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

21st Meeting of the
Cures Acceleration Network Review Board

Minutes of Virtual Meeting
Dec. 15, 2017

The National Center for Advancing Translational Sciences (NCATS) Cures Acceleration Network (CAN) Review Board convened a virtual meeting, in open session, at 11 a.m. ET on Dec. 15, 2017. G. Lynn Marks, M.D., CAN Review Board chair, led the meeting. In accordance with Public Law (P.L.) 92-463, the session was open to the public.

CAN REVIEW BOARD MEMBERS PRESENT

Chair

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

Vice Chair

Ronald J. Bartek, M.A., 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

Board Members

Daniel L. Hartman, M.D.
Katharine Ku, M.S.
Richard E. Kuntz, M.D.
Geoffrey Shiu Fei Ling, M.D., Ph.D.
Brad A. Margus, M.B.A.
Megan O'Boyle
Alan Palkowitz, Ph.D.
Valerie Montgomery Rice, M.D.
Harry P. Selker, M.D., M.S.P.H.
Anantha Shekhar, M.D., Ph.D.
Todd B. Sherer, Ph.D.
Stephen P. Spielberg, M.D., Ph.D.
Sharon F. Terry, M.A.
Frank F. Weichold, M.D., Ph.D.
Paul G. Yock, M.D.

Ex Officio Member

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

OTHERS PRESENT

NCATS leadership and staff

I. CALL TO ORDER AND OPENING REMARKS: G. Lynn Marks, M.D., Former Senior Vice President for Research and Development, Senior Clinical Advisor, GlaxoSmithKline; Chair, CAN Review Board

G. Lynn Marks, M.D., opened the meeting and welcomed participants. He reminded board members that the CAN Review Board should be controlling the agenda of CAN. He and Ronald J. Bartek, M.A., plan to rework these meetings. They welcome feedback from board members.

II. MEETING RULES AND CONFIRMATION OF DATES FOR FUTURE NCATS ADVISORY COUNCIL AND CAN REVIEW BOARD MEETINGS: Anna L. Ramsey-Ewing, Ph.D., Executive Secretary, CAN Review Board

Anna L. Ramsey-Ewing, Ph.D., reviewed the procedures for the meeting. In the discussion sections following the presentations, only CAN Review Board members would be able to participate verbally, and they were required to dial in to participate via phone. Dr. Ramsey-Ewing said other participants could submit questions or comments using the Q&A box in WebEx. Dr. Ramsey-Ewing confirmed the 2018 schedule for the NCATS Advisory Council and CAN Review Board meetings:

- January 11
- May 10
- September 27
- December 14 (virtual meeting; CAN Review Board only)

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

Christopher P. Austin, M.D., gave a brief update on policy, legislative and budget issues.

- **Fiscal year (FY) 2018 budget.** The president's budget request for FY 2018 was made in May 2017. It included a large reduction in the National Institutes of Health (NIH) budget. The bills passed by the House and Senate Appropriations Committees included higher levels of funding. The new fiscal year began October 1, 2017, with the government funded under a continuing resolution (CR), which extends government funding at the FY 2017 level. The first CR ran through December 8, 2017. The second CR runs through December 22, 2017. Another CR is expected to follow. This creates uncertainty about funding. If a budget is eventually passed with an increase in funding, NCATS would like to be ready with new programs or expansions in existing programs to use any increased funding. All federal money must be spent in the same fiscal year it is appropriated.
- **21st Century Cures Act.** Hearings were held recently on Capitol Hill to celebrate the first anniversary of the 21st Century Cures Act. Francis S. Collins, M.D., Ph.D., mentioned NCATS multiple times, in both House and Senate committee hearings. As part of the 21st Century Cures Act, NCATS received permission to do Phase III studies in rare diseases. The Center is working on implementation plans.

Discussion

Ronald J. Bartek, M.A., asked about future budget requests for CAN. Dr. Austin explained that the original authorization for CAN, part of the Affordable Care Act (ACA), was for $500 million. This year, the budget was about $25 million. Dr. Austin said that the budget request process is a back-and-forth with the Department of Health and Human Services and the congressional

committees. He and Dr. Collins are trying to highlight CAN's accomplishments; emphasize the special authorities given to CAN, some of which CAN has not yet been able to use; and argue to Congress that the purpose for which the program was started is still important and that, if fully implemented, CAN would advance the health of the American people.

Dr. Marks asked whether CAN and NCATS could facilitate connections between academia and the government in ways that do not require funding but make advances possible.

IV. OVERVIEW OF CAN AND CAN PROGRAMS: G. Lynn Marks, M.D., Former Senior Vice President for Research and Development, Senior Clinical Advisor, GlaxoSmithKline; Ronald J. Bartek, M.A., Co-Founder and Founding President, FARA

Overview of CAN

Mr. Bartek reviewed CAN's origins, vision, establishment and experience.

- **Origins.** In 2003, Sen. Joseph Lieberman suggested a $150 billion, 10-year federal initiative to bring cures to market quickly. In 2009, Sen. Arlen Specter began drafting a bill for a $1 billion program outside of NIH that would be able to give large awards, competitive prizes and other funding. CAN was part of the ACA, signed March 23, 2010. CAN was originally in the NIH Office of the Director and moved to NCATS when the Center was formed in 2011.
- **CAN Review Board.** The CAN Review Board is supposed to advise and provide recommendations to the NCATS director. It should have 24 members, including researchers, leaders in venture capital or private equity, and people representing disease advocacy groups. The CAN Review Board is well below those numbers.
- **Budget.** CAN's funding has been well below the $500 million that was authorized in FY 2011; that year, no money was appropriated for CAN. For FYs 2012 through 2015, CAN's budget was a little under $10 million. For FYs 2016 and 2017, it was $25.8 million per year, which is also the request for FY 2018.
- **Funding mechanisms.** CAN can make large, renewable grants. It can make matching funds a requirement for receiving an award. CAN was granted a new authority called Other Transaction Authority (OTA) that had previously been given to a few other departments. OTAs are more flexible than the usual NIH grant process. Payment can be based on technical accomplishments, for example, and OTAs can allow for long-term strategic relationships with key suppliers.
- **Continued promise.** Although CAN has never been funded as hoped, it still has great potential. CAN was designed to be catalytic, collaborative, committed to open communication and information gathering, countercultural for NIH and disease-agnostic. Its funding mechanisms offer additional opportunities. So far, none of the 21st Century Cures Act money has been designated for CAN. CAN can work with more types of participants than a usual NIH grant, including small businesses and other parts of the U.S. government. CAN can amplify the impacts of its projects by collaborating within and outside of NIH.

Discussion

Dr. Marks observed that Congress's vision for CAN is compelling. He asked about the disconnect between this vision and the lack of appropriation. Mr. Bartek noted that Senators Lieberman and Specter are no longer in the Senate, and CAN needs new champions. He mentioned that the

tax reform bill includes some aspects that are important to the rare disease community and could lead to additional champions for CAN. Dr. Austin noted that Congress's focus in recent years has been on particular diseases, citing the Cancer Moonshot as an example. He also mentioned the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative and the Precision Medicine Initiative (PMI). These programs have had a lot of support. CAN represents the idea that putting money into overcoming generic roadblocks could allow efficient, rapid translation for all diseases. Mr. Bartek said that idea will be easier to explain when CAN has more clear wins. Dr. Marks said that focusing too much on individual disease areas can be a problem.

Mr. Bartek asked Dr. Ramsey-Ewing to talk about the CAN Review Board membership numbers. She explained that the Department of Health and Human Services hiring freeze made it impossible to hire special government employees, including the CAN Review Board members. That barrier has been lifted, and the new board members are being processed and added. In the next six months, she said, membership should be strong.

Dr. Austin said that the CAN Review Board is unique within NIH. It includes representation across the biomedical spectrum. The councils at most Institutes and Centers (ICs) react to ideas and proposals from the staff. The CAN Review Board is supposed to be proactive, and NCATS is supposed to react to it. Dr. Marks said that the diverse group should be able to accelerate growth. The board's job is to challenge NCATS leadership.

Geoffrey Shiu Fei Ling, M.D., Ph.D., asked why CAN has not received any of the 21st Century Cures Act money. Dr. Austin said it is a result of the negotiations that occur in the budget process. He also noted that because NCATS showed how effective OTA is, PMI and half of the NIH Common Fund have received OTA, but CAN has not received more OTA. This was a disappointment and an unintended omission.

Dr. Marks asked how the CAN Review Board can help. Dr. Austin said that board members can be involved in education, the same as other interested constituents.

Institute of Medicine (IOM) Workshop

Dr. Marks reminded the group of an Institute of Medicine (IOM) workshop that some board members participated in. Partnerships among institutions emerged as a theme for CAN, which should incentivize, de-risk and facilitate research at the interface between academia and industry. Another theme was that CAN should plan on a programmatic, not episodic, basis. Another topic discussed at the workshop was CAN's place in the drug development ecosystem, including interactions with the Food and Drug Administration (FDA) and the potential to produce a blueprint or master plan to establish a vision for that ecosystem. The workshop proposed ways to maximize CAN's goals, such as supporting individuals and companies that are outside the mainstream and tolerating risk and failure.

Discussion

Todd B. Sherer, Ph.D., said that the disease areas that have gotten significant funding could be opportunities for partnering. For example, there are many rarer diseases related to Alzheimer's disease that could serve as test cases to establish platforms. CAN could find ways to use that funding to have broad impact across diseases. Dr. Austin agreed and said that Richard J. Hodes,

M.D., the director of the National Institute on Aging (NIA), recently spoke to the other NIH IC directors about this topic. Several NCATS staff members are talking with NIA about how NCATS can help use the funding.

Overview of CAN Programs

Dr. Marks began by reminding board members of CAN's potential focus areas, selection criteria and selection process, as well as the concepts that CAN approved in 2014 and 2015. Dr. Austin noted that the processes were from 2013 and 2014. NCATS would like the CAN Review Board to tell the Center what the compelling opportunities are.

An attendee asked about a concept from 2014, on studying wearable sensors, which moved to PMI. Dr. Austin said it would be possible for CAN to take over part of that work. Dr. Ling said that PMI should be asked to show that it has made progress on this project.

Automated Synthesis Platform for Innovative Research and Execution (ASPIRE)
Dobrila D. Rudnicki, Ph.D., Program Officer, Special Initiatives, Office of the Director, NCATS

Dobrila D. Rudnicki, Ph.D., reviewed the Automated Synthesis Platform for Innovative Research and Execution (ASPIRE) program, which was proposed as a concept in September 2017. The world of possible chemicals, known as chemical space, is vast. Biological space is comparatively small, but 90 percent of biological space is currently undrugged. Finding new chemical space to modulate the undrugged biological space is a core translational challenge. Currently available tools for chemistry can access less than 1 percent of relevant chemical space.

ASPIRE's goal is to address this challenge by combining automation, engineering, synthetic chemistry, biological screening and deep machine learning. In the process, ASPIRE aims to transform chemistry from an empirical science to a predictive science.

In October 2017, the ASPIRE Workshop on Automated Chemical Synthesis was held in Bethesda, Maryland, with 90 national and international stakeholders from academia, industry, government, scientific journals and professional societies. Attendees identified many of the same gaps and challenges that NCATS had previously identified.

The intended users for ASPIRE include chemists, biologists, informatics scientists and anyone who can formulate a molecular hypothesis. ASPIRE could aim to create either a small number of capital-intensive, robotic automatic sites or robust, affordable devices that are widely available.

The workshop identified the following key areas that need to be addressed to advance automated chemistry:

- Predict function from structure, including ability to predict toxicity
- Predict reaction conditions
- Know the scope and limitations of reactions
- Make published data less biased
- Include additional data points (more than one measurement at a set of conditions)
- Evolve production from artisanal to engineered, to increase reproducibility and scalability

- Improve consistency in reports and in drawing chemical structures
- Use big data for automated decision making

Because data are not standardized, using big data is not currently possible in chemistry. Therefore, short-term goals for ASPIRE include the following:

- Defining standards for reporting data, including chemical structures
- Creating open databases and domain-specific repositories
- Creating affordable, open-source electronic laboratory notebook software
- Analyzing reaction space
- Making standardized, reconfigurable synthesis machines available

Long-term goals include linking bioassay data to chemical structure to synthesis and linking chemical structure to biological function.

Discussion
Dr. Marks asked about the mood in the workshop. Dr. Rudnicki said it was dynamic and exciting. Unlike a typical biology workshop, there was little immediate chance for consensus, but at the end of two days, everyone agreed that this is an important topic, and something needs to be done.

Dr. Sherer asked whether some of the outcomes could be chemicals that are laboratory tools to provide more insights about technology. Dr. Rudnicki said that the main interest is in drugs, but ASPIRE could bring about changes to all of chemistry by introducing novel chemistry. Dr. Austin said that finding new probes would be part of NCATS' mission of translation.

Alan Palkowitz, Ph.D., attended the second day of the workshop and noted that ASPIRE is uncovering key problems in the community, such as reproducibility. Automation platforms could provide a way to quickly validate work. ASPIRE could bring together many emerging areas, such as artificial intelligence, and give them immediate purpose and applications to benefit the community.

Dr. Austin said that the next challenge for ASPIRE is to determine which challenges it can take on and how ambitious to be.

NCATS Pilot Program for Collaborative Drug Discovery Research Using Bioprinted Skin Tissue
Dobrila D. Rudnicki, Ph.D., Program Officer, Special Initiatives, Office of the Director, NCATS

Dr. Rudnicki gave an overview of this program for 3-D bioprinting of skin for use in drug discovery. Modern drug discovery fails 90 percent of the time. More than 50 percent of failures are due to lack of efficacy. Another 25 percent are due to safety issues. With recent advances in induced pluripotent stem cells (iPSCs), gene editing, imaging and 3-D printing, it is now possible to develop more physiologically relevant models. The goal of this project is to establish a multidisciplinary laboratory that uses 3-D bioprinting to create both normal and diseased 3-D bioprinted materials that are validated, qualified and screenable and can be accessed by extramural investigators. These materials could be used for drug efficacy and toxicology data, leading to shorter drug development times and fewer failures in clinical trials.

In addition to the internal project on skin, NCATS is collaborating on bioprinting projects on the blood-retina barrier, blood vessel wall and cancer metastasis niche.

The bioprinter prints the dermal layer first, then deposits the epidermis on top. The process is automatable and reproducible. It takes about five minutes. Each piece is about 300 µm thick and 7.5 mm across.

A pilot program for the skin tissue was funded in February 2017. Extramural investigators were invited to contact NCATS and discuss ideas. The first pilot project is testing a microscopy process that does not require sacrificing tissue to analyze the effects of a drug, using squamous cell carcinoma as a model. If successful, this process will apply to many diseases. A second project is developing a model of psoriasis that can be used to screen drugs. If these projects are successful, more will be added.

Discussion

Dr. Marks asked about the connection between bioprinting and tissue chips. Danilo A. Tagle, Ph.D., M.S., explained that drug discovery could be done on bioprinted tissues, then good candidates could be tested on tissue chips to supplement or replace animal tests. Dr. Rudnicki said that her program is about screening, with the hope of making the screening high-throughput.

Dr. Sherer asked how the bioprinting work could be shared outside of NCATS. Dr. Rudnicki said that dissemination is one of the goals. Once the technology is established, it will be shared. Dr. Tagle added that the patient-derived iPSC lines, scripts for bioprinted materials and best practices will also be made available.

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

Dr. Tagle gave an update on the Tissue Chips Program. In 2010-2012, the program was funded through the Common Fund as part of a program on Advancing Regulatory Science.

The full-fledged program ran for five years, 2012 through 2016, with the goal of developing an *in vitro* platform that uses human tissues to evaluate the efficacy, safety and toxicity of promising therapies. The program targeted development of 10 major organ systems on chips. The first two years focused on platform development and developing cell resources. The projects were not guaranteed funding; they were milestone-driven. The next three years were spent on functional validation of the chips and integration into multi-organ platforms. Dr. Tagle described some of the features of the program and the tissue chips.

- **Funding and partnerships.** Over five years, NIH spent $75 million, the Defense Advanced Research Projects Agency (DARPA) spent $75 million, and the FDA provided insight and expertise. The FDA is a key partner for NCATS and needs to be engaged for the devices to be qualified as regulatory decision-making tools. Industry partners (AstraZeneca, GSK and Pfizer) were also involved. NIH encouraged the formation of spinoff companies from academic institutions to provide hardware or services to access the platforms, and several have been created.

- **Mimicking organ function.** Dr. Tagle showed an example of how a tissue chip mimics human organ function. A lung tissue chip mimicking the alveoli has epithelial cells on the top, endothelial cells on the bottom and a cyclic vacuum to move the tissue in the same way that it would move with respiration. This mechanical signaling on the cells is what sets these tissue chips apart from other static cell culture systems; they model the biomechanical stresses on a particular organ or tissue. The microphysiological systems are also intended to mimic microvasculature. Tissues can be embedded into an iPSC-derived capillary bed. Innervation is another feature. Female hormones have also been considered.
- **Metrics for success.** The CAN Review Board developed metrics for success of the program in the categories of administrative outcomes, project outcomes and transformative outcomes. Transformative outcomes include wide adoption by the pharmaceutical industry and a reduction in animal testing.

Dr. Tagle described the new and upcoming programs related to tissue chips.

- **Testing centers.** As part of developing a validation process for the chips, NCATS has funded two Tissue Chip Testing Centers. These are a partnership among NCATS, the FDA and the IQ Consortium, a nonprofit group of pharmaceutical companies. NCATS' support is $12 million over two years, awarded in September 2016. The testing centers are at the Massachusetts Institute of Technology and Texas A&M University. Funding also has been awarded to support a database center at the University of Pittsburgh Drug Discovery Institute; this center will house all data related to tissue chips. A concept clearance has been submitted to fund these sites for two more years. The idea is to expand testing to more chips and make the testing centers self-sustaining and revenue-generating.
- **Addressing efficacy.** Another current program, Microphysiological Systems for Disease Modeling and Efficacy Testing, is addressing the larger issue of efficacy, which causes much attrition in the drug development process. It is a five-year program with funding partnerships between NCATS and other NIH ICs. The program includes a diverse group of disease models, from atrial fibrillation to polycystic ovarian syndrome and influenza infection. Some diseases being modeled included single Mendelian disorders; others are radiation- or drug-induced diseases.
- **Tissue chips in space.** The NIH-Center for the Advancement of Science in Space (CASIS) Coordinated Program in Tissue Chip Systems for Translational Research in Space is taking advantage of the microgravity environment to induce aging and working with space engineers to rapidly evolve the tissue chip technology. Five projects have been awarded and a reissue of the funding opportunity announcement is currently underway.
- **Symposium.** A Keystone symposium on organs and tissues in chips will be held in Montana in April 2018.

Discussion

Mr. Bartek noted that the Tissue Chips Program was initiated before NCATS was established and is an excellent example of how NCATS and the CAN Review Board want to operate. He asked whether the Common Fund still has a program on Advancing Regulatory Science. Dr. Tagle said the program still exists but ends when the first tissue chips awards end in 2017. The Common Fund reduced its support for tissue chips when the program moved to NCATS. Mr. Bartek asked whether Common Fund support is available for other projects. Dr. Tagle explained that the

Common Fund sometimes requests new concepts and ideas from all NIH ICs, and he personally runs through programs that are funded by the Common Fund. Mr. Bartek asked whether the Tissue Chips Program uses OTA. Dr. Tagle said that OTA is not needed for this program and the NCATS Office of Strategic Alliances has been a great help.

Dr. Ling asked to see a timeline showing the milestones for the program from the beginning and over the next few years, to show how the program accelerated development and implementation of the technology. Dr. Tagle said he has those slides and can send them to Dr. Ling. Dr. Marks added that it is helpful to see the vision for the future in these updates.

Biomedical Data Translator: Christine M. Colvis, Ph.D., Director, Drug Development Partnership Programs, Office of the Director, NCATS

Christine M. Colvis, Ph.D., spoke about the Biomedical Data Translator (Translator), which aims to bring together data from the preclinical and clinical spaces to facilitate and accelerate new discoveries and the development of new interventions. It should help researchers improve disease classification and run better clinical trials.

An open meeting was held in October 2017 in Chapel Hill, North Carolina. A second day of meetings, called the Hackathon, was held with awardees only. It included many software developers and was a fun and stimulating meeting.

The initial awards for the Translator were made in September 2016. They included specific goals to be addressed and specific items to be evaluated with a feasibility assessment. The feasibility assessment is underway for high-value data, quality control, barriers to integrating datasets, queries that could be asked of the Translator and requirements.

The architecture of the Translator includes knowledge sources, a blackboard and a reasoning tool. The reasoning tool does not yet exist. The funding opportunity announcement (FOA) was issued in September, using OTA. By the time the awardee is chosen, about 10 months will remain in the feasibility assessment. The reasoning tool FOA used a unique three-step application process. First, potential applicants had to complete a series of computational tasks. When these were complete, they saw the instructions for submitting a concept letter. NCATS evaluated the concept letters and invited a subset of applicants to submit a full proposal in writing.

The computational tasks began with a puzzle. The process received attention on Reddit and Twitter. Part of the idea of OTA is to encourage nontraditional applicants, and NCATS was pleased at the interest on social media. More than 5,000 attempts were made on the first puzzle in two weeks. The tasks can be reviewed at this link.

The selected teams developed proof-of-concept software, submitted it and demonstrated it to NCATS. Negotiations with the teams are about to start.

Discussion

Dr. Ling expressed great enthusiasm for the FOA process and asked whether a prize mechanism could work. Dr. Colvis said that is a possibility for later in the process. She added that issuing an FOA was not intended to narrow down the number of applications received. Although it did

have this effect, the goal was to ensure that applicants would have the right skill sets. Dr. Ling said that a prize would also have this effect.

Dr. Marks suggested consulting the Critical Path Institute on data standardization.

V. CLEARANCE OF CONCEPTS: NCATS Staff

Biomedical Data Translator: Christine M. Colvis, Ph.D., Director, Drug Development Partnership Programs, Office of the Director, NCATS

Dr. Colvis shared the new concept for the Biomedical Data Translator. The criteria for evaluating success are, initially, the number and variety of data types integrated into the Translator; in the short term, the frequency of use by the research community; and in the long term, more efficient translation and more success with clinical trials. The major obstacle being addressed is the siloing of data. NCATS is discussing data standards with many groups that are working on efforts related to data standardization, including the *All of Us* Research Program and a program at DARPA.

The discrete and measurable outcomes for the project are new lines of investigation for prevention or therapeutic development and an increase in the number of innovative trials. The impact will first reach translational researchers in all areas of medicine, then clinicians and patients as consumers and contributors of information. The project is disease-agnostic and has the potential to change how scientists and clinicians think about disease and treatment.

Dr. Colvis shared the contract project criteria. Dr. Ramsey-Ewing said it is important to be aware of the issues related to contracts.

Discussion

Dr. Ling was the first discussant. He said the Translator is an important project and will be transformative if it works. He said the project could work with the normal investigator-initiated, peer-reviewed grant mechanism, but the contract approach also has potential. He suggested that a milestone-based cost-reimbursement contract might create faster progress. Using OTA for this project could be a model for the rest of NIH.

Dr. Palkowitz was the second discussant. He agreed with Dr. Ling on the contract issue. He said that the Translator is a well-designed, thoughtful approach to the problem. He emphasized that use cases should be part of the ongoing development, to make sure that the data sources and architecture will be useful to the community for advancing concepts and hypotheses and will help educate the community about the tool.

Dr. Sherer added that some of the projects mentioned earlier in the call that had received significant funding from Congress in recent years could offer opportunities to partner and pilot this approach.

The CAN Review Board unanimously approved this concept.

NCATS Collaborative Rare Disease Platform Vector Gene Therapy Trials: P.J. Brooks, Ph.D., Program Director, Office of Rare Diseases Research and Division of Clinical Innovation, NCATS

P.J. Brooks, Ph.D., presented the concept for NCATS Collaborative Rare Disease Platform Vector Gene Therapy Trials. Thousands of diseases are caused by single genes and could be treated by gene therapy, but it has been difficult to implement. Recent clinical success stories have brought new hope. The usual approach focuses on one disease at a time. NCATS proposes to study the vectors that deliver nucleic acids to particular cells as a platform that could be used across multiple diseases.

The concept is a pilot project to carry out trials on three or more diseases in the Rare Diseases Clinical Research Network (RDCRN). The trials will use the same viral vector route of administration and production and purification methods to deliver a different gene for each disease. The work will leverage resources and expertise across NCATS divisions.

The potential outcomes for the project are identifying roadblocks and developing strategies to overcome them; bringing human gene therapy trials to more patients in the RDCRN; and creating a faster, less expensive, more efficient path to clinical trials and drug approvals. The potential impact is bringing more gene therapy treatments to more rare disease patients more quickly.

Criteria for success are the identification of obstacles and solutions, the number of patients enrolled, how long it takes for Investigational New Drug applications to be filed and the number of other clinical trials that follow using the same platform. The major obstacles to address are intellectual property and business considerations, concerns and benefits for different collaborators and stakeholders, and regulatory challenges. Several gene therapy projects have succeeded lately, and responses to a Request for Information earlier this year showed interest and enthusiasm for this topic and identified potential partners.

The project would include collaborations with various parts of NCATS, biotechnology companies and the FDA's Center for Biologics Evaluation and Research. Discrete and measurable outcomes for the project include the number of patients enrolled, filings with the FDA and whether others are inspired to use the same platforms. The impact of the project would be to broaden the field of gene therapy, moving away from a focus on individual diseases. The project applies to many diseases and to gene editing therapy trials.

Discussion

Megan O'Boyle was the first discussant. From a rare disease perspective, she applauded the idea of moving away from a focus on single diseases. Rare disease advocates are enthusiastic about gene therapy and want to try it for their diseases, but it is difficult to do. She also approved of leveraging the RDCRN, which already has the infrastructure and makes for a perfect pilot project.

Mr. Bartek was the second discussant. He recommended that the project not limit itself to diseases in the RDCRN; other diseases outside of the RDCRN could also be very good matches with RDCRN diseases.

Petra Kaufmann, M.D., M.Sc., said that the goal is to make this technology scalable and available to as many families and for as many diseases as possible. The pilot is intended to leverage existing investments to start this process. She said it may be possible to make the language more open, but she is confident that at least three candidates can be found within the RDCRN.

She added that concept clearance was given at a recent meeting for the recompetition of the RDCRN.

Mr. Bartek asked how NCATS is making sure that the right vector is being used and handling potential legal issues with rights to vectors. Dr. Brooks said that addressing these issues is a large part of the experiment. He expects the business questions to be particularly interesting. This will make a trail that other investigators can follow. Dr. Kaufmann said that the project may identify generalizable principles for the best framework for this kind of partnership.

The CAN Review Board unanimously approved this concept.

VI. BRAINSTORMING: G. Lynn Marks, M.D., Former Senior Vice President for Research and Development, Senior Clinical Advisor, GlaxoSmithKline; Ronald J. Bartek, M.A., Co-Founder and Founding President, FARA; Christopher P. Austin, M.D., Director, NCATS

Mr. Bartek asked CAN Review Board members to share their thoughts about the largest current barriers to development from bench to bedside.

Ms. O'Boyle said that for intellectual disabilities and autism-related diseases, the barrier is finding biomarkers. Biomarkers are required before industry is willing to partner on research using existing drugs for these conditions. For now, finding and recruiting patients is not a barrier for rare diseases.

Dr. Palkowitz said that from the pharmaceutical industry perspective, a major challenge is identifying and selecting the best targets for intervention, based on existing information sources and translational experience. Identifying the right disease targets, pathways and potential mechanisms is one of the most important parts of the journey to new therapeutics. How to improve this process is one of the long-standing questions for the industry.

Katherine Ku, M.S., said that she sees Stanford faculty who have a target but struggle to find a compound; she would like to bring them more help with that part of the process.

Stephen P. Spielberg, M.D., Ph.D., said that imprecision in understanding the natural history of disease has led to failure of many clinical trials in many diseases. Lack of understanding of natural history leads to imprecision in defining entry criteria and clinically relevant outcome variables. Molecular targets can be very precise, with thoroughly understood interactions between molecules and druggable targets, but this knowledge is not useful without a clear understanding of which patients they apply to.

Frank F. Weichold, M.D., Ph.D., agreed with Dr. Spielberg. At a recent workshop on rare diseases, the quality of natural history data emerged as an area that needs more work. Data quality is also a problem, and adaptive trial design is important. Rare diseases are a good area to demonstrate the principles, and the FDA is interested in collaborating with NCATS and stakeholders.

Mr. Bartek said that better drugs are needed. He wondered if CAN and NCATS could collaborate with the FDA to find better outcomes that fit the regulatory requirements; for example, they could include data on how a clinical trial participant is feeling and functioning in daily life. Wearable sensors could be an important part of this question, and Mr. Bartek is disappointed

that NCATS is no longer pursuing this research. Dr. Marks suggested that wearables could be discussed at a future meeting.

VII. ADJOURNMENT OF THE CAN REVIEW BOARD MEETING

Dr. Marks thanked the participants and presenters for their time and engagement and thanked NCATS staff for their good work. He adjourned the meeting at 2:31 p.m. ET.

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

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

_____ _____

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