. Ginsburg, M.D., Ph.D., Director, Center for Applied Genomics & Precision Medicine; Professor of Medicine, Pathology and Biomedical Engineering, Duke University Medical Center; Vice Chair, CAN Review Board**

Freda C. Lewis-Hall, M.D., asked the CAN Review Board members to brainstorm models for the various types of partnerships discussed. What are some examples of alternative funding models and collaborations or partnerships across disciplines? Examples could include philanthropic funding or matching funds from other institutions and agencies.

Geoffrey S. Ginsburg, M.D., Ph.D., underscored the importance of targeting good opportunities for CAN despite the current flat funding. The CAN Review Board members could serve as ambassadors to foster partnerships as an excellent way to leverage available funds.

Collaboration has served as a means to amplify funding for projects that are under way and some others that have already succeeded, according to Lewis-Hall. She recalled, for example, that the Discovering New Therapeutic Uses for Existing Molecules (New Therapeutic Uses [NTU]) program of NCATS resulted in pharmaceutical companies providing compounds to allow a group of academic investigators to explore potential new indications for the drug candidates. Are there other models whereby NIH could increase its reach to investigators, support further studies of existing compounds or provide access to additional compounds?

Anantha Shekhar, M.D., reported on efforts in the Midwest by a group of regional Clinical and Translational Science Awards (CTSA) grantees and local, large industry partners Eli Lilly and Co. and Takeda Pharmaceuticals to put together resources to find

targets for unique disease mechanisms. CTSAs can help spark in-kind contributions and expertise, and the industry partners have contributed funding. The current project is focusing on new targets in autoimmune mechanisms. He asked how CAN could partner with such a consortium and whether CAN could fund joint research between industry and academic scientists. Lewis-Hall thought that this could be a helpful model for further consideration in an offline discussion to more fully understand the concept and then match with possibilities for CAN.

Pamela B. Davis, Ph.D., M.D., said several investigators at Case Western Reserve University have identified targets and also existing drugs that bind the targets. She asked whether NIH has template agreements available that could allow companies that have these drugs (or comparable ones) to collaborate with the academic scientists on studies of the drugs' effects on the targets. Christopher P. Austin, M.D., said that templates for the NTU were set up for companies that had compounds they were willing to share. NCATS accelerated the process with template agreements to shorten the negotiation time between companies and academic institutions from a year or more to just 11 or 12 weeks. Those templates are fully accessible on the Web and could certainly be used by others that want to engage in this type of collaborative work.

Frank L. Douglas, Ph.D., M.D., asked about ways to facilitate the transfer of technology (devices in particular) from CTSAs to industry partners and what the current mechanisms are for sharing. Dr. Austin responded that such transfers have been based on one-to-one relationships between individual CTSA grantees and local companies and that most of the CTSA grantees have such relationships.

Davis mentioned the Ohio Clinical Trials Collaborative, a pilot project involving the three CTSA grantees in Ohio. The collaborative has a single entry point to query the CTSA grantees about their interest and expertise in particular drugs or devices. For example, it engaged a practice-based research network on vaccine testing to recruit a large number of participants for a trial very quickly. Davis recommended starting with modest networks to establish trust and work out the challenges before expanding to larger groups.

Scott J. Weir, Pharm.D., Ph.D., said that a collaboration between the University of Kansas and the Leukemia & Lymphoma Society has generated partnership models that could be shared. One initial project was a laboratory discovery that was translated to the clinic as a pilot project of the Therapeutics for Rare and Neglected Diseases (TRND) program. With TRND funding to get things going, the partnering organizations were able to raise an additional $2.1 million to run two clinical trials. This experience with the partnership and NCATS' initial investment has been quite successful. Dr. Weir then asked about a role for the Foundation for NIH in helping to raise money for partnerships and to demonstrate leverage. Lewis-Hall said that the NIH Foundation has indeed been able to facilitate partnerships.

Dr. Douglas suggested convening a "technology transfer fair" at which the CTSA grantees could present their ideas to industry.

Referring to ways for NCATS or the CTSA grantees to showcase technologies to industry, Davis spoke of her experience with the National Center for Accelerating Innovation in Ohio, which is funded through a grant from the National Heart, Lung, and Blood Institute. She said that industry participants must be interested and knowledgeable about the technology and must have the power to make decisions about obtaining more information if they are interested. She said that developing a public one-pager on each technology would be ideal.

Austin recalled an event in Cambridge, Massachusetts, in which 15 projects were presented to about 200 people in relevant industries. He said this approach was valuable for both academia and industry. Austin also said that currently, many companies are changing their business models to take up projects coming out of academic institutions. NCATS has assembled templates that can be shared broadly for collaborations with companies in the pharmaceutical, venture capital and biotechnology sectors.

Dr. Ginsburg suggested that NCATS could set up an office to broker relationships to stimulate partnerships for sharing compounds, targets and technologies with clinical programs. Austin said that this is a goal of the NCATS Strategic Alliances for Technology Transfer office and that he does not envision any restrictions on this type of activity as long as the institutions are willing to contribute. NCATS intramural division investigators already are engaged in these activities, but it might be possible to engage CTSA grantees in a similar way in the future.

Weir discussed partnering early in the development process, when someone wants to move forward with a concept. For example, patients or citizen scientists could approach their local CTSA grantee to work on bedside observations that patients or citizen scientists envision. Alternatively, NCATS could serve as a matchmaker on a nationwide basis to "crowdsource" CTSAs to work on identified challenges. The CTSAs could come up with the resources to work on the problems. This role would dovetail with NCATS' mission. Ginsburg applauded this idea, saying that for small amounts of investment, NCATS could be a social networker to bring groups together to solve problems. In terms of the NCATS and CAN portfolios, Ginsburg encouraged Austin to think about this proposal as a key strategy for the organization. Austin recalled that a similar effort is under way in the NCATS Office of Rare Diseases Research that is based on patient input. Lewis-Hall was interested in exploring how the CAN Review Board could facilitate matchmaking by NCATS to transfer device and drug technologies.

Ginsburg recommended that NCATS consider partnering with other networks, such as the Patient-Centered Outcomes Research Institute (PCORI), which focuses mainly on creating a network for research in comparative effectiveness. Austin said that PCORI

Director Joe V. Selby, M.D., M.P.H., spoke at the September 2014 joint meeting of the NCATS Advisory Council and the CAN Review Board. Austin suggested that Petra Kauffman, M.D., M.Sc., director of the NCATS Division of Clinical Innovation, could include an update on PCORI during her update on the CTSA program at an upcoming joint meeting. Austin also said that NCATS staff meet regularly with PCORI representatives and that there is coordination between CTSA and PCORI working groups.

Ginsburg thanked the CAN Review Board members for the rich discussion on various collaborative models. He said that the chairs and NCATS leaders and staff will thoughtfully consider and follow up on some of the suggestions. Lewis-Hall thanked the meeting participants and the NCATS staff who facilitated the webinar.

**ADJOURNMENT OF THE CAN REVIEW BOARD MEETING**

Freda C. Lewis-Hall, M.D., adjourned the meeting of the CAN Review Board at 12:45 p.m. ET.

**CERTIFICATION**

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

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Freda C. Lewis-Hall, M.D. Date
Chair, Cures Acceleration Network Review Board
and
Executive Vice President and Chief Medical Officer, Pfizer

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Danilo A. Tagle, Ph.D., M.S. Date
Executive Secretary, Cures Acceleration Network Review Board
and
Associate Director for Special Initiatives, NCATS