

**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  
June 18, 2015**

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 June 18, 2015, 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 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.

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***

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

***Council Members***

Margaret A. Anderson, M.A. (by  
telephone)

Jorge L. Contreras, J.D.

Pamela B. Davis, M.D., Ph.D.

Mary L. Disis, M.D. (by telephone)

Geoffrey S. Ginsburg, M.D., Ph.D.

Eric D. Kodish, M.D.

Freda C. Lewis-Hall, M.D.

Bernard H. Munos, M.B.A.

Harry P. Selker, M.D.

Anantha Shekhar, M.D., Ph.D.

Todd B. Sherer, Ph.D.

Scott J. Weir, Pharm.D., Ph.D.

***Representative Members***

Ankit A. Mahadevia, M.D., M.B.A., Atlas Venture (by telephone)

***Ad Hoc Member***

Paul G. Yock, M.D., Stanford University (by telephone)

***Ex Officio Member***

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

**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 in the Duke Institute for Genome Sciences & Policy; 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**

Margaret A. Anderson, M.A. (by telephone)	Bernard H. Munos, M.B.A.
Robert J. Beall, Ph.D.	Harry P. Selker, M.D.
Jorge L. Contreras, J.D.	Anantha Shekhar, M.D., Ph.D.
Mary L. Disis, M.D. (by telephone)	Lawrence A. Soler, J.D.
Eric D. Kodish, M.D.	Myrl Weinberg, M.A.
	Scott J. Weir, Pharm.D., Ph.D.

**Representative Members**

Ankit A. Mahadevia, M.D., M.B.A., Atlas Venture (by telephone)

**Ex Officio Members**

David Atkins, M.D., M.P.H., Department of Veterans Affairs  
S. Rao Kosaraju, Ph.D., National Science Foundation  
Terry Rauch, Ph.D., Department of Defense  
Frank F. Weichold, M.D., Ph.D. (attending in place of Steven Ostroff, M.D.),  
Food and Drug Administration

**INVITED PRESENTER**

Stephen M. Strittmatter, M.D., Ph.D., Professor of Neurology and of Neurobiology, Director of Cellular Neuroscience, Yale University

**I. CALL TO ORDER AND WELCOME**

Christopher P. Austin, M.D., welcomed members and guests to the ninth meeting of the NCATS Advisory Council and the 11th meeting of the CAN Review Board. He reminded attendees that the open session was being videocast. He welcomed *ex officio* members David Atkins, M.D., M.P.H.; S. Rao Kosaraju, Ph.D.; Terry Rauch, Ph.D.; and Frank F. Weichold, M.D., Ph.D.

**II. CONSIDERATION OF MINUTES AND CONFIRMATION OF MEETING DATES: Danilo A. Tagle, Ph.D., M.S., Associate Director for Special Initiatives, NCATS; Executive Secretary, NCATS Advisory Council and CAN Review Board**

The minutes of the joint meeting held on Jan. 15, 2015, were approved as written. Danilo A. Tagle, Ph.D., M.S., reminded the group that the remaining joint meeting in 2015 is scheduled for September 3 and 4. In addition, the CAN Review Board will meet by teleconference on Dec. 11, 2015.

**III. INTRODUCTION OF NEW STAFF: Petra Kaufmann, M.D., M.S., Director, Division of Clinical Innovation, NCATS**

Petra Kaufmann, M.D., M.S., introduced two new Division of Clinical Innovation staff members:

- **Redonna K. Chandler, Ph.D.**, who previously was chief of the Services Research Branch at the National Institute on Drug Abuse.

- **Michelle A. Culp, B.S.N., M.P.H.**, who previously worked at the National Institute of Dental and Craniofacial Research and the National Institute of Allergy and Infectious Diseases.

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

Each meeting participant received a booklet containing in-depth information and background on recent NCATS accomplishments. NCATS' successes have increased, and providing a comprehensive description of all progress during the director's report would be impractical.

NCATS' executive officer M. Janis Mullaney, M.B.A., retired June 1, 2015, after a 41-year career at NIH. Christopher P. Austin, M.D., thanked her for her service and dedication. Dr. Austin said NCATS has identified and approved a new executive officer who will be announced soon.

Three CAN Review Board members have finished their terms: Alta Charo, J.D.; Sue Siegel, M.S.; and Paul Yock, M.D. A new cohort will be appointed to the CAN Review Board soon.

NCATS recently launched a new public website that better reflects the Center's science, style and mission. Austin thanked the Advisory Council and CAN Review Board members for their input and feedback throughout the design process, and he encouraged them to continue sharing their thoughts.

Todd B. Sherer, Ph.D., asked whether NCATS was tracking traffic on its new website and analyzing the site's use. Cindy McConnell, director of the NCATS Office of Communications, said she and her staff are indeed gathering and regularly reviewing analytics.

#### **Selected Translational Innovation Highlights**

Austin presented examples of progress in early-, middle- and late-stage development along the translational science spectrum:

- **Early-stage translation:**
  - A team of NCATS scientists was selected for a highly competitive award from the U.S. Department of Health and Human Services (HHS) for its Collaborative Use Repurposing Engine (CURE). CURE is a Food and Drug Administration (FDA)-NCATS collaboration to centralize information about repurposing of drugs in the treatment of neglected diseases.
  - The plate-saving initiative described during the last meeting has since won the Green Champion award from HHS. Thanks to the new technology, NCATS has kept nearly 50,000 microtiter plates out of landfills and saved nearly a half million dollars. The initiative currently is being commercialized.
  - Since the January 2015 Advisory Council/CAN Review Board meeting, the NCATS Pharmaceutical Collection (NPC) has yielded two important discoveries.
    - T. Jake Liang, M.D., of the National Institute of Diabetes and Digestive and Kidney Diseases, and his team, in collaboration with NCATS scientists, identified a generic antihistamine called chlorcyclizine that successfully ameliorates hepatitis C infection in cellular and animal models of the disease. The repurposed drug is now in a Phase IB clinical trial at the NIH Clinical Center.

- Investigators at Case Western Reserve University, in collaboration with NCATS scientists, found that two previously approved drugs, clobetasol and miconazole, promote remyelination in mice. These drugs have the potential to reverse some of the effects of demyelinating disorders, such as multiple sclerosis.
- **Mid-stage translation:**
  - Through the NCATS New Therapeutic Uses (NTU) program, Stephen M. Strittmatter, M.D., Ph.D., of Yale University has determined that a drug developed by AstraZeneca to treat cancer has the potential to treat Alzheimer's disease. (See details in Section V of these Minutes.)
  - A paper in *Science Translational Medicine* analyzed the NCATS rare disease portfolio in the Therapeutics for Rare and Neglected Diseases (TRND) and Bridging Interventional Development Gaps (BriDGs) programs for cost, productivity and efficiency. The authors found that NCATS' success rates are higher and its costs lower than the industry standard for orphan drug development.
  - The Tissue Chip for Drug Screening program continues to advance, and NCATS recently produced a short [video](#) to promote this scientific initiative.
- **Late-stage translation:**
  - NCATS and the NIH Clinical Center co-hosted Rare Disease Day on Feb. 27, 2015. More than 1,000 people participated in person or via videocast.
  - The Clinical and Translational Science Awards (CTSA) program released funding opportunity announcements (FOAs) on April 2, 2015, and June 5, 2015. These Collaboration Innovation Awards, Recruitment Innovation Centers and Trial Innovation Centers FOAs are designed to foster collaboration across CTSA hubs and increase the efficiency and effectiveness of multisite clinical studies.
- **Policy and legislative updates:**
  - On Feb. 2, 2015, President Obama released the budget request for fiscal year (FY) 2016, which included \$660.1 million for NCATS, representing an increase of \$27.4 million over the FY 2015. The House Appropriations bill was released June 16; the Senate Appropriations bill has not yet been released.
  - The U.S. House of Representatives' 21st Century Cures bill is a bipartisan initiative to "accelerate discovery, development and delivery of treatments and cures for disease." The bill would reauthorize NIH, establish an innovation fund and require an NIH-wide strategic plan. The bill was unanimously reported out of the House Energy and Commerce Committee in May 2015. NCATS-specific provisions include:
    - Allowing NCATS to support clinical trial activities through Phase IIB and for rare disease conditions through Phase III.
    - Removing the Other Transaction Authority (OTA) restriction that no more than 20 percent of CAN funds may be used for OTA.
  - The Senate Health, Education, Labor and Pensions committee held hearings on biomedical innovation in March and April of 2015. Austin and Roderic I. Pettigrew, M.D., Ph.D., director of the National Institute of Biomedical Imaging and Bioengineering, delivered remarks and answered questions at the March hearing.
  - Senator Barbara A. Mikulski (D-MD) visited the NCATS Division of Pre-Clinical Innovation intramural research facility on March 31. She also held a press

conference at which Francis S. Collins, M.D., Ph.D., director of NIH, announced the NTU program's Alzheimer's disease advance. Senator Mikulski then called for a 10 percent increase in the NIH budget, with subsequent increases to \$45 billion by 2020.

- Senators Lindsey O. Graham (R-SC) and Richard J. Durbin (D-IL) formed the Senate NIH Caucus as "a bipartisan strategy to restore the purchasing power that NIH has lost and provide steady, predictable growth for biomedical research in the future." The caucus has 21 other members.
- The CROmnibus (as well as the draft 21st Century Cures bill) mandates that NIH develop a strategic plan by the end of 2015. NIH is currently engaged in an internal planning process. The public comment period and engagement with stakeholder groups regarding the planning process will take place over the summer, and NIH advisory councils will be updated in the autumn on the progress.
- Separately, NCATS is in the process of developing its own strategic plan. Dorit Zuk, Ph.D., director of the NCATS Office of Policy, Communications and Strategic Alliances, and her colleagues have collected and are currently analyzing internal feedback from NCATS staff. They will launch an external feedback process at the September Advisory Council/CAN Review Board meeting and hope to publish the strategic plan by March 2016.

### **Discussion**

Following Austin's remarks, S. Rao Kosaraju, Ph.D., asked whether NCATS supports a tissue chip-type program in software emulation. Austin responded that the current focus is on developing biological organoids that can reproduce the structure and function of human organs. The process does require the engineering of microfluidics for the chips. Danilo A. Tagle, Ph.D., M.S., added that part of the program involves machine-learning algorithms, saying that FDA has an *in silico* human physiological systems unit, which is used for modeling.

Frank F. Weichold, M.D., Ph.D., director of Critical Path and Regulatory Science Initiatives at FDA, confirmed that his agency is making efforts in pharmacological modeling and simulation.

Harry P. Selker, M.D., noted that NCATS is working hard to collaborate with other NIH Institutes and Centers (ICs). He asked whether there was anything that Council members could do to help enable those collaborations. Austin encouraged Council members to remind their home ICs about NCATS' willingness, expertise and capabilities.

Robert J. Beall, Ph.D., reminded the Council to include biotech and the pharmaceutical industry in its efforts to inspire collaboration.

Pamela B. Davis, M.D., Ph.D., asked whether Congress expected the NIH strategic plan to address specific themes, elements or diseases. Austin responded that the strategic plan was intended to account for how NIH would spend its budget. He said that there was also an ongoing political discussion about disease prioritization. He asked Dr. Davis to ask her question again when the strategic plan draft is released for feedback.

Eric D. Kodish, M.D., asked how the prohibition on Phase III studies for NCATS came to be. Austin said that it was an artifact of NCATS' creation and that the restriction came from Congress, not NIH. NCATS is working to have the restriction lifted.

Myrl Weinberg, M.A., said that several years ago, Congress commissioned the Institute of Medicine to analyze the NIH prioritization process. She suggested that Austin and his committee review the resulting report as an aid to developing the NIH strategic plan.

Geoffrey S. Ginsburg, M.D., Ph.D., asked how NCATS projects interface with the Precision Medicine Initiative (PMI). Austin said he is on the Institute Directors working group on the PMI and that he believes there will be many opportunities for NCATS to be involved with the initiative. The NIH plan for the PMI will be released in September.

Anantha Shekhar, M.D., Ph.D., asked whether there is a coordinated infrastructure for managing Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs and whether other ICs could use NCATS innovations. Lili M. Portilla, M.P.A., said the goal is collaboration with other ICs but that NCATS cannot accept funds from SBIR recipients to defray costs. Weichold said the Office of the Chief Scientist at the FDA faces similar challenges.

**V. DISCOVERING NEW THERAPEUTIC USES FOR EXISTING MOLECULES PROGRAM:  
Christine M. Colvis, Ph.D., Director, Drug Development Partnership Programs, NCATS**

Christine M. Colvis, Ph.D., provided a brief overview of the NTU program and its recent progress. For this program, NCATS partners with pharmaceutical companies that offer investigational drugs to researchers interested in repurposing. These are drugs that already have a safety profile for which development had been discontinued because of efficacy or business concerns. Pharmaceutical companies provide the drugs and matched placebos while NCATS provides support for the research.

One project funded by the program is Stephen M. Strittmatter, M.D., Ph.D.'s repurposing of Fyn kinase inhibitor AZD0530, which has the potential to become a groundbreaking treatment for Alzheimer's disease.

**Stephen M. Strittmatter, M.D., Ph.D., Vince Coates Professor of Neurology; Director of Cellular Neuroscience, Neurodegeneration, and Repair; Director of the Memory Disorders Clinic, Yale University School of Medicine**

Dr. Strittmatter explained the steps that led to his team of investigators' selection of Fyn kinase, their early research and their work with AZD0530.

**Background**

Alzheimer's disease is characterized by a buildup of plaques in the brain. Amyloid beta peptide molecules come together in small oligomers, which then impair synapses. The impaired synapses eventually lead to dementia. Without amyloid beta or a protein called Fyn kinase, however, this impairment does not happen. In a 2012 paper in the journal *Nature Neuroscience*, Strittmatter and his colleagues reported on the significance of Fyn kinase. His team showed evidence of the relationship between Fyn kinase activity and synapse destruction in both cell

culture and mouse models. If a drug could inhibit Fyn kinase, it might be able to slow Alzheimer's disease-related synapse damage.

### **Finding a Drug**

The first FOA from the NTU was released around the time of Strittmatter's journal publication. The list of available drugs included an AstraZeneca drug, AZD0530, which acts as a Fyn kinase inhibitor. Strittmatter applied, and his team began work with the drug shortly thereafter. AZD0530 had originally been developed as a cancer drug, and in Phase II clinical trials, the drug had proved to be orally bioavailable, safe and long lasting. Strittmatter and his colleagues still had several important questions to answer:

- Can AZD0530 cross the blood-brain barrier?
- Is it effective in Alzheimer's disease patients?
- Is it safe for chronic use by elderly patients with Alzheimer's disease?

### **Early Trials**

Strittmatter's team tested the drug in a mouse model of Alzheimer's disease. AZD0530 was in fact able to cross the blood-brain barrier, and it proved safe for chronic use. The drug was also effective: Transgenic Alzheimer's disease mice that had developed memory deficits, when treated for a month with AZD0530, showed a regrowth of synapses as well as renewed learning and memory functions. In learning and memory tasks, treated mice performed as well as the wild-type group. Within a month, the drug had reversed their memory deficits.

Also during the first year, a Phase I trial was conducted at Yale University Medical Center's Alzheimer's disease unit. The trial enrolled patients with mild to moderate Alzheimer's disease and administered 0 milligrams (mg), 50 mg, 100 mg and 125 mg of AZD0530. The purpose of the trial was to monitor for adverse effects and assess tolerability to the drug in Alzheimer's disease patients. The cerebrospinal fluid of patients was measured to determine how much of the drug they were getting and whether it matched the effectiveness of a similar dose in mice.

The drug began inhibiting Fyn kinase at 100 mg and 125 mg, which is consistent with dose levels in mice. Only one patient experienced a serious adverse event, which may or may not have been related to the drug.

### **Latest Trials**

Based on the drug's safety and efficacy profile, Strittmatter and his team initiated a Phase IIA trial. This trial is a placebo-controlled, randomized study to test whether AZD0530 slows, halts or reverses Alzheimer's disease over a 12-month period and to monitor safety and tolerability.

This is a multisite trial that will enroll 152 subjects. As of the NCATS Advisory Council/CAN Review Board meeting, the trial has been approved by the institutional review boards (IRBs) of 17 out of 22 sites.

### **Discussion**

Todd B. Sherer, Ph.D., asked what the next step would be if the Phase IIA trial is successful. Strittmatter said that the goal of his work is to provide strong data and that it will be up to AstraZeneca to move the product forward into the market.

Myrl Weinberg, M.A., asked whether AZD0530 is patented. Strittmatter said that the composition of matter is already well protected and that Yale has filed a patent for the drug's use in Alzheimer's disease.

Geoffrey S. Ginsburg, M.D., Ph.D., asked whether Strittmatter and his team had considered other Src-family inhibitors and whether pharmaceutical companies were looking into them. Strittmatter said he had not looked into all of them.

Scott J. Weir, Pharm.D., Ph.D., asked about the nature of Yale and AstraZeneca's interactions with the FDA to date. Strittmatter said that AstraZeneca had provided his team with the initial Investigational New Drug (IND) package and their previous filings for cancer. For the Alzheimer's disease studies, Yale filed an IND and designed the Phase I and II trials. AstraZeneca provided some feedback on trial design.

Anantha Shekhar, M.D., Ph.D., asked whether there were any concerns about bone damage with long-term use of AZD0530. He also asked whether Fyn kinase might be critical to other neurodegenerative pathways. Strittmatter said that there was no evidence of adverse effects on bone at the 100 mg and 125 mg doses that the studies are using.

Pamela B. Davis, M.D., Ph.D., asked whether the drug could have a role in treating traumatic brain injury. Strittmatter said that that hasn't been studied yet, but it would be worth looking into.

Jorge L. Contreras, J.D., said that NCATS has several drug repurposing programs but that he was not sure how they relate. He asked which program was responsible for the hepatitis C virus and remyelinating drugs that Christopher P. Austin, M.D., mentioned in his director's report. Dr. Austin said that the NTU program is for investigational drugs that are not yet on the market and that the NPC program consists of existing drugs that might be repurposed. Mr. Contreras asked whether either initiative was associated with the high-throughput screening (HTS) robot. Austin said that the HTS robot is a part of the NCATS Division of Pre-clinical Innovation and used in studies with the NPC.

Dr. Shekhar asked whether there was a way to promote interaction between CTSA awardees and NCATS' drug repurposing programs to change the way early clinical testing is done across diseases. Petra Kaufmann, M.D., M.S., said that NCATS does encourage researchers to use existing outcome measures rather than inventing new ones. She also said that outcome data would need to set the stage for the regulatory pathway and that the NCATS Rare Disease Clinical Research Networks program is designed to work via a consortium to focus on groups of rare diseases rather than individual disease entities.

Austin asked whether the "inclusion criteria" would select for participants who would respond to AZD0530. Strittmatter said the studies were focused on early- to mid-stage Alzheimer's disease because people in those states are more likely to respond to treatment. In the later stages of the disease, neurons are lost. Unlike synapses, they cannot be recovered.

Austin asked Strittmatter what he would have done without the NTU initiative. Strittmatter said that it would have been much more difficult for him to acquire a drug to study without the NTU program.



Shekhar noted that disease phenotyping and longitudinal cohort studies are ideally suited for a CTSA environment.

**VI. REPORT FROM ADVISORY COUNCIL SUBCOMMITTEE ON PARTNERSHIPS WITH PHARMACEUTICAL AND BIOTECHNOLOGY COMPANIES AND VENTURE CAPITAL FIRMS:  
Freda Lewis-Hall, M.D., Chief Medical Officer, Pfizer**

Freda Lewis-Hall, M.D., provided an overview of the subcommittee's purpose and progress to date. The subcommittee's charge was to provide recommendations to NCATS on how to maximize the awareness and effectiveness of existing programs with commercial partners, such as the pharmaceutical and biotechnology industries. The subcommittee also explored ideas and models that can further NCATS' visibility and effectiveness by developing strategic public-private partnerships that stimulate and facilitate innovation in translational science.

The May 2014 Advisory Council/CAN Review Board meeting featured a discussion of concepts the subcommittee might consider. Promising ideas included:

- Expanding existing NCATS programs like the NTU to allow for co-funding from other stakeholders.
- Increasing the capacity of existing "de-risking" programs like TRND and BrIDGs to allow for co-funding from other stakeholders.
- Developing a rare-disease meta-registry to allow data to be mined for commonalities. This would be the first step toward promoting meta-collaborations.

The subcommittee made two groups of recommendations to the Advisory Council and the CAN Review Board: proposed concepts and proposed approaches.

**Recommendations: Proposed Concepts**

- Identify "game-changing" transformational science, technology platforms and projects such as the Tissue Chip program, devices, tissue printing, electroceuticals and synthetic biology.
- Identify existing translational projects that need additional resources to move to the clinic and beyond, such as TRND, BrIDGs, molecular probes and engineering/information technology, or a rare-disease meta-registry to mine data for commonalities.
- Assess the scientific, technological and business barriers to advancing these projects rapidly.

**Recommendations: Proposed Approaches**

- Consult pharmaceutical, biotechnology and venture capital experts and stakeholders from NIH translational programs to define the scope of qualified programs.
- Identify gaps in existing programs.
- Develop processes and business models to connect project owners with external partners with interest, capabilities and funding resources. These may include crowdsourcing, venture capital or NTU-like models.
- Develop metrics to assess success in project progress, business and partnership models, and funding innovation.

Dr. Lewis-Hall described a triangle, with points labeled “funding,” “compounds” and “investigators.” Which angle, she asked, should the subcommittee recommend expanding?

### **Discussion**

Robert J. Beall, Ph.D., asked whether there was any way for NCATS to recover any money from its work with AstraZeneca. Christopher P. Austin, M.D., said that the only way for NCATS to claim any money would be if the Center had an intellectual property claim. AZ0530 belongs to AstraZeneca and Yale University.

Dr. Beall asked how much NCATS had invested in Stephen M. Strittmatter, M.D., Ph.D. Dr. Strittmatter said that his trials were 100 percent paid for by NCATS, which amounted to about \$10 million. Beall encouraged NCATS to think creatively about ways to recover some of that investment. Lili M. Portilla, M.P.A., noted that there is no new intellectual property to claim through the NTU program.

Lewis-Hall asked the Advisory Council/CAN Review Board for more creative funding ideas. She asked whether the group liked the idea of bringing in disease foundations to fund research. Ms. Portilla said that that model would be different but still possible.

Harry P. Selker, M.D., suggested trying to bring non-patented agents into public use. Lewis-Hall said that she liked that idea and that doing so would increase the number of available compounds for research. Dr. Selker said that it can be difficult to pursue treatments that have no financial leverage, but they are no less valuable to the public. Lewis-Hall said that the World Intellectual Property Foundation has done something similar by collecting, curating and offering off-patent agents.

Todd B. Sherer, Ph.D., supported the idea of engaging with disease foundations. He said it would be attractive to the foundations as well, as NCATS could facilitate partnerships with pharmaceutical companies that the foundations could not arrange alone. He suggested drawing up a proposal to consider how much the idea might appeal to foundations.

Lawrence A. Soler, J.D., suggested that the Advisory Council/CAN Review Board invite NIH general counsel to provide information on what kinds of models are and are not possible. He encouraged the group to continue considering creative funding models.

Jorge L. Contreras, J.D., said that the only impediment to thinking outside the box is cultural. NCATS is different from the other ICs, he said, and should therefore think differently about how to support research. Other ICs are better suited to grant-funding models, but NCATS deals directly with pharmaceutical companies, something that may provide the opportunity for a new paradigm.

Geoffrey S. Ginsburg, M.D., Ph.D., encouraged the subcommittee to pursue crowdsourcing. He said that the resulting collaborations might be attractive to pharmaceutical companies as well as NCATS.

Lewis-Hall told the Advisory Council/CAN Review Board that she and Dr. Austin had met with the Foundation for NIH (FNIH). She said they had sought FNIH’s input and that she would share more on that later in the day.

## VII. CONCEPT CLEARANCES

### ***NCATS Exploratory Clinical Trials for Small Business: Lili M. Portilla, M.P.A., Director, Office of Strategic Alliances, NCATS***

The purpose of this proposed FOA is to support applications from small business concerns for clinical trials of drugs, biologics, devices or diagnostics, as well as surgical, behavioral or rehabilitation therapies, that contribute to the justification for these interventions or diagnostics and provide the data required to design a future trial to confirm their efficacy.

Todd B. Sherer, Ph.D., emphasized the importance of selecting the right disease expertise for each study. He recommended that the concept clearance be approved.

Danilo A. Tagle, Ph.D., M.S., called for a vote to approve the concept clearance. A motion was made and seconded, and the motion was passed.

### ***Small Business Translational Science Innovation Award Program: Lili M. Portilla, M.P.A., Director, Office of Strategic Alliances, NCATS***

The goal of this FOA is to incentivize small businesses through the SBIR/STTR program to develop products that will address bold and innovative new solutions to problems in translational sciences, as outlined in the ***Collaborative Innovation Award, Clinical and Translational Science Award (CTSA) Program (U01) (PAR-15-172)***.

Anantha Shekhar, M.D., Ph.D., asked what was meant by “partnership.” Philip J. Brooks, Ph.D., said that the term could apply to the SBIR and STTR programs, as well as to coordinated efforts with academic medical centers. It could involve engaging with the Collaborative Innovation Awards. Dr. Shekhar said there are often limitations to how much work can be subcontracted to an academic institution. Lili M. Portilla, M.P.A., said this would be a way to engage these institutions via SBIR or STTR and to connect the CTSA program with small businesses.

Geoffrey S. Ginsburg, M.D., Ph.D., asked whether the approach would be hands on and whether NCATS would actually connect small businesses with CTSA partners. He said that it would help small businesses to know how and with whom to connect. Frank F. Weichold, M.D., Ph.D., said a clinical trial coordinating system at Vanderbilt provided a similar service. He encouraged the team to think about how the costs for clinical trials would be substructured within the interaction with the small businesses or supplemented through other funding opportunities from NCATS.

Dr. Tagle called for a vote to approve the concept clearance. A motion was made and seconded. The motion was passed.

### ***Development of Stem Cell- or iPSC Cell-Based Assays for Compound Toxicity Evaluation: Lili M. Portilla, M.P.A., Director, Office of Strategic Alliances, NCATS***

For the Phase I contract, the goal is to develop toxicology-related assays in a homogenous format that can be used in human stem cell or induced pluripotent stem cell (iPSC)-derived cells

with short-time compound treatment. For Phase II contracts, the goal is to miniaturize the assays into 384- and 1536-well plate formats.

Bernard H. Munos, M.B.A., said the project addresses one of the key challenges in drug research and development: the rapid assessment of toxicology. He also noted that rapid toxicology screens would have biodefense applications. Dr. Sherer concurred. Dr. Weichold said that this is an area of research competition; thus, he suggested that NCATS define priority areas.

Shekhar asked why the concept clearance was limited to toxicology. He made a motion to approve the concept clearance with the recommendation for NCATS to explore whether the project could be expanded to include efficacy. His motion was seconded and passed.

***Development of SmartPlate Technology: Lili M. Portilla, M.P.A., Director, Office of Strategic Alliances, NCATS***

The key goal of this SBIR solicitation is to fundamentally transform the idea of a microtiter plate from being a single-use vessel for an experiment to becoming an instrument that could provide more data about the samples under test and actually provide measurements in the plate itself. Sherer said the concept clearance did not make it clear what this technology was, how it would work or what it would do. Mr. Munos said the project proposed an advanced SmartPlate technology that would enable microprocessing and microfluidics as well as interfacing with other equipment. He said the project had great potential.

Anton M. Simeonov, Ph.D., NCATS acting scientific director, described the project as a convergence of technologies. He said that semi-smart plates have already been invented and that the proposed project would incorporate existing technologies into a plate that collects multiple data streams.

Sherer expressed his support for the project but encouraged the team to clarify the descriptions of the proposed technology.

Tagle called for a vote to approve the concept clearance. A motion was made and seconded, and it was passed.

***R&D Contract Support for NCATS Translational Sciences: Anton M. Simeonov, Ph.D., Acting Scientific Director, Division of Pre-Clinical Innovation, NCATS***

The key goal of this proposal is to provide NCATS with the ability to establish its own contracts with research and development services in various pre-clinical and clinical therapeutic development areas. These services would complement internal scientific and acquisition resources within NCATS and enable programs like TRND and BRIDGS to continue to operate in the way in which they have been operating. Until recently, NCATS has had access to contracts with Leidos, a contractor for the Frederick National Laboratory for Cancer Research, via the National Cancer Institute (NCI). These contracts will not be available in the future.

Sherer supported the approval of this concept clearance but emphasized that the contracts should be carefully monitored and include terms that require adherence to budget. He proposed using time and budget management as additional success metrics. He asked whether

each service would require a separate vendor. Dr. Simeonov confirmed that different services will have different contracts. Typically, he said, NCATS will seek to have at least two vendors for each service to ensure competition and capacity.

Munos also supported the approval of this proposal. He cautioned the team that contract research organizations (CROs) can become expensive. He suggested that CROs could be a second option, with crowdsourcing as a first choice.

Pamela B. Davis, M.D., Ph.D., asked why NCATS was no longer available to contract with Leidos via NCI. Simeonov said that NCI is restricting the use of Leidos to cancer-specific and AIDS projects and limiting the ability of other Institutes to access that contractor.

Shekhar suggested that the pool of potential contractors include the CTSA network.

Tagle called for a vote to approve the concept clearance. A motion was made, seconded and passed.

***Tissues-on-Chips, Part II: Danilo A. Tagle, Ph.D., Associate Director for Special Initiatives, NCATS***

The goal of this project is to further develop and evolve tissue chip technology to fully exploit its use as a pre-clinical and clinical tool.

The proposed initiative has four components.

- **Clinical trials-on-chips:** Develop multiple sets of the complete human-bodies-on-chips from a number of well-characterized iPSC lines from a variety of individuals representing the demographics of the general population. Tissue chips could inform the composition of a treatment cohort or (given sufficient statistical power) even reduce the number of patients needed to show the desired effect.
- **Disease modeling:** This involves the use of tissue chips to represent familial mutations derived from the iPSCs of patients with rare diseases for studies on pathophysiology, customized therapy development and representation of the full spectrum of mutations for the disease. In addition, with the use of gene-editing technologies, it is possible to introduce genetic polymorphisms on an isogenic iPSC line to dissect the contributions of genetics versus environment in human disorders. Potentially, this approach can also dissect the contribution of genetic polymorphisms as risk factors in polygenic diseases.
- **You-on-a-Chip:** This component would be part of the PMI. Select iPSC lines from a subset of the PMI's million-person cohort could be used to develop human body-on-a chip models. Multiple, linked-tissue mimics can act as test beds to stratify populations into drug responders and nonresponders, examine multi-organ toxicities, study susceptibilities to environmental toxins, and explore the effect of the microbiome in human health and disease, all at a scale that would not be possible in studying the whole human.
- **Homunculus:** Organ representation in the tissue chips developed to date is weak for lung, bone, adipose tissue and pancreas. These need development.

Munos and Sherer both supported the approval of this concept clearance. Sherer asked whether there were plans to make this second stage of the project more widely available. Tagle said that

there is a commercialization plan built into the program and that industry partners are very interested.

Dr. Ginsburg asked whether there were enough data from the first stage of the Tissue Chip program to support the launching of a second stage or whether it might be premature. Tagle said that those data do exist and are currently being prepared for publication. He assured the Advisory Council/CAN Review Board that there are data to support the launch of the second stage and that he will share them as soon as possible.

Ginsburg asked whether all components of the second phase would begin at once or whether it would be a staged process. Tagle said that will depend on the available funds. If there is sufficient funding, NCATS will begin with the homunculus and follow with the other three initiatives.

Harry P. Selker, M.D., expressed a wish to see more validation of the concept. Tagle said that the Tissue Chip program has planned its first public meeting, which will take place in August. He invited all Advisory Council/CAN Review Board members to attend.

Dr. Selker asked whether the Tissue Chip program will be formally linked to the PMI. Tagle said that NCATS will be in communication with that initiative's leaders at NIH.

Weichold encouraged NCATS to consider incorporating real-time physiologic measurements into the tissue chip development process, particularly in the early clinical stages.

A motion was made to approve the concept clearance. The motion was seconded, and it was passed.

***Collaborative Innovation Supplements for the CTSA Program: Philip J. Brooks, Ph.D., Division of Pre-Clinical Innovation, NCATS***

The goal of this project would be to support investigators from different CTSA hubs in carrying out collaborative, innovative projects in translational science. The supplements would allow novel approaches to be quickly evaluated, and it would generate a sufficient quantity and quality of data to decide whether the proposed innovation is feasible or practical.

Sherer said that it was not clear to him from this proposal why an additional or unique collaborative funding opportunity for the CTSA program was necessary. Dr. Brooks said that existing opportunities are too limited and that some collaborative innovative approaches may not be well suited to current funding opportunities.

Munos agreed that collaboration was important, but he said that it may not need additional support. He also emphasized the importance of collaboration across disciplines. Pamela McInnes, D.D.S., M.Sc.(Dent.), NCATS deputy director, said this collaborative supplement is modeled on the program from the National Institute of General Medical Sciences and that it is intended to foster collaboration between different disciplines. Munos concurred that such a thing is worthwhile and encouraged NCATS to update the description to be more explicit.

Jorge L. Contreras, J.D., asked how much each award would be. Dr. McInnes said that the parameters had not yet been defined but that the supplements would likely not be very large.

Shekhar and Selker both expressed approval for the project. Sherer asked why the supplements are limited to CTSA participants. McInnes said that the CTSA program is the largest program at NCATS. She added that funded investigators from any program can apply for administrative supplements but that this one is restricted to CTSA researchers.

A motion was made to approve the concept clearance. The motion was seconded and then passed, with three abstentions.

#### **VIII. CTSA PROGRAM UPDATES: Petra Kaufmann, M.D., M.Sc., Director, Division of Clinical Innovation, NCATS**

Petra Kaufmann, M.D., M.Sc., introduced three key themes in the transformation of the CTSA program: common metrics, collaboration and strengthening network capacity. She said that these new approaches will be tested and re-evaluated.

- **Common Metrics:** These metrics must be useful to and used by the CTSA principal investigators (PIs) and NCATS staff. They will help to maximize the impact of the CTSA program. These metrics must be used in context, and it is important to understand the story behind the data. This work is building on prior work to maximize efficiency. Development of common metrics will entail collaborative leadership, identifying partners who have roles to play in improvement and working with PIs. Dr. Kaufmann said that the working group will engage with PIs over the summer and that she will report back on their progress at the September Advisory Council/CAN Review Board meeting.
- **Collaboration:** Based on the recommendations of the Advisory Council Working Group on the IOM Report, *The CTSA Program at NIH*, NCATS has established five task forces: workforce development, collaboration and engagement, integration across the lifespan, methods and processes, and informatics. The task forces include NCATS team members as well as representatives from the CTSA hubs, the broader NIH, the FDA and the community. This new communication structure will help to address translational science roadblocks, encourage teams from CTSA hubs to work together, demonstrate multisite utility, disseminate approaches and develop new methods that can be applied to different disease areas.
- **Strengthening Network Capacity:** Most clinical studies have delays in start-up and participant recruitment. NCATS has released two FOAs to overcome this barrier:
  - **Recruitment Innovation Centers (RICs):** These centers will build national recruitment capacity by using data from electronic health records to find potential trial participants who meet entry criteria for a given study. The RICs will also provide expert staff to guide and support participant recruitment during trial implementation. Kaufmann said that many NIH ICs have expressed interest in the RICs. She said that the RICs could be used not only for clinical trials but also for natural history and cohort studies, as well as for precision medicine efforts. The National Library of Medicine is participating in this FOA.
  - **Trial Innovation Centers (TICs):** These centers will tackle the issue of accelerating trial start-up and improving the efficiency of trial implementation. The TICs will be connected to CTSA hubs. They will streamline contracting,

budgeting and the IRB process. Many NIH ICs have supported the concept of a single IRB for multisite studies; TICs are one way of facilitating it. The National Institute on Aging is participating in this FOA.

Harry P. Selker, M.D., asked Kaufmann to clarify the difference between RICs and TICs, and he asked whether the two types of centers might not work together. Kaufmann said the TICs focus on innovation in study implementation, including a single IRB. They will streamline the contracting process in addition to budgeting and monitoring. Kaufmann said that in other networks, TICs might be called clinical coordinating centers. RICs, on the other hand, enable participant recruitment. Kaufmann said that the two types of centers will work together by necessity. In the first six months, the RICs and TICs will collaborate to craft joint operating procedures. There will soon be a technical assistance webinar on RICs and TICs.

Jorge L. Contreras, J.D., asked Kaufmann to define the ultimate goal of the new metrics and asked whether stricter metrics might not produce better results. Kaufmann explained that stronger oversight already is in place in the form of peer review and progress reports. She said that the new metrics are intended to track and explore the context of each outcome and create standardized measures that could be adopted by investigators to support strategic management across the CTSA hubs.

David Atkins, M.D., M.P.H., asked whether NCATS had discussed the TICs and RICs with the Patient-Centered Outcomes Research Institute (PCORI). Kaufmann said that the CTSA Network and the PCORI's PCORnet (National Patient-Centered Clinical Research Network) share numerous goals. In addition, 50 CTSA hubs are also PCORnet sites, and many of the investigators and experts involved with the CTSA hubs are also working with PCORnet. Kaufmann said that her team had recently met with PCORnet to discuss how the two programs might become interoperable.

Christopher P. Austin, M.D., said that the problem of orchestrating and streamlining problems is one that no one has solved but that, by working to do so, NCATS will position itself to continue to perform exciting science.

Dr. Selker and Frank F. Weichold, M.D., Ph.D., commended NCATS for its work in transforming the way science is performed.

#### **IX. ADVISORY COUNCIL AND CAN REVIEW BOARD-INITIATED DISCUSSION: Advancing Partnerships and Collaborations through the Foundation for the NIH**

Freda C. Lewis-Hall, M.D. said that NCATS had approached the FNIH to begin a conversation about how the FNIH might facilitate collaborations and partnerships. She said that early conversations were successful. NCATS brought a portfolio of opportunities for review by the FNIH. Dr. Lewis-Hall said that the conversations will be ongoing and that she welcomes any input from Advisory Council/CAN Review Board members.

Christopher P. Austin, M.D., added that the basis of their discussion was a set of ideas generated by the CAN Review Board. He said that the FNIH is extremely interested in collaborating with NCATS and has asked for additional information on several concepts before discussions resume.



Once the two groups identify a project or area of mutual interest, the collaboration can move forward.

Lewis-Hall said that the FNIH board was very enthusiastic about the Tissue Chip program. Geoffrey S. Ginsburg, M.D., Ph.D., noted that the FNIH recommended drawing on individuals from the business sector to develop a business plan for the Tissue Chip program. He suggested that the program needs a strategic plan that will sketch out intended goals for the next 5 to 10 years. Such a plan could include potential partners and relationships, a financial model and more. He asked the Advisory Council/CAN Review Board to give some thought to the best way to guide the Tissue Chip program's strategy.

Myrl Weinberg, M.A., encouraged the Advisory Council/CAN Review Board to keep patient engagement in mind during all discussions. Lewis-Hall said that they should be included in collaborations and that NCATS could become a model of patient engagement for the entire NIH and beyond. Frank F. Weichold, M.D., Ph.D., concurred. He said that NCATS has done an excellent job thus far communicating with and educating the public, and he strongly encouraged NCATS to continue this work.

Scott J. Weir, Pharm. D., Ph.D., supported the idea of a business plan, suggesting the consideration of a business plan for all platform technologies moving forward, even those that are not commercial products.

#### **ADJOURNMENT OF JOINT MEETING**

Christopher P. Austin, M.D., thanked all participants for their input. He adjourned the meeting at 3:00 p.m. ET.

#### **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 absented themselves from the meeting during 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.

#### **ADJOURNMENT OF CLOSED SESSION OF THE NCATS ADVISORY COUNCIL MEETING**

Christopher P. Austin, M.D., adjourned the closed session of the NCATS Advisory Council meeting at 4:00 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

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

\_\_\_\_\_  
Date

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

\_\_\_\_\_  
Date