**NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES POLICY WORKSHOP**

**MEETING SUMMARY**
**DECEMBER 11, 2012**

**INTRODUCTION**

The mission of the National Center for Advancing Translational Sciences (NCATS) is to catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. Accelerating the translation of biological insights into new medicines requires developing powerful new scientific knowledge, methodology and tools, as well as the thoughtful navigation of translational research policy issues. NCATS is partnering with stakeholders to prioritize key issues and specific policy goals in the areas of informing regulatory science; navigating intellectual property challenges; streamlining clinical research; and forming efficient strategic alliances. Given NCATS;' mission as a hub for catalyzing innovations and creative partnerships in translational science, the goal is to expand the understanding of relevant policy issues in order to overcome hurdles that slow the development of effective treatments and cures.

**PURPOSE**

On Dec. 11, 2012, NCATS convened a one-day workshop to discuss issues and obtain advice on proactively building a solid policy research and analysis agenda to inform translational research within the scope of the Center's mission. This meeting provided an opportunity to collaborate with key stakeholders in the regulatory, academic, nonprofit and private sectors to obtain views on how policy research and analysis can inform translational research and to identify barriers in translation that could benefit from policy research and analysis.

Following opening remarks from NCATS Director Christopher P. Austin, M.D., Dr. Kathy Hudson, former Acting Deputy Director, NCATS, and Deputy Director for Science, Outreach and Policy, National Institutes of Health (NIH), provided an overview that included what is meant by "policy;" a review of NCATS legislation and congressional expectations; a brief discussion of the National Human Genome Research Institute's (NHGRI) Ethical, Legal and Social Implications (ELSI) Research Program as an example of a research policy precedent at the NIH; and, lastly, goals for the day. Dr. Hudson mentioned that although most of NCATS efforts are focused on overcoming barriers to translation through research, it was important to recognize that there were some barriers that could be addressed through science policy research and analysis and that NCATS was uniquely positioned to inform consideration on these policy matters. She noted that not only could NCATS tap its own internal resources, but it could potentially support policy-relevant research through grants and contracts.

The workshop then commenced with an introductory panel on lessons learned from existing and successful high-impact policy programs. Panel members discussed how policy questions were formed and addressed within their organizations and fields; provided examples of how data collection and analysis can be used to inform policy options; and discussed their experiences engaging policymakers and other individuals who influence policy decisions. The following cross-cutting themes emerged from the panel discussion:

- State-of-the science must be ready for policy change

- Focus on the most fertile areas — you can't and don't want to respond to everything
- Ensure the solution is policy amenable and that goals and objectives are clearly defined and measureable
- Communication and transparency are key to successfully developing and implementing policy
- Balance risk versus benefit
- Be proactive (long-term solutions ), not reactive (putting out fires)
- Implementing policy decisions is always the hard part, but you can use a cyclic process of ASK-ANSWER-ACT to refine decisions and gain acceptance of policy changes
- In some cases, implementation may need a change in the law or regulation; so, be patient

**BREAKOUT SESSIONS**

Next, a series of four concurrent breakout sessions focused on policy challenges associated with specific aspects of advancing the NCATS mission.

**Informing Regulatory Science**

NCATS aims to develop new tools and methodologies that could prove useful in shaping how new medical products are regulated. The objective of this session was to identify challenges in the regulatory process that could hinder progress in moving potential new discoveries forward. Panelists were asked to consider feasible strategies for developing prospective processes to guide regulatory decisions for new tools and technologies while minimizing layers of review. An additional consideration was how the NIH and the Food and Drug Administration (FDA) can work together to evaluate if a new tool or technology is a viable candidate for replacing the current "gold standard." A case study on the development and adoption of new tools for pre-clinical toxicity testing was used to illustrate the complexity and uncertainty behind how a new technology — a 3-D human tissue chip that mimics the structure and function of a human organ and better allows scientists to predict how effective a therapeutic candidate would be in clinical studies — could be integrated into the current regulatory framework to circumvent some of the challenges associated with regulating pre-clinical studies in animal models.

***Discussion and Recommendations***

After listening to the case study, panelists universally agreed that tools to enhance predictability in drug development are useful in predicting safety and efficacy and in helping to understand exposure. Emerging fields, such as the translational sciences, are yielding innovative approaches to improving human health while at the same time are posing challenges to FDA's ability to reliably evaluate the products derived from this new science. Panelists identified three barriers to progress in this area — collaboration, standardization and validation — and stated that there was a causal and bi-directional relationship between them. For example, large-scale collaboration is necessary to generate and gather the data needed for standardization and validation because the funding and expertise required is far beyond any single stakeholder. Yet many barriers to collaboration currently exist, such as funding mechanisms, investigator credit and advancement, coordination and communication, and intellectual property rights, just to name a few. Panelists suggested the need for transparency and to redefine the intellectual property playground such that all information regarding safety would be shared widely for the good of the patient.

Scientists trained in a discipline tend to speak a specific language and adopt the analytical and methodological constructs for that discipline. Although this is an important part of the training experience, it can present obstacles to interdisciplinary research. First, investigators may not understand

the languages of the other disciplines. Second, although the same or similar terms may be used in different disciplines, they could mean something very different. As a solution, panelists recommended standardizing common data collection terminology among regulatory agencies and the global research community that can be used for validation. As an example, they suggested developing guidance on the qualification process for drug development tools that would complement the FDA qualification process for assessing the risks and benefits of new tools. This would require a set of compounds that are standardized to use as a test set to teach models how to predict, while leaving a subset of compounds that can be used to validate the model. As for how to evaluate if a new tool or technology is a viable candidate for adding to replacing existing technologies, panelists suggested examining the risk/benefit of the new versus the old tests. They also stated that replacement of a technology should depend on the continued utility of the old test.

As for areas amenable to NCATS policy research, panelists offered the following considerations:

- Identify the priorities and biggest unmet need
- Initiate collaborative efforts to standardize and validate
- Ensure that new technologies are evaluated
- Assess the utility of new technologies and communicate globally

The group also recommended that NCATS continue to work closely with the FDA, industry, academia and patient advocacy organizations.

**Navigating Intellectual Property Challenges**

During this breakout session, participants explored the challenges associated with moving a product into the commercial sector when traditional intellectual property incentives are no longer in play. Panelists were asked to consider what incentives NCATS can develop to ensure that promising products yielding uncertain returns are brought to market and, if an industry partner cannot be identified for further investment, how the public sector can work with other stakeholders to bring the product to market. As an example, NCATS highlighted how the Therapeutics Discovery Program and the Pharmaceutical Collection provide investigators with collections of compounds that serve as a valuable research resource. Many of these compounds are "rescued" or "repurposed" and have limited to no patent exclusivity and, therefore, the predicted return on investment is variable. This often deters commercial entities from investing in further development. The question then becomes what type of incentive(s) can be put in place to encourage investment in areas with little perceived financial gain.

***Discussion and Recommendations***

Article I, Section 8 of U.S. Constitution states that Congress will have the right… "*To promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries."* Patenting and licensing are used to help ensure new technologies are developed fully and commercialized to advance public health, but they can sometimes be seen as impediments to moving collaborative science projects forward. It was noted that in the private sector, patents equal incentive for invention (approved drugs), while for government-funded research, grants equate to incentive for innovation (basic research discoveries). In the therapeutic drug discovery pipeline, this translation gap, or "Valley of Death," is the work required to turn basic research discoveries into treatments that help people. Conventional patent-based strategies for commercialization of academic research, as envisioned by the Bayh-Dole Act, are unlikely to foster the intensive collaboration required to move drug candidates across the so-called "valley." This need to successfully translate research into potential drugs has led to an increased interest in drug repurposing to discover therapies for unmet needs. Because existing drugs have known pharmacokinetics and safety

profiles and are often approved by regulatory agencies for human use, any newly identified use can be rapidly evaluated in Phase II clinical trials. In this way, investigators can reduce the overall cost of bringing a drug to market by eliminating much of the required testing. Panelists noted that oftentimes in these instances, the options for intellectual property protection are limited, and that NCATS should consider novel models of public-private partnerships (PPP) to overcome this barrier and encourage investment. Various models were discussed as successful examples and included:

- ***Public-Private Consortia (SNP, HapMap).*** In this model, forming a consortium provided the critical mass necessary to enable the generation of large-scale data needed for innovation. In addition, placing data in the public domain with non-patenting covenants ensured transparency and eliminated redundancies.
- ***Rai, Reichman, Uhlir, Crossman — Pathways Across the Valley of Death: Novel Intellectual Property Strategies for Accelerating Drug Discovery.*** This paper highlights models for multi-firm, public-private collaboration with a "pooling" structure for privately owned molecules whereby academic researchers are granted access via a trusted third-party intermediary.
- ***California Institute for Regenerative Medicine***. This model provides state funding for research with post-publication sharing of biomedical research materials.

Panelists also referred to the PCAST (President's Council of Advisors on Science and Technology) Report to the President on Drug Discovery, recommendations 1 and 8 in particular, which focus on supporting federal initiatives to accelerate therapeutics and studying current and potential economic incentives to promote innovation in drug development respectively. The latter recommendation focused on compelling issues such as patent protection and led to discussion on optimizing exclusivity periods for repurposed therapeutics and data exclusivity.

Panelists suggested that NCATS should consider if research on rescued or repurposed compounds would best be served by more or less intellectual property (IP) protection and how to effect changes. They also suggested that NCATS work to define the boundaries of the pre-competitive space and to develop policies on allocating rewards for those stakeholders involved in drug rescue and repurposing. Additional suggestions were establishing new legislation (patent and data exclusivity); changing NIH funding requirements (data sharing and publication of negative results); disseminating best practices; offering additional economic incentives (prizes and taxes); and implementing regulatory tie-ins (FDA approval and patenting for secondary uses).

They concluded by highlighting policy areas for NCATS consideration, including optimizing exclusivity periods for repurposed therapeutics; patenting for secondary uses; efficiently allocating innovation rewards among participants (academic, industry, government and patients); managing the cost burden associated with obtaining patent protection; requiring the publication and sharing of negative results (impact on trade secrecy); and defining the boundaries of pre-competitive research. There was discussion about the long development and approval cycles in the pharmaceutical industry, prompting panelists to question whether there could be alternatives to purely patent-based incentives. For instance, could an agency other than the Patent and Trademark Office — such as the FDA or the Federal Trade Commission — provide adequate data-exclusivity or market-exclusivity cover for developing new uses for existing drugs or drugs for rare and neglected diseases? These incentives could take into account the developmental times and costs involved by computing a cost-plus model of incentives, so that risk taking is encouraged. At present, the only sure way to recapture the costs of bringing repurposed drugs is through the development of a new formulation or delivery mechanism, but this only adds to costs to the consumer.

**Streamlining Clinical Research**

NCATS, in an effort to make translational research more efficient and less costly, is exploring new ways to accelerate the conduct of clinical research, including experimenting with innovative trial designs and harnessing the power of patient databases. It is imperative that adoption of any new acceleration strategy not occur at the expense of the patient. For this reason, NCATS must ensure that emerging ethical issues and challenges associated with new strategies are addressed proactively. In this breakout session, panelists were asked to brainstorm about both current and prospective challenges facing the ethical conduct of translational research and the role of NCATS in facilitating a resolution. They also were asked to identify a potential framework for addressing ethical issues associated with developing and testing innovative therapies; to discuss how to best promote policies that provide for broad research use of clinical data while maintaining confidentiality; and to address issues surrounding consent.

To help illustrate current challenges and novel solutions, NCATS staff presented a case study highlighting how meaningful clinical results often rely on data from diverse populations collected from multiple institutions and geographic sites. While the current multi-site Institutional Review Board (IRB) model has succeeded in protecting human subjects enrolling in clinical trials, it has not kept pace with addressing the challenges associated with data collection and sharing across multiple sites and often introduces inefficiencies. Recognizing these impediments, the NCATS-supported Clinical and Translational Science Awards (CTSA) Consortium is developing a multi-site IRB model that reduces duplicative reviews and supports policies and tools to expedite consistent data collection and sharing. The goal of the new model is to maintain the highest ethical and regulatory standards in the review and oversight of clinical trials while minimizing duplicative effort among IRBs across multiple study sites and institutions.

***Discussion and Recommendations***

The group kicked off the session by identifying challenges and barriers to progress in this area, including the length of time to IRB approval and variability across institutions; overlapping and redundant reviews and oversight for multi-site trials; lack of master agreements; systems inefficiencies; high cost; difficulty and delays in patient recruitment; and too few advocates for efficiency. Panelists also discussed that, oftentimes, the purpose of an IRB is not adequately aligned with research practices and behavior. Members recommended movement towards a centralized IRB approach but recognized that this will be difficult as IRB review processes are often culturally embedded within an institution. Additional considerations regarding a centralized approach related to the potential misunderstanding of regulations and perception of liability concerns. They suggested that NCATS work with the CTSA institutions to develop metrics for improving IRB processes.

The group felt that there was much policy research that could help inform this area. They highlighted the success of the University of California, San Francisco as part of the NCATS-supported CTSA program and also suggested that NCATS examine models adopted by other industries such as the biotechnology arena. Members also felt that public engagement and widespread data sharing are critical for the future of clinical research and ripe for study, as few mechanisms exist to involve and empower research participants in the research process. There was also a recommendation to consider “experiments” in recasting the system of translation science, including exploration of changes to the “privacy” paradigm and developing new tools for sharing information to enhance and simplify patient recruitment and enrollment while protecting the use of individual information. Group members also felt that current mechanisms for clinical trial oversight were impeding translational science and suggested examining the appropriate role of an IRB with regard to oversight — for example, what oversight functions could be

centralized versus conducted at the local level. The group suggested leveraging technology, for example Web-based systems, as a tool to develop and implement new models of consent and recommended tying funding to the development of metrics for review and oversight. They cited "learning health care systems" as a model whereby the availability and use of evidence should drive the health care choices of patients as well as ensure innovation, quality, safety and value in drug discovery. Not only would this type of system get the right care to people when they need it most, it would capture results for improvement. Lastly, panelists encouraged NCATS to examine ways to predict clinical trial probability of success, thereby reducing the number of failed trials. Similar to recommendations in the other breakout sessions, the group suggests that NCATS continue to work closely with the FDA, academia, advocacy organizations and voluntary health organizations. Voluntary health organizations are particularly good at what is often a missing link in the process: working with the medical community and patients once a treatment is commercialized. The direct connection enables awareness of the disease from a patient perspective.

**Forming Efficient Strategic Alliances**

Advances in technologies and knowledge are creating new avenues and opportunities for the discovery and clinical development of innovative therapies and diagnostics. However, despite these opportunities, only a small fraction of investigational products are successfully developed into cures and therapies that can be accessed by patients. Collaboration between federal agencies, academia and industry to cross-leverage expertise and resources can de-risk and enhance translational efforts. Unfortunately, such partnerships require significant investment in time, effort and communication to be successful. The new Cures Acceleration Network (CAN) authorities provide opportunities to overcome some of the impediments and were highlighted in a recent Institute of Medicine (IOM) workshop. In this session, participants were asked to identify what they thought were the predominate barriers to collaborating across sectors and with the NIH; to identify tools or mechanisms that NCATS could develop to overcome these barriers; and to identify ways in which NCATS can further build upon the findings of the IOM regarding the use of new authorities to engage nontraditional partners. Lastly, panelists were asked to consider lessons learned from other sectors or government agencies that NCATS can use to engage collaborators while ensuring barriers to translation are addressed effectively and expeditiously.

As background for discussion, staff indicated that NIH currently collaborates on initiatives primarily through the use of cooperative grants, contracts, and Cooperative Research and Development Agreements (CRADAs). These "standard" NIH collaboration tools have various limitations, including insufficient intellectual property protection, complex data/resource sharing requirements, and lengthy procedural delays. NCATS has been afforded authorities through CAN which include matching funds and flexible research authority. These "new" authorities offer much promise, but their use will require careful consideration and close monitoring.

***Discussion and Recommendations***

The group began by discussing what they thought were barriers to progress in the formation and execution of successful strategic alliances. They include the status quo (fear of doing things differently); overcoming cultural differences between and among organizations; lack of standards for collaboration and defining the terminology used in the translational research field; regulatory uncertainty; lack of effective leadership and management skills; and administrative mismatch among stakeholders.

Areas for policy research that could strengthen the formation of strategic alliances include issues associated with disclosure of clinical research data and economic incentives for out-of-patent therapies. When discussing areas thought to be amenable to policy research, the group recommended that NCATS

focus on quick wins. Examples were defining what constitutes pre-competitive research space and where IP-protected research should begin; enforcing disclosure requirements for clinical research data; turning discoveries into translatable therapies; developing and defining best practices and metrics for tracking performance; and public-access data sharing to include negative results. Understanding why something failed can sometimes yield important information that helps researchers move an idea forward or suggest entirely new directions for research. Panelists also suggested that NCATS not only support innovative science and bold new ways of funding science (e.g., use of the CAN authority), but that the Center host forums for discussion on innovative and successful partnerships and translation and bring in economic players such as foundations and international funders.

Over the longer term, efforts should center on developing management practices focused on the leadership skills and attributes necessary to deliver results across organizations and disciplines and on refining clinical research requirements for various diseases. Also worthy of consideration is how to leverage data, analytics and processes to accelerate collaborative research. By focusing on data that are common to the partnering organizations, research can be advanced at the intersections of these disciplines. Panelists felt that key stakeholders to involve in forming successful and sustainable strategic alliances include NCATS leadership, NIH, industry, FDA, advocacy and voluntary health organizations, academia, and venture capitalists.

**CLOSING REMARKS**

Dr. Austin thanked the speakers, moderators, rapporteurs and participants for their time, enthusiasm and input and said that he would be reviewing the workshop recommendations with the goal of developing a policy research and analysis framework that will inform translational research. For research to influence policy, it has to be relevant, valid, timely and presented in a way that policymakers can understand. Furthermore, policymakers need to develop an effective demand for data and evidence to facilitate the translation of research into policy and practice. To this end, NCATS will focus on high-priority issues amenable to changes in policy and ensure that goals and objectives are clearly defined and measureable. Dr. Austin concluded by once again thanking workshop participants for their invaluable insights and stated that he will continue to solicit feedback from members of this group as follow-up activities are planned.