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

May 17, 2013

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, convening at 8:30 a.m. ET on May 17, 2013, 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 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 review and consideration of grant applications.

NCATS ADVISORY COUNCIL MEMBERS PRESENT

Chair

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

Executive Secretary

Danilo A. Tagle, M.S., Ph.D., Acting Director, NCATS Office of Grants Management and Scientific Review

Council Members

Margaret A. Anderson, M.A.
R. Alta Charo, J.D.
Jorge L. Contreras, J.D. (by telephone)
Pamela B. Davis, M.D., Ph.D.
Mary L. Disis, M.D.
Frank L. Douglas, Ph.D., M.D.
Geoffrey S. Ginsburg, M.D., Ph.D.
Freda C. Lewis-Hall, M.D.
Bernard H. Munos, M.B.A.
Franklyn G. Prendergast, M.D., Ph.D.
Todd B. Sherer, Ph.D. (by telephone)
Scott J. Weir, Pharm.D., Ph.D.
Paul G. Yock, M.D.

Representative Member

Ankit A. Mahadevia, M.D., M.B.A., Atlas Venture

Ad Hoc Member

Kate C. Beardsley, J.D.

CAN REVIEW BOARD MEMBERS PRESENT

Chair

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

Vice Chair

Geoffrey S. Ginsburg, M.D., Ph.D., Director of Genomic Medicine, Duke University Health System

Executive Secretary

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Todd B. Sherer, Ph.D. (by telephone)
Lawrence A. Soler, J.D.
Myrl Weinberg, M.A.
Scott J. Weir, Pharm.D., Ph.D.
Paul G. Yock, M.D.

Representative Members

Ankit A. Mahadevia, M.D., M.B.A., Atlas Venture
Susan E. Siegel, M.S., Healthymagination (by telephone)
Tadataka Yamada, M.D., Takeda Pharmaceuticals International

Ex Officio Members

Susanne Hambrusch, Ph.D., National Science Foundation (by telephone)
Joel Kupersmith, M.D., Department of Veterans Affairs
Terry M. Rauch, Ph.D., Department of Defense
Tania M. Simoncelli (for Peggy Hamburg), Food and Drug Administration (FDA)

Ad Hoc Member

Kate C. Beardsley, J.D.

INVITED PRESENTERS

Janine A. Clayton, M.D., Office of Research on Women's Health, NIH
Meredith D. Temple-O'Connor, Ph.D., NIH Office of Extramural Research

OTHERS PRESENT

Katie Cleffi, RTI International
Lori Pellnitz, SRI International
Catherine Pugh, Parkinson's Action Network
Shimere A. Williams, Ph.D., Lewis-Burke Associates, LLC
NCATS leadership and staff

I. CALL TO ORDER AND WELCOME

Dr. Austin welcomed members and guests to the third joint meeting of the NCATS Advisory Council and the CAN Review Board. He advised attendees that the open session was being videocast. He also introduced new members Kate Beardsley, J.D., and Terry Rauch, Ph.D.

Dr. Lewis-Hall also extended a welcome to those in attendance.

Dr. Tagle announced that the next joint meeting is slated for September 16, 2013.

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

The minutes of the joint meeting held on January 23, 2013, were approved as written.

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

Dr. Austin first reiterated NCATS' mission: "to catalyze innovative methods and technologies that enhance the development, testing and implementation of diagnostics and therapeutics for a wide range of human diseases and conditions." Austin noted that though this statement does not explicitly include medical devices or behavioral interventions, they are integral parts of NCATS' mission.

Austin spoke about the common but inaccurate perception that NCATS works only in the "T1" translational space (basic research to clinical testing). In fact, NCATS is committed to improvements across the spectrum of translational science, sometimes referred to as "T1–T4." Given that the role of NCATS is to improve human health, the Center's purview must reach all the way to the health of populations (T4).

Austin then showcased recent staffing changes at NCATS, including the addition of M. Janis Mullaney, M.B.A., as associate director for administration. Elaine Collier, M.D., has taken over for Austin as acting director of the Division of Clinical Innovation, and the second round of interviews for the permanent director of the Division of Clinical Innovation is ongoing. The search committee has selected candidates for the position of NCATS deputy director, and Austin is reviewing their applications. NCATS also is recruiting for the position of director of the Office of Grants Management and Scientific Review. The position description for the director of the Office of Policy, Communications and Strategic Alliances is being drafted.

Regarding the financial picture at NIH and NCATS, Austin indicated that NIH will continue to operate under a continuing resolution at fiscal year (FY) 2012 funding levels for the remainder of FY 2013. Sequestration cuts further reduced the NIH budget, resulting in a FY 2013 NIH budget that is 5.5 percent lower than the FY 2012 budget and

an FY 2013 NCATS budget that is 5.7 percent lower than the prior year's budget. Austin remarked on the challenges posed by this difficult economic climate.

In the proposed FY 2014 budget, NCATS' appropriation increases significantly; however, the additional amount is due largely to an accounting change: multiple NCATS programs that are currently funded via the NIH Common Fund will be moved to NCATS' appropriation.

Austin presented information about the America COMPETES (Creating Opportunities to Meaningfully Promote Excellence in Technology, Education and Science) Reauthorization Act of 2010, which mandates coordination of science, technology, engineering and mathematics (STEM) education among federal agencies. A committee (CoSTEM) is developing recommendations to implement the mandate. The first steps involved an inventory of federal programs focusing on STEM and review of a series of reports, including one by the Institute of Medicine (IOM), calling for reduced overlap among the programs. Several programs are slated to be moved from their current agencies to the U.S. Department of Education, the Smithsonian Institution or the National Science Foundation. CoSTEM recently released a 5-year strategic plan.

This change will affect several NIH programs. For example, a hold will be placed on re-issuing the Program Announcement for the Science Education Partnership Award program, and there will be a pause in funding new K–12 STEM grants and contracts in FY 2013. Starting in FY 2014, decisions about noncompeting projects will be made by the relevant NIH Institutes and Centers (ICs).

According to Austin, thus far, the proposed changes are aimed mainly at K–12 STEM initiatives, which are important to NIH but not central to its mission. Of great concern is the possibility that graduate and postgraduate programs — the heart of NIH educational and training efforts — might be included in future iterations of the consolidation. Because some Clinical and Translational Science Awards (CTSA) institutions' educational initiatives include STEM education components, Austin has informed them about the trend and advised them that NIH funding of STEM activities might be subject to closer scrutiny.

Regarding the Big Data initiatives at NIH, Austin shared an overview of new efforts to construct and integrate large data sets comprising myriad data types — not only genomic data, but also imaging, clinical, proteomic, metabolomic, exposure and clinical data from patients in biomedical research — and to develop new informatics tools for managing and analyzing these resources. The NIH Advisory Committee to the Director's Working Group on Data and Informatics delivered a report encouraging the development of informatics tools and a transformation of the organizational culture at NIH to make the best use of available data for scientific and medical purposes.

Austin listed some of the actions under way: Eric Green, M.D., Ph.D., is serving as the acting associate director for data science, a new leadership position reporting to the NIH

director, and NIH is forming an internal governing body — the Scientific Data Council — to oversee the Big Data initiatives.

A major new trans-NIH initiative called Big Data to Knowledge (BD2K) aims to be catalytic and synergistic. Its goal is to enable a quantum leap by the end of this decade in the ability of the biomedical research enterprise to maximize the value of the data, which is growing in volume and complexity. Austin reported that resources for BD2K initially will come from the Common Fund and then shift to the budgets of the ICs. As an integrative Center, NCATS will have a critical role in the initiative.

Austin then presented an extensive list of recent meetings he had recently held with NCATS' diverse and numerous stakeholders. He had arranged the meetings to introduce himself to the stakeholders and communicate his vision for NCATS and translational research. He reported that his biggest surprise was the extent of education needed regarding the nature of translational research and the urgent need for scientific and operational advances in the area. Austin commended the NCATS Office of Communications for its efforts to communicate accurately the challenges in translation and the important and unique role of NCATS in overcoming these challenges to bring new interventions to patients. He also lauded new public website pages that highlight NCATS technologies available for licensing and the Gift Fund page, which provides the means for NCATS to accept donations from public and private entities to support its work.

Austin also highlighted a *Federal Register* notice published on May 15, 2013, at the request of congressional appropriators as a way of ensuring that NCATS is complementing, not competing with, the pharmaceutical industry. The notice, Austin explained, informs private sector entities about how NCATS promulgates its activities and offers another way to provide comments. He underscored that the role of NCATS is to work on general tools and paradigms to help all sectors working on intervention development and to help de-risk translational programs.

Austin then reported that he had met recently with Democratic and Republican appropriation subcommittee staff in both the House and the Senate. He also shared that House Majority Leader Eric Cantor had visited NIH recently and that the Senate Appropriations Committee members had engaged NIH Director Francis Collins, M.D., Ph.D., and four IC directors. (Austin was not among them.)

Austin then highlighted a number of key NCATS accomplishments since the last joint meeting:

- The IOM's study of the CTSA program is slated for release in June 2013. Until the report is out, Austin will not make major changes to the program.
- A paper on the Fragile X screening project, a collaboration of the University of California, Davis, and other CTSAs; the Centers for Disease Control and

Prevention; and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), appeared in *Genome Medicine.*

- An article resulting from a collaboration of NCATS, Johns Hopkins University, and institutions in Japan and France was published in *Proceedings of the National Academy of Sciences*. The authors reported on the outcome of a search for novel targets for retinal ganglion cell death in glaucoma. Using small-molecule technology and siRNA (small interfering RNA), they identified a kinase inhibitor for use in a proof-of-principle project.
- NCATS' Tox21 initiative led to an important paper in *Environmental Health Perspectives* on identifying potential endocrine-disrupting chemicals.
- The Chordoma Foundation bestowed its Uncommon Collaboration Award on an NIH Chemical Genomics Center scientist and an investigator at Johns Hopkins University who worked together to identify a class of drugs that show promise in treating chordoma, a rare spinal column tumor.
- The Therapeutics for Rare and Neglected Diseases (TRND) program has adopted 15 projects since its inception in 2009. Of particular note is a collaboration with Cincinnati Children's Hospital to develop aerosolized granulocyte macrophage colony-stimulating factor for treating pulmonary alveolar proteinosis, a rare disease characterized by accumulation of proteins in alveoli due to inadequate function of alveolar macrophages.
- The Rare Diseases Clinical Research Network — managed by the NCATS Office of Rare Diseases Research (ORDR) in collaboration with eight other NIH Institutes — carried out a study that found that Sturge-Weber syndrome and port-wine stains are the result of somatic mutations in one gene, *GNAQ.*
- The International Rare Diseases Research Consortium held its first conference in April 2013 in Dublin, and Austin delivered the meeting's keynote address. Stephen Groft, Pharm.D., ORDR director, serves as liaison to the steering committee. The consortium has the ambitious goals of developing 200 new therapies for rare diseases and delivering diagnostics for most rare diseases by 2020.
- The National Organization for Rare Disorders, which was a major force behind the passage of the Orphan Drug Act, gave Groft an award for vision on behalf of patients .
- The Microphysiological Systems Program— also called Tissue Chip for Drug Screening — awarded its first grants in July 2012. All the grantees have achieved or exceeded project milestones. By mid-2013, an avenue will be established for periodic assessment of the progress of individual NIH projects based on the milestone plan for each award. The program is collaboration of the FDA, the Defense Advanced Research Projects Agency and NCATS.
- The Discovering New Therapeutic Uses for Existing Molecules (New Therapeutic Uses) program has been a remarkable success. Eight pharmaceutical companies provided data on 58 compounds. Sixteen drug rescue/repurposing projects were proposed based on "crowdsourcing" potential therapeutic uses. Austin presented a chart showing that of the 16

compounds receiving applications, 15 received applications for four or more indications.

- A new NIH Common Fund effort administered by NCATS, the Extracellular RNA (exRNA) Communication program, will enable researchers to investigate the roles of exRNA in normal body fluids and as biomarkers in disease. At NCATS, Tagle is leading the program, which will facilitate the establishment of a repository for standards, protocols and data and discovery of fundamental biological principles of exRNA and their clinical utility for biomarker and therapeutic development.
- NCATS and the National Institute of Diabetes and Digestive and Kidney Diseases will co-lead another new NIH Common Fund program called Illuminating the Druggable Genome. The effort will focus on unannotated proteins from four highly targeted gene families known to be highly druggable (i.e., known to, or predicted to, bind with high affinity to a drug): GPCRs (G-protein coupled receptors), kinases, ion channels and nuclear receptors. Initial steps will aim to develop a knowledge management center and foster development of scalable technology.

Finally, Austin suggested several topics that he would like Council subcommittees to address: patient engagement, partnerships with pharmaceutical and biotechnology companies and venture capital firms, regulatory science, informatics, data sharing (Big Data), medical technologies (devices and diagnostics), and precompetitive collaborations. He underscored the need to encourage patient engagement in every project to ensure that NCATS' efforts are meeting human medical needs.

Austin asked that the members contact NCATS staff to share other ideas for subcommittees or indicate whether they would like to serve on a particular group.

IV. PRESENTATION FROM THE CAN REVIEW BOARD SUBCOMMITTEE[1]: Freda C. Lewis-Hall, M.D., Executive Vice President and Chief Medical Officer, Pfizer, Inc.

Lewis-Hall reiterated that during the last joint meeting, Austin had suggested that a subcommittee of the CAN Review Board establish some priorities and metrics. In her presentation, Lewis-Hall proposed general principles for evaluating the work of CAN and measurable outcomes to track the success of the program, and she asked for the participants' feedback.

The metrics would be organized into three groups: administrative outcomes, project outcomes, and transformative outcomes that would indicate a project or program advanced science or helped patients.

[1] Members of the subcommittee were Pamela B. Davis, M.D., Ph.D., Geoffrey S. Ginsburg, M.D., Ph.D., and Bernard H. Munos, M.B.A.

Lewis-Hall used the example of the Microphysiological Systems Program, which is developing organ-on-chip devices, to demonstrate how the proposed metrics might work. Pamela B. Davis, M.D., Ph.D., explained that the end point for the program is having a chip that can accurately predict adverse events and can generate data acceptable to regulators. Intermediate administrative and operational steps must be taken to get to that point, and that is where the metrics come into play. Lewis-Hall explained that the metrics could be designed prospectively and built into the programs to use as a monitoring tool.

Administrative outcomes could include the following metrics:

- Number of proposals submitted for each organ model in [time frame]
- Prioritization of organs for model development support
- Number of proposals reviewed by [time frame]
- Dollars of funding granted per proposal (milestone driven)
- Follow-on funding from original proposal
- Collaborations with industry or consortia to advance findings
- Number of papers published from each of the funded centers (19 award recipients)

In terms of possible project outcomes, Lewis-Hall proposed the following metrics:

- Number of distinct organ models (hepatic, alveolar, cardiac) developed in [time frame]
    - Proof of concept that organ-on-chip technology predicts adverse drug reactions (ADR) from compounds known to cause them
    - For FDA-approved and "safe" compounds, demonstration of safety using organ chip metrics
- Dates of milestone completion for each proposal
- Number of projects that moved to the next phase of development or approval over [time frame]
- Defined regulatory path for use in the approval process
    - Number of chips transferred
    - Therapeutic areas of Investigational New Drug applications containing chip data
- Identification of signals for toxicity
- Number of compound screens performed using organ-on-chip device
- Identification of compounds with high likelihood of ADRs and compounds that are designated as safe

Lewis-Hall presented the following proposed metrics to evaluate transformative outcomes from the Microphysiological Systems Program:

- Establishment of a standard for quality of predictability and reproducibility compared with animal models and human studies

    - Number of projects that meet the standard for toxicity
    - Number of projects that meet the standard for potential therapeutic effects
- Predicted percent reduction of speed of medicine development or failure in areas of unmet need
    - Integration and use of organ or tissue chip technology as part of compound selection in pharmaceutical development programs
    - Demonstration of changes in cost of compound advancement in clinical development programs
- Reduction of serious adverse events in human studies and clinical use
    - Predicted percent reduction of serious adverse events in phase I/II/III
    - Predicted percent reduction of animal use in research program
- Number of organizations using organ-on-chip devices in their programs
- Insights that might not have been discovered without the device
- Number of projects that failed to meet the primary outcomes but informed additional study or ongoing research ("noble failures")

The meeting participants offered several ideas to bolster the proposed metrics. Suggestions for additional metrics for the Microphysiological Systems Program included number of requests for collaborations, number of times an organ-on-chip device was requested for use in licensure, number of times a chip was used in pilots and number of times collaborations led to clinical trials. Measures could assess demand for different chip devices, utilization rates and outcomes of research using the chips.

Another idea was to align metrics with the goals of NCATS: Is translation being sped up or enhanced somehow? Also, the metrics could be considered in terms of process and outcome measures. Number of publications is an important measure in the academic world.

This activity could be viewed as a means of figuring out whether programs are on the right trajectory to justify public investment in NCATS. Furthermore, having "metrics with teeth" could influence go/no-go decisions for programs; failure to achieve defined metrics should be a basis for eliminating programs.

Building metrics into programs would help investigators understand how they will be judged at all stages of the project. Metrics could be applied prospectively: Should a proposed project be funded? Applying metrics retrospectively could help assess impact: Did the program meet its goal? Is the tool or technology or resource being used? In addition, several of the metrics could contribute to calculation of return on investment (e.g., reduced use of animal models).

Several comments addressed the challenges in measuring reductions in adverse events or attributing such reductions to an organ chip, which is essentially a platform technology. However, measuring adoption of the technology would be important.

Lewis-Hall presented another set of proposed metrics, using New Therapeutic Uses as an example. The participants offered a number of suggestions for improvement. To capture successes and noble failures, one could compare the number of Investigational New Drug applications and Investigational Device Exemptions to the number of therapeutics and devices that are eventually approved. Number of approvals would be the ultimate measure, perhaps, but it also would be important to gauge the number of compounds that progress to proof-of-concept studies in humans. The number of companies expressing interest in commercializing the compounds would be another relevant metric.

One principle to bear in mind is that metrics should flow from the request for proposals.

Lewis-Hall thanked the participants for sharing their ideas, which the subcommittee will integrate with its proposed metrics and formulate as recommendations and a framework.

V. NIH INCLUSION POLICY: Meredith D. Temple-O'Connor, Ph.D., NIH Inclusion Policy Officer, NIH Office of Extramural Research, and Janine A. Clayton, M.D., Associate Director for Women's Health and Director, NIH Office of Research on Women's Health

Temple-O'Connor reviewed NIH inclusion policies, which cover both intramural and extramural programs, regardless of funding mechanism. The policies mandate that women, minorities and children be included in research funded or supported by NIH.

Temple-O'Connor clarified that not every study has to reflect U.S. demographics. The degree to which a study must include women and minorities depends on the population under study and the scientific goals of the research. The goals of the research should reflect the population at risk for the disease or condition.

Temple-O'Connor further noted that investigators are required to conduct valid analysis of group differences on the basis of sex/gender, race and ethnicity when conducting an NIH-defined Phase III clinical trial. Most NCATS research is phase I or phase II, meaning that this policy does not pertain to most NCATS projects.

She outlined roles and responsibilities for making sure that NIH-supported research adheres to the inclusion policy. Investigators must address the inclusion of women, minorities and children as they prepare their research plans, submit applications or set up studies on the intramural side. Each year, investigators must report participants' race, ethnicity and sex/gender. In accordance with standards set by the Office of Management and Budget, race and ethnicity are separate concepts. Participants must self-report their ethnic and racial identification.

NIH scientific review officers ensure that inclusion plans are assessed and documented as part of the peer review process, and program officers ensure compliance with the inclusion policy by monitoring the inclusion plans and annual enrollment in the study

after the award. Grants management staff are responsible for ensuring that investigators comply with award procedures.

Biennially, NIH reports on the inclusion of women and minorities in NIH-funded clinical research studies. The Biennial Report of the Director assures Congress that NIH ICs are adhering to the legislation and that each IC has prepared a report approved by its advisory council, certifying compliance with the NIH Inclusion Policy.

Temple-O'Connor concluded by saying that efforts are under way to standardize the ICs' reports to simplify the task of incorporating them into the Biennial Report of the Director.

Clayton reviewed the goals of inclusion and explained the governance structure of the Extramural Activities Working Group Subcommittee on Inclusion Governance (E-SIG). E-SIG is co-chaired by Clayton and Alan Guttmacher, M.D., of NICHD and is staffed by Temple-O'Connor, the NIH Inclusion Policy officer.

E-SIG has articulated the guiding principles for the NIH Inclusion Policy:

> NIH-supported clinical research should address/include the population(s) at risk for the disease or condition under study. The purpose of the NIH Policy on Inclusion of Women and Minorities as Subjects in Clinical Research is to ensure that the distribution of study participants by sex/gender, race, ethnicity and age reflects the population needed to accomplish the scientific goals of the study, rather than enumeration of research participants. All NIH-funded studies that meet the NIH definition for clinical research are subject to the NIH Inclusion Policy, regardless of funding mechanism.

Is there a risk that applying the criteria might make a trial impossible? For small studies with rare diseases, how much inclusion is sufficient? According to Clayton, it may not be possible in every small trial to allow for statistical comparisons, but sex-specific results can be reported and data from studies can be combined and meta-analyses performed to look for differences between subgroups. If, over time, a particular segment of the population is understudied, that would be a problem. The policy is clear that cost is not a valid reason for excluding women or minorities as subjects in NIH-funded clinical research.

Tagle asked what the Advisory Council would like to see in the NCATS report on inclusion of women and minorities in research. The Council is responsible for certifying the report, although in the past, some members have abstained. Tagle also pointed out that some projects are exempt from monitoring. For example, any trial that receives an institutional review board exemption number 4 is not subject to the inclusion policy requirement. Also, NIH has internal procedures for granting limited exceptions for studies that do not need to be monitored. The Council is responsible for preparing a

report that ensures the IC research portfolio demonstrates compliance with the NIH Inclusion Policy.

Questions arose with regard to monitoring and reporting for directly funded research versus awards given to academic institutions. Temple-O'Connor explained that once a protocol is developed, an extramural investigator must submit a plan for review and approval before participant recruitment begins. Each year, the investigator submits a summary of demographic characteristics of accrued participants. The data are then extracted and aggregated to assess whether enrollment targets were met.

As an adaptor center, NCATS is in an interesting position because it primarily facilitates clinical studies funded by other entities. What is NCATS' legal responsibility with regard to the inclusion policy? The unique nature of the NCATS portfolio will necessitate some collaboration between E-SIG and NCATS to meet the requirements of the legislation and inclusion policy. Austin cautioned about the possibility of double-counting if both NCATS and the primary funding entity collect and report demographic data. Another challenge stems from the fact that some participants enroll on several protocols, although Clayton and Temple-O'Connor reiterated that this is not a concern. The goal of the inclusion policy is to ensure that a scientifically appropriate sample is included, rather than enumeration of specific individuals.

NCATS also could shed light on the effects of the inclusion policy on clinical research — for example, by applying metrics and providing incentives for researchers to use the data in a useful way and thereby help their research.

Austin summed up by saying that the goal of the presentation was to inform the Council about its role and responsibilities in carrying out the requirements and expectations of the NIH Inclusion Policy. The next step will be to figure out what information must be collected to ensure that the Council can certify IC adherence to the policy.

VI. CONCEPT CLEARANCE OF PROPOSED INITIATIVES: Lili M. Portilla, M.P.A., Acting Director, Office of Policy, Communications and Strategic Alliances, NCATS

Portilla explained the basics of the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs and highlighted recent changes to their eligibility criteria:

- New regulations on size: NIH is now permitted to spend up to 25 percent of SBIR funds on small businesses that are majority-owned by multiple venture capitalists, hedge funds or private equity firms.
- Cross-program awards: STTR Phase I awardees can receive SBIR Phase II awards, and vice versa. Such awards have been made only rarely, and then only with prior approval of the Small Business Administration.

- Cross-agency awards: A Phase I awardee may receive a Phase II award from a different agency.

Portilla asked for the members' input on four potential SBIR contract topics, as described below.

Development of Improved Genome-Editing Technologies

Genome-editing technologies, such as zinc finger nucleases (a class of engineered DNA-binding proteins that facilitate genome editing by creating a double-stranded break in DNA at a user-specified location), hold much promise in terms of understanding gene function, assay development and even gene therapy. However, current limitations include low efficiency and the potential for off-target editing. Improved methods would enable investigators to realize the promise of these technologies in a variety of applications and may even allow them to use these reagents in high-throughput screening format to interrogate gene function, the way RNAi is used currently. Because one firm holds quite a few relevant patents, it would be important to ensure that new efforts focus on unique aspects for which there would be more flexibility in terms of intellectual property.

Portable Parathyroid Hormone Pump and Calcium Monitoring Device

The TRND and Bridging Interventional Development Gaps programs are supporting two projects to develop improved therapy for hypoparathyroidism (decreased function of the parathyroid glands with underproduction of parathyroid hormone). A chip for controlling the dosage of a long-acting parathyroid hormone analog would be part of a pump-monitor system and included in the development aspect of this concept. John McKew, Ph.D., serving as a subject matter expert, explained that the tool would release a parathyroid hormone analog using incremental dosing and would ensure that calcium levels do not fluctuate excessively. Having an implanted device to monitor calcium levels and provide automated dosing would increase patient autonomy and reduce the need for specialist appointments. One suggestion was to review the relevant *Science* paper and include other indications for parathyroid hormone treatment in the topic.

Development of Droplet Detection System for High-Throughput Screening

The staff in the Division of Pre-Clinical Innovation suggested this topic. When a dispenser tip clogs, dozens of plates can be affected, and the error might not be detected for three days. BioRaptor and Multidrop systems do not provide direct feedback to ensure that dispensing was done properly. Machine vision or adaptation of existing pick-and-place technology might be promising approaches. Industry has not pursued a solution to this problem, and it could be a major win for NCATS.

Platforms for the Rapid Development of Cell-Based Assays for Rare Diseases

The idea is to develop a platform to rapidly produce cell-based assays for high-throughput screening and for use in other areas of rare disease research (e.g., basic pathophysiology, toxicity screens). A platform to allow the rapid production of cells suitable for a variety of cell-based assays would be beneficial, especially to the rare disease research community. These platforms could be for all cell and disease types or for individual organs and the diseases of each organ. This concept would need to be fine-tuned by figuring out what cell type to use (e.g., stem cells, induced pluripotent stem cells).

Portilla sought input on two proposed SBIR/STTR funding opportunity announcement (FOA) topics:

Development of Neurocognitive Pediatric Tools for Measuring and Analyzing Clinical Study End Points in Rare Neurocognitive Disorders

The TRND program staff suggested this topic, which could work for either an FOA or for a contract. The FOA might attract support from other ICs. McKew remarked on efforts to develop a drug in collaboration with a pharmaceutical company to treat a deficiency of a creatine transporter protein, which results in an autism spectrum disorder. The affected children have no language, making it challenging to find appropriate neurocognitive tools for assessing the effectiveness of the intervention. Such tools also might be useful in studies of Alzheimer's disease and other neurocognitive diseases.

Development of Biomarkers for Rare Diseases as End Points for Clinical Trial Measurements

Portilla proposed to issue an FOA on developing biomarkers for rare diseases as end points for clinical trial measurements. Europeans have a category of exceptional circumstances for use of surrogate end points in drug-approval processes, especially in the setting of rare diseases. The FOA should include a requirement to involve the FDA. This FOA would have particular relevance for trials that test therapeutics for Niemann-Pick type C disease because investigators have found a biomarker that seems to be useful for assessing treatment efficacy, but it also might be a diagnostic marker. Several other ICs probably would be interested in participating, given the broad interest across NIH.

The concept clearances on these six proposed initiatives took place during the closed session of the NCATS Advisory Council meeting. Additional Council members joined the meeting by phone during the closed session, meeting the minimum number of votes (13) required for a quorum. A motion to approve the six initiatives was made and seconded. The motion was passed by voice acclamation, with no abstentions or nay votes.

VII. BACKGROUND ON THE DISCOVERING NEW THERAPEUTIC USES FOR EXISTING MOLECULES PROGRAM: Christine M. Colvis, Ph.D., Director, Special Initiatives, NCATS

Colvis updated the group on the status of NCATS' Discovering New Therapeutic Uses for Existing Molecules pilot program.

Eight companies have provided compounds for study. Memoranda of understanding are in place. Full reviews occurred in February 2013, and awards will be made in a few weeks. An NIH administrator will serve as a project scientist for each project.

The template agreements helped the legal aspects of the project go smoothly. The two collaborating parties were responsible for working out the details. As part of the agreements, the companies committed to providing everything needed for any clinical trials that would result. An important question is whether providing template agreements sped up the process. If other ICs or pharmaceutical companies adopt this process, that would be a significant accomplishment for NCATS.

Colvis presented information on the library of industry-provided compounds.

NCATS staff are working closely with the applicants to establish project milestones to make sure that any failures are detected quickly.

One Council member suggested that small amounts of the compounds be made available early in the process to allow applicants to test them in their systems. That step might eliminate the UH2 phase. Austin responded that the materials are patented; therefore, the companies wanted to retain tight control. Also, project managers will make go/no-go decisions based on clear, quantifiable criteria about whether to proceed to the UH3 phase.

Another person thought it would be helpful for the companies to provide data from the compounds' clinical trials and indicate whether biospecimens were available for study.

Colvis said that a request for information will be released soon. She hopes that applicants will provide feedback to inform future efforts.

ADJOURNMENT OF JOINT MEETING

Tagle adjourned the open session of the joint meeting at 2:33 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.

VIII. APPLICATION REVIEW

The Council reviewed 340 applications (with total direct costs of $253,044,427). The Council concurred with the review of all applications.

ADJOURNMENT OF CLOSED SESSION OF THE NCATS ADVISORY COUNCIL MEETING

Austin adjourned the closed session of the NCATS Advisory Council meeting at 3:50 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, M.S., Ph.D. Date
Executive Secretary, NCATS Advisory Council
Executive Secretary, Cures Acceleration Network Review Board
and
Acting Director, Office of Grants Management and Scientific Review, NCATS

_____ _____

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