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

17th Meeting of the
Cures Acceleration Network Review Board

Minutes of Virtual Meeting
Dec. 9, 2016

The National Center for Advancing Translational Sciences (NCATS) Cures Acceleration Network (CAN) Review Board convened a virtual meeting, in open session, at 11 a.m. ET on Dec. 9, 2016. Freda C. Lewis-Hall, M.D., CAN Review Board chair, led the meeting. In accordance with Public Law (P.L.) 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, Duke University Medical Center

Executive Secretary

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

Board Members

Margaret A. Anderson, M.A.
David Atkins, M.D., M.P.H.
Ronald J. Bartek, M.A.
Robert J. Beall, Ph.D.
Jorge L. Contreras, J.D.
Daniel L. Hartman, M.D.
Eric D. Kodish, M.D.
Katharine Ku, M.S.
Brad A. Margus, M.B.A.
G. Lynn Marks, M.D.
Kalpana M. Merchant, Ph.D.
Matthew Might, Ph.D.
Bernard H. Munos, M.B.A.
Alan Palkowitz, Ph.D.
Terry M. Rauch, M.P.H.
Valerie M. Rice, M.D.
Harry P. Selker, M.D.
Anantha Shekhar, M.D., Ph.D.
Todd B. Sherer, Ph.D.
Stephen P. Spielberg, M.D., Ph.D.
Sharon F. Terry, M.A.
Frank F. Weichold, M.D., Ph.D.
Scott J. Weir, Pharm.D., Ph.D.

Ex Officio Member

Christopher P. Austin, M.D., Director, NCATS

OTHERS PRESENT

NCATS leadership and staff

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., opened the meeting and welcomed participants.

II. MEETING RULES AND CONFIRMATION OF DATES FOR FUTURE NCATS ADVISORY COUNCIL AND CAN REVIEW BOARD MEETINGS

Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, CAN Review Board

Anna L. Ramsey-Ewing, Ph.D., reviewed the procedures for the meeting. In the discussion sections that followed the presentations, only CAN Review Board members were able to participate verbally, and they were required to dial in following the correct protocol to participate via phone. Dr. Ramsey-Ewing said other participants could submit a question or comment by sending an e-mail to ncatsvirtualcouncilcan@mail.nih.gov.

Dr. Ramsey-Ewing confirmed the 2017 meeting schedule for the NCATS Advisory Council and CAN Review Board meetings:

- January 12
- May 4
- September 7
- December 15 (CAN Review Board-only virtual meeting)

III. NCATS UPDATE

Christopher P. Austin, M.D., Director, NCATS

NCATS Director Christopher P. Austin, M.D., provided an overview of the NCATS Strategic Plan, which was released Nov. 29, 2016. The Plan comprises a set of Strategic Principles and a set of Strategic Goals. All NCATS activities are intended to embody the Strategic Principles, including that the Center's efforts are catalytic, generalizable, innovative, collaborative, patient focused and measurable. Dr. Austin reviewed the Strategic Goals, which consist of four broadly aspirational goals for Center activities.

The fiscal year (FY) 2017 budget request, which President Obama released Feb. 9, 2016, requested $685.417 million for NCATS, the same as in FY 2016, per the two-year budget agreement.

House and Senate committees each passed FY 2017 appropriations bills for Labor, Health and Human Services, and Education, but the full chambers did not vote on the bills. FY 2017 began Oct. 1, 2016, and the government was operating under a Continuing Resolution (CR), which extends government funding at the FY 2016 level. The CR ran through Dec. 9, 2016, and Congress currently is working to pass another CR, which would run through April 28, 2017. The House passed the CR on Dec. 8, 2016, and the Senate was to consider the CR on Dec. 9, 2016. A slight delay to include additional language was possible, potentially blocking passage of the bill until Dec. 12, 2016. Dr. Austin does not foresee interruptions to NCATS operations or funding.

The 21st Century Cures Act, designed to spur medical innovation, was passed by the House on Nov. 30, 2016, and by the Senate on Dec. 7, 2016; the president was expected to sign it the

week of Dec. 12, 2016. The Act reauthorizes the National Institutes of Health (NIH) through FY 2020 and provides for $4.8 billion over 10 years for an NIH Innovation Account. The funds are earmarked for initiatives including the Precision Medicine Initiative (PMI), Brain Research through Advancing Innovative Neurotechnologies® (BRAIN), Cancer Moonshot and Regenerative Medicine. The funds were offset from the Prevention and Public Health Fund and the Strategic Petroleum Reserve. The Act must be appropriated each year but does not count against budget caps.

Some key NIH-related provisions are that it:

- Allows the NIH Director to require awardees to share data.
- Requires an NIH Strategic Plan.
- Establishes five-year renewable terms for Institute and Center (IC) directors.
- Requires the U.S. Department of Health and Human Services (HHS) Secretary to conduct review to reduce administrative burdens for researchers.
- Exempts NIH research from the Paperwork Reduction Act.
- Provides Other Transactions Authority (OTA) to PMI and 50 percent of the Common Fund.
- Allows NCATS to support clinical trials through Phase IIB (instead of IIA) and Phase III (instead of IIB) for rare diseases.
- Changes NCATS' annual report to a biennial report, which must include a list of methods and tools developed and whether they are being used at the Food and Drug Administration (FDA).

Dr. Austin provided an update on the new administration, which has nominated Rep. Tom Price for HHS Secretary. Dr. Austin stated that NIH has a long history of bipartisan support and stands ready to work with the new administration to carry out NIH's goals to improve health and reduce the burden of disease through biomedical research.

Dr. Austin turned to a review of the origins and establishment of the CAN. The Patient Protection and Affordable Care Act (P.L. 111-148), which was signed into law March 23, 2010, amended the Public Health Service Act to authorize the CAN. The CAN specifically directs NIH to accelerate the development of high-need cures by reducing the time it takes to move new drugs and therapies from the laboratory to the marketplace. The CAN originally was within the Office of the Director of NIHand was moved into NCATS upon its inception in 2011.

Dr. Austin summarized the five CAN functions detailed in the statute language. The CAN statute required a review board separate from the NCATS Advisory Council and that CAN membership be consumers of research, rather than the producers of the research. These members include patient advocates, patient representatives, biotechnology and pharmaceutical industry representatives, venture capitalists, nonprofit representatives and academic investigators, as well as *ex officio* members from the FDA and the Department of Defense (DoD).

The funding mechanisms given to the CAN also were unique and include grant awards up to $15 million per project for the first fiscal year; matching funds for which nonfederal funds are contributed in the amount of one dollar for every three dollars awarded; and flexible research authority to use OTA to fund projects. Dr. Austin reviewed the CAN budget funding history from FY 2011 through FY 2017.

The NCATS recipe for funding is characterized by the development of a concept, release of a solicitation and funding of awards. The CAN Review Board recommended a set of CAN project criteria that require that projects be collaborative, have discrete and measurable outcomes, have broad and significant impact, focus on a compelling disease and have a timeline of less than five years for project completion.

Dr. Austin described the timeline of the CAN project selection process. From January 2014 to June 2014, the CAN Review Board generated 10 broad focus areas, of which NCATS selected three that had received wide support. In July and August 2014, focus groups comprising CAN Review Board members and NCATS staff formed around those three areas: micro-awards for researchers who need to get past small pre-clinical hurdles; devices and sensors to detect clinical outcomes; and insufficient access to compounds, toxicology, pharmacokinetics and patient populations. The focus groups worked on potential concept ideas within the three areas. From September 2014 through December 2015, the concept clearances were presented and considered by NCATS, and three CAN-generated and four NCATS-generated concepts were revisited. In 2016, the CAN received an additional $15 million, which led to NCATS initiating the 3-D Bioprinting project and the Translator project using OTA.

The CAN Review Board project selection process in 2014 generated potential projects that included Increasing Access to Compounds and Toxicity Data, Proof of Principle Awards, and Sensors and Devices to Detect Clinical Outcomes. Of the NCATS-generated concept clearances of 2015, NCATS funded the Tissue Chip Testing Centers (TCTCs), Shared Molecular Etiologies Therapeutics and 3-D Bioprinting of Human Tissues for Drug Screening.

Discussion

Scott J. Weir, Pharm.D., Ph.D., asked whether there was an opportunity to revisit the Proof of Principle Awards. Dr. Austin confirmed the need for this kind of mechanism throughout the translational space. The pilot funding capability of NCATS' Clinical and Translational Science Awards (CTSA) Program fills some of those needs for the extramural community. This is, however, an unmet need for pre-clinical stages. Because the awards would consist of small amounts of money and would need to be carried out quickly and flexibly with minimal review, the ideal mechanism would be through additional OTA, which is not currently available.

IV. PROJECT UPDATES

Human Microphysiological Systems: Organs-on-Chips for Drug Safety and Efficacy Testing

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

Danilo A. Tagle, Ph.D., M.S., briefly explained the origins of the Human Microphysiological Systems (MPS) program, which emerged from an award for a heart-lung micromachine for safety and efficacy testing as part of the NIH-FDA joint Advancing Regulatory Science Program in 2010. This project became the premise for creating human-lung- and heart-on-chips, and the MPS program launched in 2012. The program was created to address the high attrition rates of drug development and the need for improved technologies in risk assessment. The *in vitro* models currently used for drug development do not adequately predict efficacy and safety of potential drugs in humans.

The goal of the MPS program is to develop an *in vitro* platform that uses human tissues to evaluate the efficacy, safety and toxicity of promising therapies. All 10 human physiological systems will be functionally represented by human tissue constructs and are intended to have the following features:

- Pathophysiologically relevant, genetically diverse and pathologically meaningful
- Modular, reconfigurable platforms
- Tissue viability for at least four weeks
- Community-wide accessibility

The MPS program requires a multidisciplinary, team-science approach comprising bioengineers, pharmacologists, pathobiologists and material scientists. Dr. Tagle summarized the components required to build a human tissue chip, including scaffolding, cells, structure, spatial/temporal patterning, perfusion, bioreactors, innervation, host immune response, functional readout and computational design.

The MPS program is a collaboration among NIH, the Defense Advanced Research Projects Agency (DARPA) and the FDA. NIH contributed $75 million over five years for cell sources, platform development, validation and integration. DARPA contributed $75 million over five years for engineering and platform development. The FDA provides insight and expertise throughout the program. The current goals are:

- Integration (linking various organ chips, leading to a human body-on-a-chip)
- Compound testing
- Validation
- Partnerships
- Adoption of the technology by the community

Aspects of programmatic management include a memorandum of understanding between NIH, DARPA and the FDA; a cooperative agreement award mechanism; and an MPS consortium that enables synergistic interactions and collaborations among NIH and/or DARPA investigators. Dr. Tagle reviewed the CAN Review Board's metrics for success in terms of administrative outcomes, project outcomes and transformative (longer-term) outcomes. He summarized the member makeup of the MPS Consortium, which includes the tissue chip developers, NIH/FDA/DARPA leadership, members of the pharmaceutical industry and biotechnology spin-off companies.

Dr. Tagle presented details on the liver-on-a-chip as an example. The liver's complex mixture of different cell types is being recreated on a platform by scientists at the University of Pittsburgh. He presented data showing the importance of multicellularity in the correct proportions and ratios. As the tissue complexity increases, albumin secretion and lactate dehydrogenase release become more physiological. Flow culture, compared with static culture, also confers more physiological albumin and urea synthesis. The liver chip demonstrates a fibrotic response in response to a methotrexate challenge and immune-mediated hepatotoxicity by lipopolysaccharides. The investigators are working to achieve better maturation of hepatocytes derived from human induced pluripotent stem cells (iPSCs) using a controlled microenvironment. Using this approach, pediatric responses to drugs could be evaluated. A number of optogenetic, biosensing reporter cells have been incorporated into the system and

are being evaluated. This system has been used to evaluate a number of compounds, including both known liver toxins and nonliver toxins.

Another readout being developed by investigators at the University of Wisconsin is RNA sequencing (RNA-Seq) neurotoxicity testing in a brain-on-a-chip. Data generated from RNA-Seq using numerous neurotoxins and control compounds are used to train/test the machine learning algorithm. The next step is to be able to predict the response in human cortical tissue to an unknown compound.

Dr. Tagle introduced the kidney proximal tubule on Nortis 3-D chip technology, developed by investigators at the University of Washington. These are disposable microfluidic chips containing 3-D microenvironments traversed by tubular cell structures. The kidney tubules undergo phenotypic changes depending on whether they are in 2-D or 3-D cultures. The investigators also have developed microvasculature associated with the proximal tubule. Another effort showed that a colon tumor on a chip was supported by microvasculature. The system was used to evaluate different responses to drugs in 2-D versus 3-D systems and showed that the 3-D systems produced more physiological dosing responses.

Investigators at the University of Cincinnati engineered human iPSC-derived intestinal tissues with a functional enteric nervous system, a study that was published in *Nature Medicine* in 2016. They demonstrated that the gut enteroid was able to mimic gut structure and function, including peristalsis.

The next effort in the last stages of the program involves a collaborative approach among all the investigators to connect the individual organs-on-chips to ultimately create a human body-on-a-chip. For example, University of Washington investigators showed functional connectivity of liver and kidney, which enabled physiologically relevant metabolism of vitamin D.

Dr. Tagle highlighted another functional multiorgan system (consisting of liver, cardiac tissue, skeletal muscle and neuronal tissue) that is in the process of being commercialized through a Small Business Innovation Research grant to Hesperos from NCATS.

A new initiative launched in 2016 with the aim of independently validating the technology. This initiative, the TCTCs, is a partnership with the FDA and the IQ Consortium.

Dr. Tagle presented the conceptual framework for tissue chip validation:

- Physiological
    - Mimic organ cytoarchitecture and function
    - Training set of compounds provided by AstraZeneca, GlaxoSmithKline and Pfizer
    - Performed by MPS developers (UH2/UH3 awards)
- Analytical
    - Portability, reproducibility, sensitivity, specificity, dosing paradigm, cellular versus organ toxicity, toxicity readouts, etc.
    - Reference set of validation compounds, assays, and biomarkers with input from the IQ Consortium and the FDA based on technical specifications of each platform from MPS developers
    - Independently conducted by testing centers (U24 awards — TCTC)

- Industrial
    - Adaptation by pharma for a specific "context-of-use" in drug development
    - Likely proprietary set of compounds from pharma
    - Likely through a contract research organization (CRO)-like environment

NCATS support for the TCTCs, awarded on Sept. 28, 2016, is $12 million over two years. The FDA and the IQ Consortium provide expert guidance on the reference set of validation compounds, assays and biomarkers. The TCTCs are at the Massachusetts Institute of Technology and Texas A&M University, with a database center at the University of Pittsburgh. Dr. Tagle presented the general testing strategy, as well as the plan for implementation of the database and analytics.

Dr. Tagle then introduced several other new MPS program initiatives that leverage NCATS/CAN investment through partnerships. These team efforts are organized primarily through template agreements managed and negotiated by the NCATS Office of Strategic Alliances. He listed the various partnerships and mechanisms that are currently in place to support the MPS program.

NCATS released a funding announcement for one new initiative, Tissue Chips for Disease Modeling and Efficacy Testing. Its goal is to develop models for a wide range of human diseases for testing efficacy, assessing candidate therapies and establishing the pre-clinical foundation that will inform clinical trial design. NCATS will contribute $5 million per year and will be joined by 11 other NIH ICs as funding partners, for a total of approximately $80 million over five years. The application receipt date was Dec. 13, 2016.

In another initiative, NCATS released a funding announcement for a coordinated program in tissue chip systems translational research in space. The effort is a partnership between NCATS, the National Aeronautics and Space Administration (NASA) and the Center for Advancement of Science in Space (CASIS). The program's goal is to use tissue-on-chips technology toward biomedical research at the International Space Station that will lead to a better understanding of the molecular basis of human disease and the effectiveness of diagnostic markers and therapeutic interventions. Understanding of the effects of microgravity on human organ systems could provide better insight into the molecular basis, including epigenome changes, for many human conditions in space and provide information for novel drug targets for use on Earth. NCATS support is approximately $12 million over four years; NASA will contribute $3 million over four years; and CASIS will provide $8 million in-kind support. The application receipt date was Dec. 15, 2016.

Dr. Tagle concluded with future directions, which include using the technology to interrogate the druggable genome, incorporating the PMI (you-on-chip) and conducting clinical trials on chips.

Discussion

Alan Palkowitz, Ph.D., asked whether the technology will be used to study the effects of drug combinations across different tissues. Dr. Tagle said that capability has been built into the platforms. Fluid flow from organ to organ can be isolated, and flow can be reversed to test combination drug and metabolite effects on individual or multiple organs.

Biomedical Data Translator

Christine M. Colvis, Ph.D., Director, Drug Development Partnership Programs, Office of the Director, NCATS; Noel T. Southall, Ph.D., Leader, Informatics, Division of Pre-Clinical Innovation, NCATS

The Translator initiative is aimed at addressing the issue that clinicians and biologists think of disease in different ways and speak in different languages. Physicians diagnose and treat disease based on signs and symptoms affecting specific target organs. Biomedical researchers think of disease in terms of molecular changes in specific proteins, pathways or cell types.

A vast amount of data exist (e.g., research, health records, clinical trials and adverse event reports), providing an opportunity to tackle the issue. However, the challenge is that these very rich yet different data sources are housed in various locations, often in forms that are not compatible or interoperable.

The vision of this project is to accelerate the development and dissemination of therapies by creating a biomedical "data translator" for the research community. The translator would integrate multiple types of existing data sources relevant to understanding pathophysiology and would be open source and completely publicly available.

The fields of data science, computer science and translational research are converging. Translator presents an opportunity to extract more from the data by not only gathering the data but also integrating those data to enable new analyses. Doing so could lead to the reclassification of disease based on molecular pathophysiology or molecular etiology and could result in new intervention opportunities, new patient populations and more success with clinical trials.

The goals for the two-year program are to:

- Conduct feasibility and design assessment:
    - Determine what will be technically and scientifically possible.
    - Determine cost at scale.
- Identify high-value data sources.
- Develop a plan for integrating across a comprehensive variety of data types:
    - Identify barriers to integration or data inclusion.
- Develop and test a plan for data quality control and data updates.
- Develop a demonstration project.
- Define the requirements for a comprehensive Translator.

The Translator program was launched via the OTA, setting it apart from traditional funding mechanisms. For the solicitation, a notice was released in the NIH Guide for Grants and Contracts, and the funding opportunity was published on the NCATS website. Unlike traditional mechanisms, under OTA, awards can be made to individuals as opposed to organizations. The application content and submission included a five-page project plan submitted via e-mail as a single PDF. The evaluation included an objective review of the science and complementarity among applicants, as well as in-person presentations by invitees. In terms of implementation, the OTA programs are highly collaborative, and projects or components can be expanded, modified, partnered or discontinued.

Christine M. Colvis, Ph.D., reviewed the fast turnaround Translator timeline, in which the call for projects was posted April 29, 2016, and negotiations began in July 2016. In September 2016, NCATS issued awards to five awardees and their sub-award institutions, for a total of 15 participating institutions, 31 investigators and co-investigators, and a number of staff. The investigators' expertise spans epidemiology, pharmacology, medical genetics, cheminformatics, clinical informatics, environmental science and clinical science.

The Translator kick-off meeting was held Oct. 12-14, 2016. To start, the investigators are focusing on identifying high-value data sources, synergies across teams and data-sharing challenges and developing queries. The process of developing queries involves identifying the questions Translator should answer, a process that has proved challenging. Example queries are:

- What other pathophysiologies could drive this constellation of signs and symptoms?
- Could treatment nonresponders for disease X be classified differently?

Dr. Colvis urged the CAN Review Board members and broader meeting audience to send ideas for queries to translator-questions@nih.gov.

Discussion

Geoffrey S. Ginsburg, M.D., Ph.D., asked whether there is a plan to integrate the various types of clinical and molecular data streams associated with various NIH ICs. Dr. Colvis said that the starting point is to look at various datasets in the public domain and figure out how to integrate them. Dr. Ginsburg's suggestion is something the Translator staff may want to implement in the future in a more targeted way.

Lynn Marks, M.D., suggested the possibility of strategically overlapping the Tissue Chip for Drug Screening and Translator programs.

Dr. Ginsburg noted that the PMI is collecting disparate datasets and that it may set up a clear integration point with Translator. Dr. Colvis said there have been discussions with PMI leadership about how to maximize both programs and have Translator ready for PMI data.

Christopher P. Austin, M.D., said data-sharing plans associated with grants funded with taxpayer dollars through NIH have historically all been negotiated individually over the years. It's possible for an individual to use the existing databases as look-up tables without problems. However, if one wants to download all the data and integrate them with 5 or 30 other kinds of databases and pre-compute the relationships between each entity and database, the process is not straightforward or even possible within current license agreements. This project requires integration at a level that is at least an order of magnitude greater than anybody has ever done. Like everything at NCATS, this initiative has evolved from a challenging scientific problem to an operational, social science and legal problem.

3-D Bioprinting of Human Tissues for Drug Screening
Anton Simeonov, Ph.D., Scientific Director, NCATS

Bioprinting is the use of 3-D printers to robotically manufacture multicellular, layered tissues with *in vivo*-like features. The goal is to produce an array of tissue types to allow the testing of hundreds if not thousands of samples at a time in various disease models. In terms of throughput and *in vivo* relevance, the bioprinted tissue models exist as an intermediate drug screening approach between microtiter plates and organs-on-chips.

The 3-D Bioprinting program aims to establish a multidisciplinary laboratory that uses 3-D bioprinting to generate high-throughput, screenable assay models of human tissues for drug discovery. The program also would enable access by outside investigators to establish human tissue models by differentiating iPSCs to the tissue cells of interest.

The program's desired outcome is a catalog of reproducible, disease-relevant, screenable human tissues to be used for efficient drug discovery and development. 3-D bioprinting of live human tissues derived from human patient stem cells is expected to provide drug efficacy data that is better able to predict whole-body responses. It also has the potential to decrease clinical trial failure rates and to enable faster development times than using the current simplistic *in vitro* and *in vivo* models.

The first 10 to 11 months of the program were spent establishing the laboratory. FY 2016 funding was used to purchase major equipment and establish a team of four bioprinting scientists and two bioengineers.

The Bioprinting team has been collaborating with several experts both inside and outside NIH to begin building the first tissue types and finding ways to characterize them. Ultimately, the laboratory will be opened to outside investigators to bring disease models related to the tissues of interest. Current pilot projects with collaborators to carry out these tasks include work on the retina, blood vessel wall and skin.

Activities planned for FY 2017 include:

- Continued optimization of skin, retina and blood vessel wall models.
- Continued evaluation of bioprinters and associated technologies.
- Issuance of request for applications for access to the bioprinting laboratory by external collaborators.

Discussion
Dr. Austin explained NCATS' unique intramural program, which lacks principal investigators or a tenure-track program. Staff work on project teams, and every project is a collaboration with external disease researchers, either inside or outside NIH. This approach applies to the 3-D Bioprinting program and the Stem Cell Facility.

Valerie M. Rice, M.D., said several companies currently are engaged in bioprinting. She asked whether academic institutions have the capacity to respond to a request for applications and whether they would need to partner with a company in this space. Anton Simeonov, Ph.D., said the intention at the moment is to issue solicitations for one tissue type at a time. Because this platform is so new, it is unclear how much of a response there will be, and it will depend on the

tissue type and the ease of producing large numbers of relevant cells. Dr. Austin said most companies are focused on regenerative medicine, whereas this platform is for drug screening, which is a poorly populated field. The 3-D Bioprinting program's mission to disseminate the resulting tools, technological approaches and protocols to the broader scientific community sets it and other NCATS initiatives apart. This program also addresses issues of statistical robustness and reproducibility. Dr. Rice said she sees the 3-D Bioprinting program as an opportunity to incentivize collaboration; the people who are working on diseases are not the people who understand bioprinting. This program would be a new model for incentivizing researchers to advance their learning in a new area. She urged an intentional push by NCATS to make academic investigators aware of these opportunities.

Kalpana M. Merchant, Ph.D., asked how the 3-D Bioprinting program would address the immaturity challenge of differentiated iPSCs. Dr. Simeonov cited NCATS' newly established Stem Cell Translation Laboratory, which aims to stabilize the stem cell field by finding better ways to characterize cells as they differentiate to a final lineage and to characterize cells functionally to better know when differentiation is complete. The stem cell lab also aims to improve protocols of differentiation to make them cheaper, more reproducible and higher yielding. The ability to produce sufficient numbers of cells must be advanced before the promise of the 3-D Bioprinting program and organs-on-chips can be realized.

Brad A. Margus, M.B.A., asked how successes are measured. Dr. Simeonov said that much model validation work must be done, as is currently being done in the Tissue Chip for Drug Screening program. Validation in this case means comparing responses obtained in a new system with those of traditional models and recapitulating the effects of well-established drugs in the new models before dispatching the new platforms to the community. Dr. Austin said each of these programs is addressing a particular translational roadblock, and success is measured via intermediate outcomes, not through direct delivery of a therapeutic to a person. All NCATS programs address a generic roadblock on the road to therapeutic delivery and thus should catalyze success across innumerable diseases. Success is measured by a project overcoming a particular roadblock and the subsequent promulgation of the solution to other scientists for their own use in overcoming similar roadblocks.

V. FULFILLING THE MANDATE TO INNOVATE: PANEL

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

NCATS is unique among NIH ICs in that innovation is built into its mission. The CAN is expected to be particularly innovative. Immutable truths and expectations for NCATS funding include science as the primary driver, fair competition, objective review, terms of award, federal funding, stewardship and regulatory compliance. Anna L. Ramsey-Ewing, Ph.D., noted the importance of achieving administrative and managerial synergy by using currently available and new tools or combinations of tools to support innovative biomedical translation activities.

She summarized the types of NIH funding instruments, both traditional (i.e., grants, contracts, cooperative agreements, supplements, inter- and intra-agency agreements, resource-access awards, and cooperative research and development agreements) and new (i.e., pre-applications/concept papers, challenges/prize competitions and OTA). Effective funding instruments facilitate attracting nontraditional awardees, establishing nimble collaborations,

interactive decision making, milestone-driven progress and streamlined processes. Additional resources are available to leverage in conjunction with traditional and new funding instruments. These additional resources include:

- HHS IDEA laboratory
- Evaluation set-aside needs assessments
- Workshops and requests for information
- Conditional and unconditional gifts
- Matching funds
- Federal Demonstration Partnership
- Council on Governmental Relations projects

Dr. Ramsey-Ewing stressed amplifying the impact of CAN projects by establishing collaborations with non-NIH entities and among NIH components. Potential collaboration participants include:

- For-profit and not-for-profit private entities (small businesses, advocacy groups, etc.)
- Public institutions (academic centers, research institutes, etc.)
- NIH Office of the Director and extramural and intramural programs of NIH ICs
- Other HHS components (FDA, Centers for Disease Control and Prevention, Biomedical Advanced Research and Development Authority, etc.)
- Other U.S. government components (NASA, DoD/DARPA, etc.)
- Other governmental entities (domestic and foreign)

Examples of NCATS collaborations include the IQ Consortium, New Therapeutic Uses, the Therapeutics for Rare and Neglected Diseases Program and the Tissue Chip for Drug Screening program.

Dr. Ramsey-Ewing cited other models of collaboration that require matching funds, such as the Challenge Grants issued by the National Institute of Allergy and Infectious Diseases and construction grants for improving extramural research facilities. She showed several slides listing numerous examples of initiatives across NIH that capture the variety of types of collaborations. Examples include:

- The National Eye Institute's U.S.-India Collaborative Vision Research Program,
- The National Cancer Institute's Collaborative Consortia for the Study of HIV-Associated Cancers: U.S. and Low- and Middle-Income Country Partnerships,
- NCATS' Limited Competition: Exploratory CTSA Collaborative Innovation Awards,
- BRAIN Initiative: Pre-Applications for Industry Partnerships to Provide Early Access to Devices for Stimulation and Recording in the Human Central Nervous System, and
- Industry-Academic Partnerships for Development of Biomedical Imaging Systems and Methods that Are Cancer Specific.

Dr. Ramsey-Ewing concluded by opening the meeting for discussion, particularly regarding preparing for project transitions after CAN.

Discussion

Danilo A. Tagle, Ph.D., M.S., discussed his ideas for transitioning the tissue chip technology to the stakeholders. The aim is to commercialize the platforms, either through spin-off companies

funded through investors and NIH Small Business Innovation Research awards, or by bringing awareness of the potential of the technology by providing the information and data to the community, which is where the TCTCs come in. The aim is to fund the TCTCs for two years to generate a validation set of data that is made available to the community to increase the visibility of the program. The infrastructure of the TCTCs could be used to create a CRO environment, where pharmaceutical companies and other private sector entities invest in maintaining the TCTCs and avail of their services for compound testing.

Christopher P. Austin, M.D., introduced NCATS' 3Ds: NCATS develops new ways to solve problems in translation, demonstrates that they work and disseminates the outcomes and results so that others can use them. Within the 3D paradigm, the Tissue Chip for Drug Screening program is an example of developing novel technology to improve the problem of drug failure. The demonstration stage involves testing that the chips can mimic the structure and function of normal human tissue and respond to chemical and drug perturbations in a way that would be expected and that can be reproduced across labs not involved in developing them. The ideas Dr. Tagle discussed about transitioning the chip technology to stakeholders fall into the dissemination stage.

Dr. Austin referred to the process he described in his presentation, through which the CAN members developed concepts and suggested projects, starting in 2014. He said that process will start again soon. Every NCATS project is designed to address the problems CAN Review Board members encounter in their various roles within the clinical and translational ecosystem.

He then opened the floor for general discussion, inviting CAN Review Board members to provide comments, questions, feedback and ideas, either operational or scientific. Harry P. Selker, M.D., said he was impressed by the particularly audacious nature of the Translator project. While it is almost unfathomably complex, it could make scientists' and clinicians' work much more simple and effective. Translator also fills out NCATS' portfolio of approaches as a great exemplar of the kind of research that pertains to translation.

Geoffrey S. Ginsburg, M.D., Ph.D., encouraged the members, particularly the new ones, to think about innovation across the translational continuum. Dissemination has many connotations. Dr. Ginsburg expressed his hope that the CAN Review Board can generate creative ideas to enhance diffusion to the patients, clinicians and scientists who need the tools, technology and molecules being developed. Beyond the pre-clinical and clinical arenas, there are opportunities to innovate in policy and data. CAN's opportunities have large dimensionality. He encouraged the members to consider this vast spectrum of opportunities as they plan for the next three to five years.

ADJOURNMENT OF THE CAN REVIEW BOARD MEETING

Geoffrey S. Ginsburg, M.D., Ph.D., adjourned the meeting at 2:05 p.m. ET.

CERTIFICATION

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

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

Date

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

Date