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

September 19, 2014

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 Sept. 19, 2014, convening at 8:30 a.m. in Conference Room 6, Building 31, on the National Institutes of Health (NIH) main campus. Christopher P. Austin, M.D., NCATS Advisory Council chair; and Geoffrey S. Ginsburg, M.D., Ph.D., CAN Review Board vice 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 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.
Jorge L. Contreras, J.D.
Pamela B. Davis, M.D., Ph.D.
Louis J. DeGennaro, Ph.D.
Mary L. Disis, M.D. (by telephone)
Frank L. Douglas, Ph.D., M.D. (by telephone)
Geoffrey S. Ginsburg, M.D., Ph.D.
Eric D. Kodish, M.D.
Bernard H. Munos, M.B.A.
Franklyn G. Prendergast, M.D., Ph.D.
Todd B. Sherer, Ph.D.
Scott J. Weir, Pharm.D., Ph.D.
Paul G. Yock, M.D. (by telephone)

Representative Members

Ankit A. Mahadevia, M.D., M.B.A., Atlas Venture (by telephone)
Robert I. Tepper, M.D., Third Rock Ventures, LLC

Ad hoc Members (pending ethics clearance)

Harry P. Selker, M.D., Institute for Clinical Research and Health Policy Studies, Tufts Medical Center

Anantha Shekhar, M.D., Indiana University School of Medicine

CAN REVIEW BOARD MEMBERS PRESENT

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

Margaret A. Anderson, M.A.
Robert J. Beall, Ph.D.
Jorge L. Contreras, J.D.
Mary L. Disis, M.D. (by telephone)
Frank L. Douglas, Ph.D., M.D. (by telephone)
Eric D. Kodish, M.D.
Bernard H. Munos, M.B.A.
Todd B. Sherer, Ph.D.
Lawrence A. Soler, J.D.
Myrl Weinberg, M.A.
Scott J. Weir, Pharm.D., Ph.D.
Paul G. Yock, M.D. (by telephone)

Representative Members

Ankit A. Mahadevia, M.D., M.B.A., Atlas Venture (by telephone)
Robert I. Tepper, M.D., Third Rock Ventures, LLC
York Tomita, Food and Drug Administration (FDA)

INVITED PRESENTERS

Robert Finkelstein, Ph.D., Director, Division of Extramural Research, National Institute of Neurological Disorders and Stroke

D. Lansing Taylor, Ph.D., Director, University of Pittsburgh Drug Discovery Institute

OTHERS PRESENT

Bethany J. Drehman, Ph.D., Federation of American Societies for Experimental Biology

Andrew D. Peck, Waters Corporation

Matthew M. Rechler, M.D., National Institute of Diabetes and Digestive and Kidney Diseases

NCATS leadership and staff

I. CALL TO ORDER AND WELCOME

Christopher P. Austin, M.D., welcomed members and guests to the seventh meeting of the NCATS Advisory Council and the eighth meeting of the CAN Review Board. He said the open session was being videocast. Dr. Austin noted the absence of Freda C. Lewis-Hall, M.D., chair of the CAN Review Board; however, Dr. Lewis-Hall delivered brief remarks via a prerecorded video. Geoffrey S. Ginsburg, M.D., Ph.D., vice chair of the CAN Review Board, then extended a welcome to those in attendance.

Austin said Dorit Zuk, Ph.D., director, NCATS Office of Policy, Communications and Strategic Alliances (OPCSA), had prepared and distributed to the members laminated 3" x 5" cards printed with NCATS talking points, including how NCATS defines translation and translational science. The cards are useful for discussing NCATS and translational science with stakeholders.

Dr. Zuk and Pamela M. McInnes, D.D.S., M.Sc.(Dent.), NCATS deputy director, announced several changes among the Center's leadership positions:

> **Penny W. Burgoon, Ph.D.,** is the new director of the Office of Science Policy, OPCSA.
> **Dan Rosenblum, M.D.,** is retiring as a Division of Clinical Innovation (DCI) medical officer.
> **Eugene R. Passamani, M.D.,** joined DCI and will be helping to implement some innovations in the Clinical and Translational Science Awards (CTSA) program.
> **Joan Nagel, M.D., M.P.H.,** will be taking over Dr. Rosenblum's portfolio.
> **Abby Bronson** is now the DCI director of operations.

Danilo A. Tagle, Ph.D., M.S., informed the group that the CAN Review Board (but not the Advisory Council) will meet by teleconference on Dec. 12, 2014, in accordance with its four-meetings-per-year charter. The next joint meeting is slated for Jan. 15, 2015. Starting in June 2015, joint meetings may be scheduled for a day and a half, depending on the number of agenda items.

II. CONSIDERATION OF MINUTES: Danilo A. Tagle, Ph.D., M.S., Executive Secretary, NCATS Advisory Council and CAN Review Board

The minutes of the joint meeting held on May 16, 2014, were approved as written.

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

Dr. Christopher Austin welcomed two new ad hoc members to the NCATS Advisory Council: Harry Selker, M.D., executive director of the Institute for Clinical Research and Health Policy Studies at the Tufts Medical Center, and Anantha Shekhar, M.D., associate dean for translational research in the Department of Psychiatry at the Indiana University School of Medicine. Dr. Austin also acknowledged the contributions of three outgoing

Advisory Council/CAN Review Board members: Franklyn Prendergast, M.D., Ph.D.; Susan E. Siegel, M.S.; and Tadataka Yamada, M.D.

Austin provided an update on filling leadership positions within NCATS. Recruitment plans are in process for the Office of Grants Management and Scientific Review director and Office of Rare Diseases Research director. He said negotiations are underway for the Division of Pre-Clinical Innovation director role.

Regarding NCATS' fiscal year (FY) 2015 budget, Congress has approved a Continuing Resolution, which is awaiting the President's signature. It would fund agencies at the FY 2014 level through Dec. 11, 2014.

In terms of updates on congressional activities, Austin presented information about the congressional 21st Century Cures Initiative, designed to assess the full arc of the drug and device development process. He also mentioned the Research for All Act of 2014 (H.R. 4879), which, if passed, would amend the Public Health Service Act to enhance the consideration of sex differences in basic and clinical research. Austin shared a recent article published in *Nature* about NIH's commitment to having balanced male-to-female ratios in cell and animal studies, as well as in clinical trials carried out by NIH grantees.

Austin spoke of NCATS' involvement with the NIH-wide Intramural Research Program long-range planning efforts. He anticipates having more to share during the next joint meeting.

Other updates included:

- NCATS Office of Communications and contractors are leading a Center-wide effort to improve the NCATS public website. A next iteration is slated for launch in March 2015.
- For the Illuminating the Druggable Genome initiative, NCATS Division of Pre-Clinical Innovation researchers are developing a knowledge management center with preliminary data to help support R01 applications.
- Bridging Interventional Development Gaps (BrIDGs) program researchers are supporting development of new treatments for chronic dry eye, acute radiation syndrome and stress-related affective illness.
- A pharmaceutical company has licensed a candidate drug for sickle cell disease that was developed in collaboration with the Therapeutics for Rare and Neglected Diseases (TRND) program.
- Toxicology in the 21st Century (Tox21) program scientists are testing 10,000 chemicals for activity against a panel of nuclear receptors and stress response pathways, with the ability and capacity to generate as many as 30,000 dose-response curves each week. To find ways to use these data effectively, NCATS issued the Tox21 Data Challenge 2014; winners will be announced in January 2015.
- The Tissue Chip for Drug Screening program has transitioned from the UH2 phase to the UH3 phase. This stage involves integrating the stand-alone chips into a whole "body."

- Building on the recommendations of the Institute of Medicine (IOM) and the subsequent report of an NCATS Advisory Council working group, NCATS issued a new CTSA funding opportunity announcement on Sept. 12, 2014.
- Regarding NCATS' Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs, Austin highlighted an effort to repurpose lisinopril for multiple sclerosis. Project researchers will employ a crowdsourcing approach that includes patient input to design the protocol, and they will try to decrease the cost of trials and minimize barriers to participation by using mobile technologies and telemonitoring.
- The I-Corps at NIH pilot program includes a partnership between NCATS, three other NIH Institutes and Centers (ICs), and the National Science Foundation. The program is designed to accelerate development of biomedical technologies into products and services.
- A paper by three NCATS leaders — Dr. Dan Tagle; Philip Brooks, Ph.D.; and the recently retired Stephen C. Groft, Pharm.D., who now is an NCATS consultant — recently appeared in *Nature Biotechnology*. In the article, the authors discuss designing clinical trials based not on clinical phenotype but rather on molecular etiology.
- Inquiries handled by the Genetic and Rare Diseases Information Center (GARD) are up 23 percent from 2013. The GARD website receives about 200,000 hits each month, which is a 400 percent increase since March 2013.

Several Advisory Council and CAN Review Board members offered comments, including:

- Dr. Geoffrey Ginsburg asked whether venture capital firms are allowed to support TRND or TRND-like entities, either directly or through a fund. Austin responded that an NCATS analysis indicated that current statutes, policies and regulations would preclude such a direct funding model. NCATS can receive donations through a gift fund.
- Prendergast spoke about the power of public-private partnerships, noting that the success of the BrIDGs program has been remarkable, given the stringencies of regulatory review. He suggested establishing mechanisms whereby philanthropically minded individuals could help fund such activities at NCATS. Dr. Pamela McInnes expressed interest in exploring possible means to receive donations to support research.

IV. TRENDS IN FUNDING OF BASIC AND APPLIED NEUROSCIENCE AT NINDS
Robert Finkelstein, Ph.D., Director, Division of Extramural Research, National Institute of Neurological Disorders and Stroke (NINDS)

Robert Finkelstein, Ph.D. reported that NINDS is the largest funder of neuroscience research in the world. Its portfolio encompasses both basic and applied research.

Dr. Finkelstein focused on a portfolio analysis conceived and implemented by the NINDS Analysis Working group, including Anna Taylor, Ph.D., health program specialist, Division of Extramural Research, NINDS. For the analysis, NINDS-supported research was sorted

into two meta-categories: basic and applied research. Basic research was subdivided further into basic-basic (not disease-related) research, focusing on normal functions of the nervous system, and basic disease-related research. The category of applied research includes (1) applied translational research for therapeutics development (i.e., animal models) up to but excluding first-in-human trials, and (2) clinical research, which includes first-in-human studies through Phase III clinical trials.

Finkelstein and 11 other neuroscientists began by coding 2,500 competing awards from 1997 through 2011, employing precise coding guidance to ensure high inter-rater reliability. An examination of specific aims and research strategy for each application differentiated basic from translational research; the coders did not rely on how the applicant framed the research but instead on the actual proposed aims. The analysis revealed that during a 14-year span, the proportion of the NINDS research budget dedicated to basic research fell from 87 percent to 67 percent. This decline was mirrored by a commensurate uptick in the budget for applied research. Within the subcategories, pure basic research went from 52 percent to 20 percent of the research budget, disease-related basic research initially stayed level but then increased, the proportion of the budget for applied translational research (animal studies) increased from 0 percent to 14 percent, and clinical research increased from 10 percent to 20 percent. Regression analysis revealed that pure basic research could become "extinct" at NINDS in 2022 if current trends continue.

Interestingly, preliminary analysis suggested that applications for basic-basic research fared better in terms of funding rates, indicating that peer review is not a significant barrier. However, investigators are submitting fewer applications in this category. One reason behind this trend is the greater opportunity for disease-related research, thanks to progress with genomic studies and the proliferation of funders of disease-related researchers (e.g., the Michael J. Fox Foundation). Finkelstein observed, however, that discussions with investigators have revealed that they believe that reviewers and NIH leaders favor disease-related research. One source of bias is the requirement for a public health impact statement in summary statements, which may lead to reductions in the scores for pure basic research proposals.

Consequently, NINDS has modified its mission statement to reflect its quest for fundamental knowledge about the brain and nervous system. When selecting grants beyond the payline for funding, NINDS staff now considers carefully the need to sustain basic-basic research. A new request for applications (RFA) will solicit applications in this area. Scientific review officers are being trained, and discussions with the Center for Scientific Review staff have underscored the importance of maintaining the basic research portfolio. Although it is too early to determine whether or not these efforts are having a significant effect, basic-basic research applications to NINDS have begun trending upward.

In Finkelstein's view, research is most productive when scientists can focus on their area of interest — "not what they think NIH wants them to work on, not what they think their department chair wants them to work on."

Another concern, according to Finkelstein, is that basic research must be rigorous and reproducible before it can be translated.

Points brought up during discussion included:

- Dr. Pamela Davis spoke of the importance of examining the whole ecosystem of research, not just that supported by NIH. Also, investigators need preliminary data to support R01 applications. Disease foundations are a primary source, but the data they provide are usually clinically based. Lawrence A. Soler, J.D., agreed about the importance of balancing the research portfolio between basic and clinical research, but he observed that the main constituencies advocating for growth of the NIH budget are patients and families.
- Margaret A. Anderson, M.A., said that communication would be the key to explaining the value of basic research.
- Dr. Harry Selker spoke of being able to measure the impact of basic research, perhaps by tracing back breakthrough drugs to their roots in pure basic research.
- Dr. Franklyn Prendergast said universities' medical center guidelines increasingly demand their scientists abandon pure basic research, in part because of concerns about reimbursement for medical services. He recommended tracking possible effects on faculty at these institutions.

V. CTSA UPDATE: Petra Kaufmann, M.D., M.Sc., Director, Division of Clinical Innovation, NCATS

Petra Kaufmann, M.D., M.Sc., reviewed the IOM's seven high-level recommendations for the CTSA program as well as the call to establish an innovation fund. She also went over the four recommendations issued by the "NCATS Advisory Council Working Group on the IOM Report: The CTSA Program at NIH" and highlighted steps being taken to implement the recommendations.

Activities at the CTSA-supported medical research centers — now called hubs — include supporting an environment that advances translational research and translational science; training the next generation of translational science researchers; and adding new capacity for carrying out multisite trials, building on the existing local strength. To support CTSA trials, NCATS is establishing a Clinical Trial Support Center, to include central institutional review boards (IRBs), and a Clinical Trial Recruitment Center to provide planning and support for innovative methods of recruiting trial participants.

Dr. Kaufmann discussed other news about the CTSA program:

- An investigator-initiated effort is under way to establish standards for reviewing CTSA-funded projects across the CTSA hubs. NCATS wants to ensure that projects are feasible, provide safeguards for human subjects' protection, contribute to training of the next generation of researchers and generate high-quality data.
- Researchers need training and support on FDA's regulatory framework.
- Funders or groups interested in research want access to designated contact people at the hubs.

- As new central resources are established, the hubs will create local units that can interact with these resources.

The network-wide resources that will be established to support multi-site studies will add collaboration opportunities to each hub's area of strength. Translational research training will be integrated through K and T awards. CTSA resources and platforms would facilitate connecting clinical research studies supported by NIH's categorical ICs with the CTSA program.

The evolving CTSA program, according to Kaufmann, does not aim to lower the per-participant cost of trials, but it does have the goal of shortening the start-up and recruitment periods to complete trials more quickly. Transforming the program through more systematic approaches is anticipated to accelerate translation and thus to benefit patients and communities in terms of improved health.

Following Kaufmann's presentation, several Advisory Council and CAN Review Board members offered comments, including:

- Robert J. Beall, Ph.D., remarked that the CTSA program comprises 70 percent of the NCATS budget and thus merits more discussion at the next meeting. The review process must ensure that the funding decisions of the hubs themselves and for projects are made on a truly competitive basis.
- Dr. Harry Selker asked about a strategy or plan for engaging the stakeholder community. Kaufmann acknowledged the importance of the categorical ICs and other stakeholders that fund research as stakeholders in the CTSA program.
- Dr. Anantha Shekhar commented that it would be good if more ICs collaborated with the CTSA program.

VI. UPDATES FROM COUNCIL SUBCOMMITTEES

Because of time constraints, the Advisory Council deferred the report from the Medical Technology Subcommittee until the next joint meeting.

Patient Engagement *— Margaret A. Anderson, M.A., and Myrl Weinberg, M.A.*

Increasingly, both the research community and industry are recognizing the need for patient involvement. Ms. Margaret Anderson pointed out tangible examples of this trend, including the development of Kalydeco (now an approved drug) with the assistance of the Cystic Fibrosis Foundation. There is a role for NCATS in the systemic integration of patient engagement into translational research. The challenge and opportunity for NCATS is to identify how the Center is engaging the patient community and then presenting that information to the world.

Among the more important recommendations of the subcommittee was to reorganize content on NCATS' website and to incorporate an "on ramp" to facilitate use by the patient community. This should be part of a larger strategy for NCATS to engage with the outside world. Second, the subcommittee underscored the importance of accountability to ensure responsiveness to feedback and "pressure testing" in a systematic way. This recommendation could be implemented by creating a patient-and-

stakeholder interest group to serve as a forum for groups to have two-way interactions with NCATS, offer courses and webinars on translation and its science, provide training for translational teams and reviewers and create an opportunity for NCATS to share with and learn from patients and stakeholders.

Ms. Myrl Weinberg distinguished between engagement of patients and engagement of the community, which may or may not include patients. The focus of this subcommittee has been engaging patients and patient groups. Patient engagement must be infused into every NCATS program; this must be an explicit expectation, including written plans for involvement, along with clear, reportable metrics for each NCATS program.

Additionally, Ms. Weinberg said that programs must be held accountable by reporting to Dr. Christopher Austin about their patient-engagement activity and what works and what does not. Dr. Austin in turn will report highlights to the Advisory Council. The subcommittee further recommended that another CTSA subcommittee be formed around best practices in patient engagement.

Weinberg announced that the subcommittee has met its objectives and, therefore, plans to cease its activities. Nevertheless, the members plan to continue to monitor NCATS activities related to patient engagement, and they are ready to help. Austin thanked the subcommittee and acknowledged that patient engagement and accountability would be the keys to a transformational paradigm.

The Advisory Council and CAN Review Board members had several comments, including:

- Dr. Franklyn Prendergast asked for clarification about what success looks like in terms of patient engagement. Weinberg responded that if patients are involved in research from the beginning (i.e., in setting goals and designing the research) to the end, it would be possible to demonstrate specific results achieved through their involvement. Determining what is important to patients is crucial. Patient engagement needs to be built in — with measurable objectives — and then evaluation can demonstrate progress toward those objectives.
- Dr. Harry Selker said the Patient-Centered Outcomes Research Institute (PCORI) has developed guidelines for patient engagement. Dr. Petra Kaufmann clarified that the CTSA Steering Committee and hubs have been working with PCORI leadership to coordinate and share best practices.
- Todd B. Sherer, Ph.D., commented on the challenge of NCATS engaging patients when it is a disease-agnostic entity; nevertheless, TRND and BrIDGs projects present opportunities for involving patients.
- Bernard H. Munos, M.B.A., said investigators revised the end points for the lisinopril trial for the indication of multiple sclerosis to include tracers of mobility because that is more meaningful to patients than microscopic lesions.
- Dr. Pamela McInnes noted that the Rare Diseases Clinical Research Network is heavily involved with community patient advocacy groups.
- Dr. Anantha Shekhar spoke about CTSA hubs partnering with the local chapters of disease organizations. Investigators can consult with patient groups about study design and recruitment strategy.

- Dr. Pamela Davis pointed out that individuals from the community can serve as members of institutional review boards.

VII. CAN REVIEW BOARD UPDATE: 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

Dr. Geoffrey Ginsburg said that under the continuing resolution, the CAN Review Board does not yet have resources to commit to new initiatives. Nevertheless, the Board presented three concept clearances to support collaborative, multidisciplinary projects with discrete and measurable outcomes, projects that offer the possibility of a significant impact in a specific disease area. The timeline for each project should be shorter than five years.

Ms. Christine M. Cutillo, special assistant to the director at NCATS, explained how working groups refined the concepts and ensured that they did not overlap with the current portfolio. Dr. Ginsburg asked the participants to assess the scientific principles behind the concepts; implementation strategies will be considered later. The hope is that these concepts will lead to a series of RFAs.

Micro-Awards for Researchers Who Need to Get Past a Small Pre-Clinical Hurdle — *Dorit Zuk, Ph.D., Director, Office of Policy, Communications and Strategic Alliances, NCATS*

Dr. Dorit Zuk said the idea behind this concept sprang from experience with the TRND and BrIDGs programs, which revealed that some applicants lacked particular critical pieces of data that would have made their projects strong candidates. Gap analysis showed that some programs exist to meet this need, but they do not apply in the translational space, nor are they aimed at projects that have already undergone the NIH review process.

This program would provide proof-of-principle (PoP) micro-awards to fund the generation of data needed to make a project more competitive or otherwise move the project forward. Measures of success could include receipt of funding and achievement of such milestones as creation of intellectual property or the preparation of an Investigational New Drug package. If PoP awards work, the approach could be shared across the entire translational research spectrum. Eric D. Kodish, M.D., emphasized the catalytic nature of the micro-awards. Scott J. Weir, Pharm.D., Ph.D., said that NCATS must be put in a position to quickly enable the applicant to generate the data needed.

Louis J. DeGennaro, Ph.D., spoke of a similar initiative of the Leukemia & Lymphoma Society. He offered to provide information documenting the success of small amounts of funding in generating data to support grant applications.

Devices and Sensors to Detect Clinical Outcomes — *Elaine Collier, M.D., Senior Advisor to the Director, NCATS*

Elaine Collier, M.D., introduced this concept, which is based on the need for many types of data from multiple sources to describe a clinically meaningful outcome. An array of devices and sensors are available to collect physiological, environmental or patient-reported information in real time, but their use is limited by a lack of information about how to collect, manage, analyze and interpret the data. There is also a need for best practices and standards.

The concept would advance a program for integrating real-time data from multiple sources to characterize patient or disease status in a clinically meaningful way. Patients would be an important part of this effort. The focus would be on devices that are already available. The data would be publicly available at the end of the program.

Dr. Franklyn Prendergast underscored the importance of interoperability among devices. Additionally, Dr. Harry Selker stated this was an opportunity for NCATS to contribute positively to interoperability of devices and sensors at this early stage with aim to prevent interoperability problems seen with electronic health records.

Dr. Todd Sherer added that this cutting-edge concept could result in technology applicable to clinical care or clinical research. NCATS could take a leadership role in developing standards based on what is meaningful to patients and clinical researchers.

Mr. Bernard Munos spoke of similar efforts, including a collaboration of Apple, Inc. and the Mayo Clinic, to integrate data and extract information useful for the patient and researchers.

Ginsburg highlighted the use of sensors for phenotyping by capturing clinical data outside of the traditional channels. Several research areas could be enabled, including gathering information about patients' attitudes, beliefs, values and knowledge of devices; addressing concerns about data privacy and security; and defining clinical validity.

Access to Compounds, Toxicology/PK Data, Patient Populations — *Christine M. Colvis, Ph.D., Director, Drug Development Partnership Programs, NCATS*

Christine M. Colvis, Ph.D., said that the working group's focus was on compounds and associated toxicity data. The underlying mechanism of toxicity discovered in phase 1 trials often goes without further investigation. Pharmaceutical companies are unlikely to underwrite such studies, and the academic community lacks access to the compounds.

A program focused on uncovering the toxicity mechanisms would help answer the question of why pre-clinical tools sometimes fail to predict toxicity. Researchers would be provided with the compounds as well as associated pre-clinical and clinical data. Once the mechanisms are identified, it would be possible to start to build complementary models or assays to increase safety.

The program would entail collaboration with pharmaceutical firms, the FDA and companies that develop predictive toxicology tools. Measurable outcomes could include the number of compounds brought into the program and the number of toxicity mechanisms elucidated. Ginsburg said there may be a need to add a research agenda around the engagement of industry in such initiatives, including socio-legal and cultural issues. Ginsburg and Sherer suggested thinking about this as a systems pharmacology or systems toxicology problem.

Dr. Shekhar spoke about academic centers' interest in obtaining "tool compounds" for studying mechanisms. He also recommended considering whether to focus on target-based or structure-based toxicities — or both. D. Lansing Taylor, Ph.D., recommended a holistic, quantitative systems pharmacology approach because drugs often affect multiple targets, and they can have both toxic and on-target effects. Prendergast mentioned a paper by William Kaelin explaining the action of drugs that was unanticipated in terms of their biological mechanisms.

Vote

Dr. Pamela McInnes called for a vote to approve the three concept clearances. A motion was made and seconded, and it passed by voice acclamation.

VIII. UPDATE ON THE TISSUE CHIP FOR DRUG SCREENING PROGRAM: HUMAN MICROPHYSIOLOGY PLATFORM FOR LIVER EFFICACY AND SAFETY TESTING AND LINKAGE TO OTHER ORGAN SYSTEMS: D. Lansing Taylor, Ph.D., Director, University of Pittsburgh Drug Discovery Institute

D. Lansing Taylor, Ph.D., recounted the history of the two-year-old Tissue Chip for Drug Screening (microphysiological systems) program — a collaborative project of NIH/NCATS, FDA and the Defense Advanced Research Projects Agency. The goal of the first phase was to develop cell sources, mostly from progenitor and induced pluripotent stem cells (iPSCs), and to come up with bioengineered platforms capable of supporting the "tissue chips" for four to six weeks to start. With the program now entering the second phase, the aim is to integrate the individual organ chips into a "human body on a chip." A significant amount of intellectual property has been generated in the developing tools and platforms. Another critical component of the project is the testing of drugs in iPSCs from distinct disease backgrounds and genomic compositions.

At the University of Pittsburgh, work has focused on a liver on a chip, including hepatocytes, endothelial cells, Kupffer cells and stellate cells. To report clinically relevant mechanistic toxicity information, the system includes real-time, fluorescence-based biosensors and micro-clinical analyzers. The liver cells survive on a tissue chip for about a month.

The investigators at the University of Pittsburgh have been working on two chip designs. In one, the cells are physically layered to create the acinar structure; the other is a self-assembly model in which the four cell types are introduced into the chip and then

organize themselves into layers resembling the liver acinus. A test of the model confirmed that control compounds induce events of interest in a reproducible way. It is possible, for example, to measure immune-mediated toxicity in the hepatocyte chip.

A line of metastatic breast cancer cells was added into the model. In one week, the cells had divided into two subpopulations. One subpopulation moved away from the hepatocytes and divided; the other population stayed with the hepatocytes and did not divide or migrate. The two subpopulations are being tested with a variety of standard drugs to explore the heterogeneity of drug response. It appears, then, that this system might serve as a model of metastatic breast cancer in the liver.

In the next phase, the liver model will be integrated with different organ systems. Having an assembly of the liver, gut and kidney would facilitate studies of drug metabolism and absorption.

According to Dr. Lansing Taylor, using the system requires a great deal of training and experience, meaning that simplification will be necessary. Another challenge is the genetic diversity of humans. The number of genetic backgrounds and disease types will necessitate migration to a higher-throughput model. In a future version, bioprinting would allow putting a number of liver models on a plate to boost throughput. If the system becomes reproducible and inexpensive, availability will expand, as was the case with gene arrays.

The UH3 phase of this program has started. The hope is that in three more years, the project will have yielded a first-generation, integrated platform with the potential to ultimately replace animal testing and provide tools to understand mechanisms of action. The devices and existing animal models would have to be tested in parallel for a time to ensure that they were equal to, if not more predictive than, animal models.

Dissemination of these accomplishments has been primarily through collaborations with clinicians. Weinberg recommended more communication with patient groups to enlist their help in lobbying for these research efforts. Engaging patients will be critical to this research, as samples and collaboration will be needed for the success of the research. Ms. Weinberg reported on discussions with the Muscular Dystrophy Association about the muscle-on-a-chip device and with the Progeria Foundation about creating a progeria model-on-a-chip. In addition, NCATS is in process of producing a video to show the promise of the technology.

VIII. COUNCIL CONCEPT CLEARANCE: CTSA INNOVATION FUND: Petra Kaufmann, M.D., M.Sc., Director, Division of Clinical Innovation, NCATS

Dr. Petra Kaufmann explained that this concept is aimed at finding ways to stimulate innovative collaborations to build on the strength of the CTSA Consortium while generating innovative tools and methods to benefit translational science. Under this concept, projects should define a positive outcome, describe how success is measured, and include plans for next steps and dissemination.

The funded demonstration projects would be deemed successful if they evaluated a new approach, regardless of whether the outcome was positive or negative. The projects should include predefined milestones and enable clear go/no-go decisions. The projects will be collaborations among CTSA investigators and could include external stakeholders or other entities, such as agency partners, commercial partners or nonprofit organizations.

Dr. Kaufmann offered several examples of possible projects that could be supported under this broad initiative:

- Advancing the use of telemedicine,
- Improving research involvement of communities and the public,
- Evolving the consent process,
- Testing nontraditional trial designs,
- Promoting shared approaches to challenges in preclinical or early clinical translational research,
- Strengthening approaches to promoting clinical research in special populations,
- Addressing critical roadblocks in the regulatory evaluation of novel therapeutics, and
- Fostering innovative training methods among CTSA hubs or experiential learning opportunities with external partners.

Ms. Myrl Weinberg recommended including another example: inclusion of the patient community in reviewing the informed consent process. Also, health literacy experts could help rewrite documents in more user-friendly language.

Kaufmann said this concept is based on input from the IOM, the CTSA investigators and others recommending establishment of an innovation fund to promote collaborative pilot studies and other novel initiatives. To support these projects, NCATS would need to make adjustments to the program structure and the funding. Some proportion of the CTSA funding would be set aside for these innovative studies. The level of support likely would depend on the merits of the applications.

Vote

Dr. Pamela McInnes called for a vote to approve the concept clearance, specifically "to support innovative research at the CTSA hubs with funds within the CTSA budget using the process outlined by Kaufmann." A motion was made and seconded. The motion passed by voice acclamation.

ADJOURNMENT OF JOINT MEETING

Dr. Dan Tagle adjourned the meeting at 3:22 p.m. ET.

CLOSED SESSION OF NCATS ADVISORY COUNCIL

This portion of the 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).

Council members discussed procedures and policies regarding voting and 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

Dr. Christopher Austin adjourned the closed session of the NCATS Advisory Council meeting at 4:30 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. Date
Chair, NCATS Advisory Council
and
Director, National Center for Advancing Translational Sciences, NIH

_____ _____

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

_____ _____

Geoffrey S. Ginsburg, M.D., Ph.D. Date
Vice Chair, Cures Acceleration Network Review Board
and
Director, Center for Applied Genomics & Precision Medicine; and Professor of Medicine, Pathology and Biomedical Engineering, Duke University Medical Center