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 12, 2017

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 May 12, 2017, convening at 8:30 a.m. ET, 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 G. Lynn Marks, M.D., CAN Review Board chair, led the meeting. In accordance with Public Law 92-463, the session was open to the public.

Following the joint meeting, the NCATS Advisory Council met in closed session for the review and consideration of grant applications.

NCATS ADVISORY COUNCIL MEMBERS PRESENT

Chair

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

Executive Secretary

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

Council Members

Daniel L. Hartman, M.D. (by telephone)
Megan O'Boyle
Alan D. Palkowitz, Ph.D.
Harry P. Selker, M.D., M.S.P.H.
Anantha Shekhar, M.D., Ph.D.

Representative Members

None present

Ad Hoc Members

Ronald J. Bartek, Friedreich's Ataxia Research Alliance
Brad Margus, Cerevance, Inc.
Kalpana M. Merchant, Ph.D., TransThera Consulting Company
Matthew Might, Ph.D., University of Utah
Valerie Montgomery Rice, M.D., Morehouse School of Medicine
Stephen P. Spielberg, M.D., Ph.D., Therapeutic Innovation and Regulatory Science
Sharon F. Terry, M.A., Genetic Alliance
Eric J. Topol, M.D., Scripps Translational Science Institute
Paul G. Yock, M.D., Stanford University (by telephone)

Ex Officio Members

S. Rao Kosaraju, Ph.D., National Science Foundation
Rachel Ramoni, D.M.D., Sc.D., Department of Veterans Affairs

Frank F. Weichold, M.D., Ph.D., Food and Drug Administration (representative for Commissioner Robert M. Califf, M.D.)

CAN REVIEW BOARD MEMBERS PRESENT

Chair

G. Lynn Marks, M.D., Senior Vice President for Research and Development and Senior Clinical Advisor, GlaxoSmithKline

Vice Chair

Ronald J. Bartek, Co-Founder and Founding President, Friedreich's Ataxia Research Alliance (FARA)

Executive Secretary

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

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OTHERS PRESENT

NCATS leadership and staff
Rachel Levinson, Executive Director,
National Research Initiatives, Office of
Knowledge Enterprise Development, Arizona State University

I. CALL TO ORDER

Christopher P. Austin, M.D., and Lynn Marks, M.D., called the meeting to order. Dr. Austin welcomed members and guests to the 15th meeting of the NCATS Advisory Council and the 19th meeting of the CAN Review Board. He reminded attendees that the open session was being videocast. Dr. Austin introduced the *ad hoc* members of the Advisory Council and the CAN Review Board.

II. CONSIDERATION OF MINUTES: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, NCATS Advisory Council and CAN Review Board

The minutes of the joint meeting held on Jan. 12, 2017, were approved as written.

Anna L. Ramsey-Ewing, Ph.D., informed the group that the NCATS Advisory Council and CAN Review Board will have joint meetings in 2017 on Sept. 7. The 2018 meetings will take place on Jan. 11, May 10 and Sept. 27. The 2019 meetings will take place on Jan. 10, May 16, and Sept. 19. The CAN Review Board also will meet by teleconference on Dec. 15, 2017, Dec. 14, 2018, and Dec. 13, 2019.

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

Christopher P. Austin, M.D., welcomed incoming members of the Advisory Council and CAN Review Board:

- Eric Topol, M.D., Scripps Translational Science Institute
- Rachel Ramoni, D.M.D., Sc.D., Department of Veterans Affairs
- Kalpana Merchant, Ph.D., TransThera Consulting Company

Translational Science Advances: Selected Highlights

- **Tissue Chip Testing Centers.** The Tissue Chip Program started in the early days of NCATS. The goal is to develop in vitro platforms to use human tissues to evaluate safety and efficacy of novel therapeutics. It is a collaboration with DARPA and FDA. The chips were made by individual developers, but designed to be modular so they could be linked. Now independent testing centers are testing eight chips at a time on a single platform. In addition to pharmacological testing, the goal is to troubleshoot the chips now so that eventually anyone can order them and use them without difficulty.
- **Drug Resistance.** NCATS has been working on questions related to drug resistance. Organisms with high mutation rate and many generations per week are hard to beat with antibiotics. NCATS developed a way to use quantitative high-throughput screening to identify three-drug combinations that are effective against 10 common multiple-drug-resistant bacteria. This method can also be used on other problems, such as cancer that becomes resistant to drugs. In collaboration with a researcher at the National Cancer Institute, NCATS has been able to find combinations of drugs that work on a form of lymphoma that is both difficult to treat and difficult study. Results in a phase 1b trial have been promising.
- **The NCATS Translator Program.** This program will develop and disseminate a translator that connects all of the classification schemes used by different groups in the translational research

community. It will connect physicians who think in terms of diseases, molecular biologists who think about proteins and genes, cell biologists who think about cells and tissues and so on. All of these people use different terminology and think at different levels of biological organization, and it is not easy to move between these different ways of thinking about diseases. This will require unprecedented amounts of different data. Goals for the current two-year program include identifying high-value data sources and developing a demonstration project. The program is using the Other Transactional Authority (OTA) mechanism and has moved quickly so far.

- **Single IRB.** Multi-site studies traditionally have had an Institutional Review Board (IRB) at each site. This does not appear to enhance participant protection and can slow down clinical trials—which means getting treatments to patients more slowly. Using a single IRB can solve some of these problems. A single IRB is usually an existing IRB that agrees to be the IRB of record for a particular study. This is different from a central IRB, which is often set up specifically for a program that includes more than one multi-site study. NCATS has developed the NCATS Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB Platform as part of the Trial Innovation Network. Resources include a master IRB authorization agreement. All of the Clinical and Translational Science Awards (CTSA) Program hubs have signed on. The goal is for 750 institutions to sign on.

Policy and Legislative Updates

- **FY 2017 Budget.** At the time of the meeting, the government was operating under a continuing resolution. An omnibus bill passed the House the day of the meeting and was expected to pass the Senate the next day. This bill included $34.1 billion for NIH, which was $2 billion above FY 2016. It includes $705.9 million ($20 million above FY 2016) for NCATS; the CAN funding stayed the same as FY 2016, at $25.8 million, and the CTSA Program funding increased to $516.1 million.
- **FY 2018 Budget.** The president released a "skinny" budget in March that proposed reducing the NIH budget by 18 percent and reorganizing the NIH ICs. The full budget is expected to be released in late May 2017. HHS Secretary Tom Price testified in front of the House Appropriations Subcommittee on Labor, HHS, and Education in March and Dr. Collins is scheduled to testify in May. The corresponding committee in the Senate is expected to hold a hearing in June.
- **Executive Order: Reorganizing the Executive Branch.** Executive Order 13781, signed March 13, directs OMB to reorganize the executive branch. An April 12 memo from OMB lifted the hiring freeze, but HHS still has a hiring freeze while it develops its plans. The hiring freeze affects the makeup of these committees because members are special government employees for the time that they are in attendance, which means they are subject to the hiring freeze.
- **Upcoming Event: NCATS Advocacy Day June 30, 2017.** This exciting event in the Porter Neuroscience Research Center will inform patients and advocates about NCATS and its programs, and educate NCATS on what patients need. It will be a full-day event with brief presentations.

Discussion

G. Lynn Marks, M.D. said that the report is very exciting, especially the tissue chips' utility for studying both toxicity and efficacy. He congratulated NCATS for the progress on the SMART IRB.

Harry P. Selker, M.D., M.S.P.H., said he looks forward to hearing more about the translator project and would like to hear from the investigators directly.

Frank F. Weichold, M.D., Ph.D., said that artificial intelligence should be leveraged in adaptive trial design. He congratulated NCATS on the translator program.

Eric J. Topol, M.D., said the translator program is impressive.

Alan D. Palkowitz, Ph.D., expressed particular interest in the tissue chip program. Putting the chip into real-life use will show its strengths and limitations in aiding translation. One company could never have tackled a problem like this and it is a great use of the combined resource. He also applauded the translator program and recommended thinking about the use cases. Creating a registry of the kinds of problems it could solve would be helpful to the community.

Anantha Shekhar, M.D., Ph.D., said that a patient perspective would be a good thing to add to the translator. Particularly for rare diseases, even the medical field is often not fully aware of the phenotypes, and this would close the loop from consumer to discovery.

IV. CTSA PROGRAM UPDATE: TRIAL INNOVATION NETWORK: Monica R. Shah, M.D., Director, Trial Innovation Network, Division of Clinical Innovation, NCATS

Monica Shah, M.D., provided an update on the Trial Innovation Network (TIN), a new NCATS program. The network is tackling the critical roadblocks in clinical trials. It can take more than a decade to develop a new molecule into a new treatment. There is a lack of harmonization of critical tasks and duplication of infrastructure. Protocols are often developed without input from key stakeholders. Protocols have also gotten much more complex. Recruitment has gotten more difficult and costs have increased. All of this has led to fewer high-quality trials and less evidence to base clinical decisions on.

The TIN is intended to be a national platform for clinical trials that focuses on operational innovation, operational excellence and collaboration. The goal is to address roadblocks rather than work around them. It is one of the collaborative initiatives of the CTSA Program.

The TIN includes trial innovation centers (TICs), a novel recruitment innovation center (RIC), and CTSA Program hubs. The TIN can do everything from study design to implementation to publication of results. What makes it different is its focus on operational innovation. It is a laboratory to study and innovate the key elements of clinical trials. It has been working on harmonized approaches to common roadblocks across clinical trials: IRB review, recruitment challenges, contracting delays, incomplete utilization of data, complex protocols, and fragmented, site-based research. The TIN approach involves innovating and collecting data and evidence to support the use of these innovations.

The TIN has had more than 40 proposals submitted since October 2016. Nineteen protocol consultations and eight services are currently underway. They represent partnerships with many ICs and some foundations. A lot of work is underway now. One is a pilot project in collaboration with investigators addressing the roadblocks involved in testing the use of steroids to reduce inflammation after neonatal heart surgery. This is a rare disease and costs of a clinical trial would be too high, so instead they are conducting a randomized registry trial based on a database of surgeries. The TIN is working with them to operationalize the central IRB and standard agreements and treating this as a use case for a harmonized case report form. They will be evaluating the success of the approach, including cost.

Discussion

Valerie Montgomery Rice, M.D., observed that many of the tools and resources mentioned with respect to recruitment are already being done at sites, and asked what benefit harmonizing these efforts would have. She also asked how the TIN's efforts will increase diversity, not just with respect to race and ethnicity, but also socioeconomic status.

Dr. Shah agreed that many sites are doing great work on recruitment. The goal is to leverage that, creating a systematic approach and sharing best practices from many places. The RIC is addressing this with engagement studios that bring in people from many communities.

Patricia Jones, Dr.P.H., M.P.H., added that there will be instruments addressing trust and other factors that are barriers to recruitment. The RIC also received a supplement to broaden its research on addressing socioeconomic, age, and rural/urban diversity.

Christopher P. Austin, M.D., added that NCATS views the recruitment problem as half informatics and half engagement. Engagement is the more difficult problem, because it requires educating people on what a trial is and why they are part of the team.

Eric J. Topol, M.D., noted that a lot of engagement and enrollment could be happening through mobile devices. His institution has been able to use digital solutions to engage people who live in rural areas and people with low socioeconomic status. This requires embracing the digital world that those outside of medicine live in. Dr. Shah agreed that this is a promising area.

Rachel Ramoni, D.M.D., Sc.D., used to be a Principal Investigator (PI) on the Undiagnosed Diseases Network. Part of the problem with recruiting was that people had to have passed through high-level hospitals to make it into the network. The project paid for their tickets and made it economically feasible for them to participate.

Megan O'Boyle asked if there is a mandate that patients be genuinely involved, beyond a focus group. Dr. Shah said that involving patients early is one of the goals. The RIC and TICs are working with investigators from the beginning to bring in stakeholders, including participants and providers to help develop protocols.

Stephen P. Spielberg, M.D., Ph.D., was glad that a pediatric protocol was included and looked forward to seeing results of the test of the randomized registry design. He also mentioned the Institute for

Advanced Clinical Trials for Children, which is associated with FDA and the Critical Path Institute and is just starting up now. It would be helpful to coordinate with them.

Lynn Marks, M.D., said that trust in the biomedical research enterprise needs to be restored and enhanced. He said the measurement component is particularly important. PJ Brooks said that the CTSA Program Collaborative Innovation Awards are also addressing the issue of trust.

Valerie Montgomery Rice, M.D. said that researchers should think differently about defining diversity. High school graduation rate can be a proxy for diversity, for example.

Brad Margus noted that CTSA Programs do only a fraction of trials in the world. How will these practices spread to the rest of the world? Dr. Shah said that the TIN will be disseminating its work so that other institutions can build on it. Dr. Marks agreed that pharmaceutical companies want to do higher-quality clinical trials and will use good ideas.

Christopher Austin, M.D. said dissemination and cooperation with the Patient-Centered Outcomes Research Institute, the *All of Us* Research Program, and other such initiatives and institutions is a large part of the effort. The idea is to make all systems interoperable. One difficulty is that, while NCATS is developing these systems, they do not have the budget to run them for everyone. It is not clear yet who will maintain the systems. Anantha Shekhar, M.D., Ph.D., said that NCATS should be spreading the word about TIN throughout NIH.

Frank F. Weichold, M.D., Ph.D., asked NCATS to keep the future of the healthcare system in mind while designing these system. This will eventually be part of a future healthcare system in which anyone who has checkups will have their information captured, and they could be enrolled in a clinical trial if they want. Large hospital systems are working on this. New drugs will be introduced and data will be continuously produced.

V. NIH POLICY PRESENTATION: ENHANCING STEWARDSHIP: NEW EFFORTS TO PROMOTE A STRONGER AND MORE STABLE BIOMEDICAL RESEARCH WORKFORCE: Lawrence A. Tabak, D.D.S., Ph.D., Deputy Director, NIH

Lawrence A. Tabak, D.D.S., Ph.D., presented a policy change announced by the NIH Director earlier in the week. The policy is intended to address the problem that many NIH grants are concentrated in the labs of a few principle investigators, and many less established researchers are unable to get funding, while also maximizing the impact of NIH funding. The policy is a work in progress and Dr. Tabak welcomed comments.

NIH is entrusted to maximize the impact of the research dollars that it expends. It is also committed to developing and sustaining the most qualified biomedical research workforce possible. The current system is hypercompetitive and discourages even outstanding students from entering the profession. It is time to rethink some of the features of the U.S. biomedical research system. In recent years the number of applicants has increased greatly while the number of awardees has stayed nearly constant. More and more of the people who are funded are over the age of 60, a trend that is not solely due to

demographics of the U.S. population. In addition, 10 percent of PIs get over 40 percent of funding, and one percent of PIs get 11 percent of funding.

A metric called relative citation ratio (RCR) was used as a proxy for productivity. This is thought to be better than other metrics of publications, such as publication counts and citation rates. Relative citation ratio is independent of field and measures the strength of the article, not the journal it appears in. Analysis shows that, as the number of grants given to an investigator increases, the RCR does not increase proportionally. Well-funded investigators are very productive, but NIH might get a greater return on a grant by awarding it to a promising investigator who would otherwise have no resources than by awarding it to someone who already has three other grants. Another possible argument is that labs with a lot of grants could be particularly good at training, but the data do not show that early-stage investigators who trained in well-funded labs are more successful.

The recommended policy intends to redistribute funds to support both junior investigators and pioneering projects. This will be painful, especially for established senior investigators, but is necessary. One of the most common responses to a 2015 Request for Information, Optimizing Funding Policies and Other Strategies to Improve the Impact and Sustainability of Biomedical Research, was to cap the number of NIH grants or amount of funds one PI can have.

The proposed plan will use the Grant Support Index (GSI) as a measure of a PI's grant support. It is not simply a measure of dollars, because some science is more expensive. It is benchmarked to the R01, which is assigned seven points. R03 and R21 are less; R35 and P50 are more. Some outstanding issues include how best to account for complex infrastructure programs such as clinical trial networks, how to account for team science and whether special considerations are required to account for the need to attract highly talented investigators into new fields of science.

The proposal will reset expectations for the support provided to any single investigator by monitoring their GSI and limiting it to 21, roughly equivalent to three R01s. This would affect about six percent of investigators and free up resources to make about 1600 new awards over the next several years. An institute/center/office director can apply for an exception through a rigorous process.

The workforce is in a precarious state, there is a lot of outstanding research that is not supported, and one cohort is outcompeting the others.

Discussion

Christopher P. Austin, M.D., said that NCATS is an outlier, with no R01 program and no team science. Dr. Tabak said that, so far, at every council meeting, the director has said that their institute is unique.

Harry Selker, M.D., M.S.P.H., said he agreed with Dr. Tabak's conclusion but not his analysis, which has many assumptions and other problems, such as comparing this to the economic theory of diminishing returns. The definition of incremental benefit is not clear in this context. The policy is a good idea, but NIH should study the effects of the policy so that they understand the value of the intervention.

Dr. Tabak said that any resources that are freed up will be monitored closely, to prove or disprove the thesis that redistributing the funds to a person who is getting their first award or a person who is about to lose their research program will affect the field as expected.

Eric J. Topol, M.D., said that penalizing someone who works on infrastructure programs like CTSA Programs, which are attempting to solve the problem, does not make sense. He would excluded training programs and team science. Dr. Tabak said that these programs take up a PI's time, and perhaps it does not make sense that a person running a CTSA Program would also have time for three R01s.

Sharon F. Terry, M.A., agreed that this is a longstanding problem. Another ecosystem effect to test would be the incubation of early-stage investigators, particularly those who study rare diseases, minority investigators and novel disease that is not usually funded. She noted that advocacy groups also infuse money, and this could change their strategy for funding research. Dr. Tabak said the NIH policy does not currently account for funding from outside of NIH. Any concern would not be about small foundations, but about the Howard Hughes Medical Institute.

Stephen P. Spielberg, M.D., Ph.D., observed, in his experience as a medical school dean and a new assistant professor, that many of the brightest graduates have left biomedical research because of the uncertainties. Funded investigators also teach and see patients, and the connection between research funding and medical education is complex. He could not have run his medical school without indirect costs, which the HHS secretary has talked about reducing. Dr. Tabak agreed that the situation is complex and NIH is responsible for one piece of the ecosystem. He hopes redistributing resources will help with one piece of the puzzle.

Anantha Shekhar, M.D., Ph.D., expressed concern that the policy would create a disincentive to apply for training grants, which do not support PI salary but would add points and make it harder to get R01s.

Kalpana M. Merchant, Ph.D., mentioned her work with the Wellcome Trust, which is trying to deal with the same difficulties. Applicants are evaluated in part based on what they have done to make younger scientists independent in their own career paths and what they are doing to collaborate outside of their own area. Dr. Tabak said that people do not need more than three R01s to collaborate and train the next generation.

Rachel Ramoni, D.M.D., Sc.D., expressed concern about people having to suddenly cut off a line of research if the policy is implemented this year. Dr. Tabak said the timeline is firm. Details on exemption processes will be worked out in advance. This will be monitored, because it is an experiment.

Valerie Montgomery Rice, M.D., suggested that the biomedical research work force should be educated in a way more similar to the health care work force. A match system could place graduates in academic centers for the slots doing research, and most would end up doing the kind of research they are interested in, with an R01 equivalent. An accreditation process could include evaluating whether people become independent, in the way that accreditation for medical schools includes looking at pass rates for boards.

Brad Margus asked, rhetorically, who grants would go to if the only goal was the biggest bang for the buck. In giving grants, does looking at someone's past track record matter or not? In an ideal world, decisions might be made on a case-by-case basis, but of course NIH has to have a policy. He expressed discomfort with the idea of funding people because they can't get funding anywhere else, because there might be a reason why they can't get funding anywhere else. Dr. Tabak said that the analysis based on the RCR surrogate suggests that more impact comes from funding someone who has less funding. Because no one can predict where discoveries are coming from, it makes sense to fund research broadly. The research that isn't being funded now is also outstanding, but can't be funded because of the hypercompetitive environment.

Alan D. Palkowitz, Ph.D., said that NIH-funded research is a critical component of the broader science ecosystem and that new people try new things. It is important to promote scientific diversity. He said this policy is a bold move and a good first step.

VI. NIH PROGRAM UPDATE: ACCELERATING PRECISION HEALTH FOR ALL: THE ALL OF US RESEARCH PROGRAM: Eric Dishman, Director, *All of Us* Research Program, NIH

Eric Dishman gave an update on the *All of Us* Research Program, part of the Precision Medicine Initiative. The mission of *All of Us* is to accelerate health research and medical breakthroughs, enabling individualized prevention, treatment and care for all of us. The objectives are (1) to nurture relationships with one million U.S. participant partners, from all walks of life, for decades; (2) to deliver the largest, richest biomedical dataset ever, that is easy, safe, and free to access; and (3) to catalyze a robust ecosystem of diverse researchers and funders, hungry to use and support it.

The hope is that *All of Us* will speed up "knowledge turns" — the cycle of hypothesis, data collection, science and translation — through core values that focus on openness, trust, and empowerment. Reflecting the broad diversity of the U.S. is a priority for *All of Us*, particularly of groups who have been underrepresented in biomedical research (UBR). The program is setting ambitious goals for diversity. *All of Us* includes a center for managing data, a biobank at the Mayo Clinic, a center that is managing web- and phone-based platforms for participants and more.

One path for joining is through health provider organizations. The other is an experiment: anyone can join as a direct volunteer. Health provider organizations are spread across the United States. Partnerships with Walgreens and other national organizations ensure that anyone can enroll, even if they aren't associated with a large academic medical center. The consortium includes entities that are working on branding and content of the whole program, while also leveraging the local plans to keep a million participants engaged.

All of Us is using a user-centered design platform development process. Mr. Dishman's background is in Silicon Valley and *All of Us* is using the OTA mechanism to work nimbly with many organizations of different sizes and different types. Version 1 of the platform is being worked on now. Version 2 will add in more features, like omics. It is important to understand that Version 1 is not final and does not include all of the features that people may hope for. Genomics is delayed not because of sequencing costs, but because of the cost of responsibly returning results.

The draft scientific framework is based on diseases, because this is how the world is organized. Across diseases, *All of Us* can help examine topics like prevention and wellness, genomics and environmental exposures. Next spring *All of Us* will be holding workshops with stakeholders to discuss the scientific framework. The program will then be able to fund the development of tools that are useful in multiple areas. This is standard for platform development.

Developing precision medicine means thinking about the ecosystem of health care that exists today—and the business models, policy landscape and provider-patient relationships that will exist 15 years from now. *All of Us* wants to build an infrastructure that researchers use and that gets innovations to the bedside.

***The Algorithm for Precision Medicine*: Matthew Might, Ph.D., Associate Professor, School of Computing, University of Utah**

Matthew Might, Ph.D., told the story of his son's rare disorder. His son was the first person identified with a mutation in the NGLY1 gene, which encodes an enzyme that is involved in recycling misfolded proteins. Symptoms include an inability to produce tears. He was told that the disease was too rare for a drug company to take an interest.

Dr. Might does not have a biology background, but used his experience in computer science to approach the problem. He estimated that there were about 500 people in the world with this disease. He wrote a blog post about the disease that was designed to go viral and now has a group of 57 patients with the disease. At the same time, NIH was starting a natural history study on a related disorder. Many of the patients have entered the study. They visit each year for a week of testing.

There is a urine test for this disease. Having a test is an important step toward getting to treatments. Diet is one approach to metabolic diseases. Based on the biology of NGLY1, it seemed plausible that supplementing the diet with a particular metabolite could help. After Dr. Might's son had a particular troublesome hospitalization, he gave his son a supplement containing the metabolite, and the boy cried for the first time ever. Through computer science work matching the structure of proteins to existing molecules, Dr. Might found that Prevacid also helps, and his son is now taking that and doing things he has never done before. A drug company is now working with them on getting the drug approved for this disease. Dr. Might's wife lobbied the Utah legislature to pass a Right-to-Try law.

Dr. Might has started applying this algorithm to other patients with rare diseases. He co-founded a company called Pairnomix to do this. Dr. Might is in the process of moving to the University of Alabama, where he will be running the Hugh Kaul Personalized Medicine Institute.

Discussion

Rachel Ramoni, D.M.D., Sc.D., asked Dr. Might what NCATS can do to help scale this up. Dr. Might said that NCATS is already doing relevant work and could use more funding.

Anantha Shekhar, M.D., Ph.D., asked Mr. Dishman how the CTSA network can help *All of Us*. Mr. Dishman said he does not have an easy answer because he is completely focused on launch at the

moment. The program is trying not to repeat the mistakes of healthcare.gov and the National Children's Study. He hopes that eventually it will be possible to apply the lessons from *All of Us* in many contexts.

Brad Margus noted that some of the challenges of research, which include an IRB's mentality that studies are designed to answer one question rather than platforms like *All of Us*, and that registries always have a catch.

Mr. Eric Dishman assured him that the data for *All of Us* will be freely available. Access is not limited to members of the consortium. Giving people access to their genomic data is part of the core values. Pharmaceutical companies are interested in working with them and are willing to adhere to the open data principles. The *All of Us* data will be accessible through Application Program Interfaces (APIs). This is more like Microsoft or Google than a traditional registry.

VII. NCATS SBIR/STTR PROGRAM: SMALL BUSINESS EARLY STAGE FUNDING: Lili M. Portilla, MPA, Director, Office of Strategic Alliances, OD, NCATS

Lili M. Portilla, M.P.A., provided an update on the Small Business Innovation Research (SBIR) Program and Small Business Technology Transfer (STTR) Program. Both are Congressionally-mandated programs. The award is always made to the small business. The main difference between them is that for an SBIR, a PI has to be employed by the company.

An NIH SBIR/STTR is a 3-phase program. These are different from FDA's clinical trial phases. Phase I is a feasibility study, for discovery. Phase II is development, including clinical R&D. Phase III is commercialization. In FY2015, there was $2.5 billion dollars for SBIR/STTR across all agencies, most of it with the Department of Defense and the Department of Health and Human Services. About 20 percent of NIH's SBIR budget goes to contracts and the rest goes to grants.

The purpose and goals of SBIR/STTR include stimulating technology innovation, using small businesses to meet federal R&D needs and fostering and encouraging participation by minorities and disadvantaged people.

The program is one of the largest funding sources for early stage life sciences in the country. The small business keeps the intellectual property (IP) rights. Projects undergo NIH's rigorous scientific peer review process, which awardees can then leverage to attract other funding and collaborations. In 2016, the success rate for SBIR/STTR applications was 15.3 percent across NIH and 26 percent at NCATS.

NCATS has been doing targeted outreach about SBIR/STTR, particularly to women-owned and minority-owned businesses. Outreach efforts have included webinars, social media and engagement with partner organizations such as postdoc groups and professional societies. Other objectives include increasing the number of high-quality applications and advancing small businesses innovation among NCATS priority areas: drug development, discovery, research tools and technologies to improve translational research and patient care.

The 19th Annual HHS SBIR/STTR Conference will be held in Milwaukee November 7-9, 2017.

***Industrializing Drug Discovery – Catalyzed by NCATS*: Christopher C. Gibson, Ph.D., Co-Founder & CEO, Recursion Pharmaceuticals, Inc.**

Christopher C. Gibson, Ph.D., is co-founder and CEO of Recursion Pharmaceuticals, an SBIR awardee with a new platform for rare disease drug discovery. His dissertation was on a disease called cerebral cavernous malformation (CCM), in which small angiomas form in the central nervous system. They repurposed a drug to target a pathway that seemed promising, but in an animal model, the drug made the disease slightly worse. This led him to the question an approach based on understanding the cell pathways, because the biology is extremely complex.

Recursion's approach is based on phenotypic screening — applying a large number of compounds to diseased cells and looking for visual changes. It leverages computers to quantify the changes that are specific to a disease and then looks for drugs that rescue the phenotype. This found two compounds that reduce the burden of lesions in CCM mouse models and the company hopes to submit an Investigational New Drug application for one of these compounds by the end of the year.

Dr. Gibson's research started with NIH funding. He thought it could be industrialized and applied to a thousand more diseases. He started a company and applied for a direct to phase II SBIR. He used the summary statement from the study section to get investments from the private sector. Overall the company has leveraged $2.5 million of NIH investment into $20 million of private investment. Initial funding from NIH and the Department of Defense has supported several companies and thousands of well-paying jobs in one small area of Utah.

The technique being developed at Recursion is automated and scalable. It can ask computationally if the drug makes the cells look healthy again. The company has built models for nearly 100 different genetic diseases. Their pipeline currently includes 20 programs. Their goal is to do more than 10 INDs next year. All use repurposed compounds, some of them FDA approved.

Recursion would like to expand beyond genetic disease. They have been working on fibrosis. They have not been able to get a grant to study infectious diseases yet, but think that the technique could be promising in this area, too. Ultimately the vision for the company is to build a map of human cellular biology, based on their very large and detailed database of images of human cells.

Discussion

Ronald J. Bartek asked Dr. Portilla what NCATS looks for in SBIR/STTR applications that another IC would not look for. Dr. Portilla said NCATS is interested in direct discovery tools, clinical research management tools and diagnostics and devices. NCATS is interested in the platform aspect of the technology.

Valerie Montgomery Rice, M.D., suggested that young people who are very comfortable with computers could get involved in this type of discovery early, rather than just the bench science.

Harry Selker, M.D., M.S.P.H., noted that the metrics described earlier by Lawrence A. Tabak, D.D.S., Ph.D., would not capture the kind of work described here. The impact on health or on the marketplace should be added.

Christopher P. Austin, M.D., agreed that measuring publications, grants and patents does not show translational value.

Rachel Ramoni, D.M.D., Sc.D., said that the Department of Veterans Affairs is preparing a pilot to measure the real-world impact. She also asked what is considered success for the SBIR/STTR programs and what proportion of funded projects have that type of success. Dr. Portilla said measures of success include sales, using something from NIH to get private sector funding and job creation. NCATS is working on other measures of success.

S. Rao Kosaraju, Ph.D., said that the National Science Foundation funds a lot of research relevant to Recursion's work. Computer scientists, statisticians and mathematicians are working on developing theory that will be useful for analysis of new kinds of data.

Matthew Might, Ph.D., said it would be helpful for NCATS to combine deep learning with medicinal chemistry to make medicinal chemistry cheaper and faster. Dr. Austin agreed and said NCATS does not have the funding for it. NCATS is planning a workshop on this. It was supposed to be this year but the travel moratorium made it impossible.

Dr. Portilla mentioned the I-Corps program, which is funding phase I SBIR grantees to have an eight-week training course in entrepreneurship. It is for SBIRs funded by NIH, FDA or CDC.

Brad Margus has been on the boards of several biotechnology companies in their early stages. He said the timeline deters people from applying for SBIR/STTR funding, and asked what Dr. Portilla would change about the program. Dr. Portilla agreed that nine months is a long time in the life of a small business. She would also like to get more resources to a company in the form of commercialization assistance programs and integrate better with states.

Dr. Austin asked if anyone had considered combining SBIR and OT, because OT takes a third of the time. Anantha Shekhar, M.D., Ph.D., agreed that this would be good, because there are also delays between Phase I and Phase II. Dr. Might said that DARPA has a new kind of funding that they can deploy rapidly to small companies working in cybersecurity.

Frank F. Weichold, M.D., Ph.D., asked how the council can help NCATS get more OT funding. Dr. Austin said there needs to be internal thinking about this, and the group should return to the topic.

VIII. ADJOURNMENT OF OPEN MEETING

Christopher P. Austin, M.D., thanked all participants for their input. He and G. Lynn Marks, M.D., adjourned the open portion of the meeting at 3:15 p.m.

IX. CLOSED SESSION OF NCATS ADVISORY COUNCIL

This portion of the Advisory Council meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under

Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code, and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

Advisory Council members discussed procedures and policies regarding voting and the confidentiality of application materials, committee discussions and recommendations. Members did not participate in 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.

X. ADJOURNMENT OF CLOSED SESSION OF THE NCATS ADVISORY COUNCIL MEETING

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

CERTIFICATION

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

_____ _____

Christopher P. Austin, M.D. Date
Chair, NCATS Advisory Council
and
Director, National Center for Advancing Translational Sciences, NIH

_____ _____

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

_____ _____

G. Lynn Marks, M.D. Date
Chair, Cures Acceleration Network Review Board
and
Senior Vice President for Research and Development and Senior Clinical Advisor, GlaxoSmithKline