National Center for Research Resources

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Decision Making in T1 Translational Research

Natcher Conference Center
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February 10 – 11, 2009

Final Workshop Report

TABLE OF CONTENTS

Executive Summary....3
Purpose and objectives....3
Summary of presentations and discussions....4
Recommendations....7
Conclusions....8
Contact information....8
Appendix: Agenda....9

WORKSHOP: DECISION MAKING IN T1 TRANSLATIONAL RESEARCH

Sponsored by the National Center for Research Resources and the Clinical Translational Science Awards Translational Key Function Committee.
Natcher Conference Center, National Institutes of Health
February 10 – 11, 2009

EXECUTIVE SUMMARY

The purpose of this workshop was to identify common problems encountered during the practice of T1 translational research and potential solutions to those problems. The workshop addressed the following topics: Pathways of T1 transaltional research, use of team science, methods for incorporating advanced technologies and animal models into T1 translation, and the specific needs of early career investigators.

Based on specific case studies and discussions in breakout sessions, major recommendations were the following: a) Better methods for supporting and nurturing team science should be developed and improved, both by academia and funding agencies such as the National Institutes of Health (NIH). A significant improvement can be realized by more active funding of positions that facilitate project management, the IRB process and liaison with industry for individual investigators and teams. Innovative methods for funding research projects that are poised to move from the basic research phase to early stage testing in humans are needed. b) Better access to and understanding of the technology transfer process is critical to the success of T1 translation. Processes of technology transfer should be standardized across institutions. Investigators should be exposed to issues regarding technology transfer as early in their careers as possible. c) The physical and intellectual infrastructure that supports T1 translation should be strengthened, for example, by increasing shared core facilities in the Clinical and Translation Sciene Award (CTSA) instittuions. d) Access to technologies and animal models should be improved, for example, by increased support for development of instrument prototypes and a database of animal models.

The detailed description, below, contains several more insights gained from the workshop.

PURPOSE AND OBJECTIVES

The purpose of the workshop was to identify common problems encountered during the practice of T1 translational research and to begin to identify solutions to those problems. Based on examples of problems and solutions, the workshop participants discussed best practices that can facilitate T1 research. These objectives were accomplished by presenting representative case studies, followed by break out sessions, in which several researchers provided comments and insights.

Specific sessions emphasized: a) Pathways and role of team science in T1 translational research; b) Use of advanced technologies and animal models; and c) The specific needs of early career investigators. For purposes of the workshop, T1 translational research was defined as those studies that include basic discoveries carried to the point of first application to human subjects.

SUMMARY OF PRESENTATIONS AND DISCUSSIONS

Welcoming Remarks

Dr. Anthony Hayward, National Center for Research Resources (NCRR), emphasized the importance of translational science to the NIH mission, including NIH programs that have matured during the past two and one half years with the advent and development of the Clinical and Translational Science Awards (CTSAs). The NIH is keenly aware of the need for infrastructure and resources to sustain advances in translational science.

Dr. Richard Hodes, National Institute on Aging (NIA), discussed the importance of translational research, including the T1 phase, for achieving advances in human health. As an example of T1 translation, Dr. Hodes discussed the development of strategies for the prevention and treatment of Alzheimer's disease. This work involved, among others, identifying mutations in mouse and monkey models, moving the studies into human clinical trials, and developing alternative strategies in an iterative fashion, including additional animal studies.

Keynote Addresses

Dr. Lynn Matrisian, NIH National Cancer Institute (NCI) and Vanderbilt University, discussed pathways of T1 translational research. In 2005, NCI formed the Translational Research Working Group to assess NCI's translational research portfolio and to develop recommendations to best organize investment to facilitate translational research (see http://www.cancer.gov/trwg/). Dr. Matrisian summarized the several pathways and modalities to be addressed in the pursuit of translational research, which apply to many diseases, including cancer.

The Translational Research Working Group concluded that opportunities are not being maximized for bringing basic science discoveries to the clinical setting. The Working Group identified several strategies to assure that the most promising concepts are developed as rapidly and efficiently as possible. As one potential solution, the NCI is establishing Special Translational Research Acceleration Project Awards to help accomplish this goal.

Dr. Janet Woodcock, U.S. Food and Drug Administration (FDA), discussed the role of academia in T1 research from the perspective of the FDA. She observed that academia has moved toward a concentration on the basic sciences in recent years, with less emphasis on drug discovery. At the same time, pharmaceutical and biotechnology companies are dealing with increased costs for research related to drug discovery, suggesting a potentially enhanced role for academia in the process.

Academia has strengths in animal and *in vitro* models, expertise in molecular biology and access to patients, all of which can be central to the success of translational research. Dr. Woodcock encouraged academia to partner with industry in discovery and translation of products to the clinic. Academia can develop and analyze new tools for predicting and understanding the mechanisms of drugs and can also focus on investigations of less common disorders, elucidation of specific pathways and mechanisms, and early bench-to-bedside translation, including proof-

of-concept studies. The FDA can help with exploratory guidance regarding Investigational New Drug Applications and good manufacturing practices for phase I clinical trials.

The panel discussion following the key note addresses included recommendations to better integrate engineering and academic research, streamline intellectual property issues, better manage resources at academic institutions, and support the standardization of research tools.

Session 1: Pathways and Teams

Case Studies described promising research that is ready to be taken to early-phase clinical trials, including a potential treatment for kidney disease and the use of gene therapy approaches for treating HIV / AIDS. Two institutional models for supporting translational research were presented: the Lupus Center at the University of Pittsburgh and the Kauffman Foundation, which fosters partnerships between researchers and industry.

The case studies pointed out several issues encountered during T1 research. Integration of a variety of types of research and support mechanisms to address a specific disease can be a critical aspect of T1 translation. Small Business Innovation Research (SBIR) grants and other types of funding to facilitate early stage commercialization are often critical. There is a need for informatics support, for example, for patient registries. Insufficient dialog between basic and clinical researchers and, in some cases, lack of knowledge regarding the processes for securing industry partners and for patenting discoveries can be barriers to success. Interactions with industry early in an investigator's career can create the level of experience necessary to form partnerships as studies and expertise mature. Program managers to handle personnel and financial issues, including grants administration, can greatly facilitate the process of T1 translation.

Breakout groups that discussed key decision points and pathways emphasized the fact that the process of technology transfer can be a major hurdle for moving basic research to clinical applications. Assessing patentability of discoveries, key to translation, requires funding and effort that is not always readily available to basic and clinical researchers. Researchers should consider the goal of developing translatable products as early in an investigation as possible. A major question is how the clinical researcher can secure funding to move an idea to an advanced stage before collaborating with a company for the final stages of development. Academic programs that include translation as a specific component should be developed and improved, with incentives for translation provided by the academic institution.

Breakout groups on team building and networks discussed the difficulty of identifying appropriate collaborators and the value of retreats and social networking tools for overcoming this problem. In general, academic institutions such as medical schools should be encouraged to promote a culture of team science and should develop the administrative structure to do so. The process of translation can be facilitated greatly by having program managers that can assist in the organizational aspects of translation. "Concierge" type systems that provide "one stop" research support, including project management and liaison with industrial partners, are needed. Specific training in technology management for researchers would be very useful and investigators should have access to this early in their careers.

Session 2: Accessing and Incorporating Advanced Technologies and Animal Models into Clinical Applications.

Case Studies described specific tools and approaches used to advance translation in research areas relating to cancer, cardiovascular disease, obesity and diabetes. The speakers described the use of imaging modalities, tissue modeling, genomics, and animal models for T1 translation. Although these tools are currently being used for discovery in the laboratory, their potential could be increased if barriers such as geographic distances between researchers, cultural and linguistic differences, legal hurdles, technology training, and navigational assistance through the regulatory process are addressed.

Breakout groups emphasized the need to connect clinicians to basic scientists, including providing easy access to research tools and to organizations such as the CTSAs. Use of tools for social networking and retreats and seminars can be used for this purpose. The discussants also cited the need for a centralized database of animal models and for mechanisms that will facilitate interaction of new investigators with current users of animal models.

Session 3: Early Career Investigators Forum

Nine early career investigators discussed their experience with T1 research. For the purpose of the workshop, early career investigators were defined as non-tenured Assistant and Associate Professors. Each speaker applied novel techniques or approaches to advance research in areas such as bone metabolism, hematology, cardiovascular biology orthodontics, cancer, liver disease, and lung disease.

The early career investigators discussed the need for interdisciplinary research teams and for facile communication across disciplines. There is a need for staff positions to handle IRB issues and patient recruitment as well as resources such as central laboratory services and scientific editing. Management leadership training would be particularly helpful. In regard to funding, the participants cited the fact that continuity of funding can be problematic and suggested that the NIH develop additional grant mechanisms specifically to fund translational, team based science. They also pointed out that pilot programs can be very useful for early career investigators.

Session 4: Panel of Panels

Dr Matrisian introduced a final session in which chairs of the various sessions summed up their views of problems and potential solutions to move T1 translation forward. Major conclusions from this discussion were as follows:

- Technologies need to be moved into the clinical setting more rapidly. There is a need for supplemental funding for building prototype instruments for clinical applications, for duplicating a technology and delivering it to sites for testing, for training researchers in a technology laboratory, and for continuing support for technology development.

- Grant mechanisms should be more closely aligned with the need to support team-based research. Translational science can benefit from the energy of young investigators, from networking, and from the support of academic mentors and venture capitalists.

- Support to validate technologies and develop animal models should be increased, including enhanced access to and resources for animal models and colonies.

- A national searchable database for animal models should be developed, so that investigators will know what resources are available.

- The CTSA program is an agent for facilitating development and access to resources and more funding mechanisms should be linked to the CTSAs.

- Specific funding for translational research should be increased, with a higher cap for NIH K-series career development awards. Institutions should be encouraged to provide supplementary support to early career investigators.

Wrap-Up and Adjournment

Dr. Matrisian noted that there are still gaps between academia and industry, between basic researchers and clinical scientists, and between individuals and teams. The government can act as an honest broker to bridge these gaps. It can bring stakeholders together and leverage resources to support the steps that will lead to solutions to many problems encountered during the conduct of T1 translational research.

RECOMMENDATIONS

The participants identified several areas in which the practice of T1 research can be strengthened, including the following:

- Nurture team science
    - Provide incentives, including considerations of promotion and tenure, for investigators engaged in team science. The culture of academic medical centers may need to be modified to accomplish this.
    - Provide project management functions, such as access to a "concierge" function, which serves as a "one stop shop" for research support.
    - Provide training to investigators in project management and leadership skills.
    - The NIH should develop and improve grant mechanisms that specifically support research teams.
    - Enhance and continue to emphasize the mentoring function of CTSAs, to include mentoring teams.
    - Adapt social networking technologies to support T1 research.
    - Find innovative ways to support research projects that are poised to move from the basic research stage to first tests in humans.

- Improve understanding of and access to technology transfer functions

- Enhance investigators' understanding of the patent process, including disclosures and patent costs.
- Standardize technology transfer functions and methods across institutions.
- Promote training for early career investigators regarding collaborations with industry.

- Improve infrastructure.
  - Expand the ability to share resources across the CTSAs, including shared core facilities.

- Improve access to technologies and animal models.
  - Increase the number and/or access to technologies and animal models specifically related to drug development.
  - Develop a centralized database of animal models.
  - Support development of instrument prototypes.

CONCLUSIONS

The workshop provided insights into issues related to the practice of T1 translational research. These can serve as the basis for improving the support of T1 research, both at institutions and funding agencies. The workshop suggested several topics that should be investigated in more detail and could be the subject of additional meetings that could focus on training of translational researchers, improving access to technologies and animal models, and enhancing the process of technology transfer.

CONTACT INFORMATION

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For more information about NCRR, please visit www.ncrr.nih.gov

AGENDA

Feb. 10, 2008

7:45 – 8:15: Registration

8:15 – 8:20: NCRR welcome and introductions
Dr. Anthony Hayward
Director, Division for Clinical Research Resources, NCRR

8:20 – 8:30: NIH Welcome
Dr. Richard Hodes
Director, National Institute on Aging

8:30 – 8:35: Introduction to the workshop and charge to the participants
Introduction of the Workshop Chairs (Dr. Lynn Matrisian, Vanderbilt University and the National Cancer Institute, and Dr. Bruce Tromberg, University of California, Irvine)
Dr. Jack Harding, NCRR

8:35 – 8:55 Keynote
Dr. Lynn Matrisian, Vanderbilt University and the National Cancer Institute
"Pathways of T1 Translational Research"

8:55 – 9:15: Keynote
Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, Food and Drug Administration
"T1 Translational Research: The FDA Perspective"

9:15 – 9:40: Questions and discussion

9:40 – 10:00: Break

SESSION 1: PATHWAYS AND TEAMS
Chair**:** Dr. Gary Gibbons, Morehouse School of Medicine

10:00 – 11:20: Case studies (20 min. presentation, 5 min. questions).
Dr. Susan Manzi, University of Pittsburgh
"The Lupus Center of Excellence: A Model of Integrated Patient Care and Clinical Translational Research"

Dr. Andrew Plaut, Tufts University
"Bacterial IgA Protease as Therapy to Reverse IgA Nephropathy"

Dr. Carl June, University of Pennsylvania
"Translational Research and AIDS"

11:20 – 11:30: Presentation

Ms. Lesa Mitchell, The Kauffman Foundation
"Ecosystems to support translational research"

11:30 – 12:30: Break out sessions.

Sessions A1 and A2: Key decision points and pathways
Chair A1: Dr. Roberta Diaz Brinton, University of Southern California
Chair A2: Dr. Andrew Plaut, Tufts University
Sessions B and C: Building teams and networks
Chair B: Dr. Ken Pienta, University of Michigan
Chair C: Dr. Jeremy Somers, University of Pittsburgh

12:30 – 1:15: Lunch

1:20 – 2:00: Reports from the break out chairs (Session 1); 10 min. each

SESSION 2: ACCESSING AND INCORPORATING ADVANCED TECHNOLOGIES AND ANIMAL MODELS INTO CLINICAL APPLICATIONS
Chair: Dr. Arthur Toga, UCLA

2:00 – 3:20: Case studies (15 min. each plus 5 min. questions)

Technologies: Dr. Clare Tempany, Brigham and Women's Hospital
"Image Guided Therapy"
Technologies: Dr. Jonathan Garlick, Tufts University
"Engineered 3D Tissue Models: Translational Tools for the Discovery Pipeline"
Animal Models: Dr. Michael Mahaney, Southwest Foundation for Biomedical Research
"Cross-species validation in complex disease genetics and genomics: Diet and genotype in primate atherosclerosis"
Animal Models: Dr. Charles Roberts, Oregon Health and Science University
"Non-human models for obesity and alcohol abuse"

3:20 – 3:40: Break

3:40 – 4:40: Break out sessions
Sessions A and B: Technologies
Chair A: Dr. Kenneth Turtletaub, Lawrence Livermore National Laboratory
Chair B: Dr. Alice Tarantal, University of California, Davis
Session C: Animals
Chair C: Dr. Joseph Kemnitz, University of Wisconsin

4:40 – 5:10: Reports from the break out chairs (Session 2); 10 min. each.

5:10 – 5:30: First day wrap up: Dr. Bruce Tromberg

February 11, 2008

8:00 – 8:30: Registration

8:30 – 8:40: Introduction to Day 2

SESSION 3: EARLY CAREER INVESTIGATORS' FORUM
Chair: Dr. Sylvia Frasier-Bowers, University of North Carolina

8:40 – 10:10: 9 investigators, 10 min. each

Dr. Edgar Charles, The Rockefeller University
Dr. Ricki Colman, University of Wisconsin
Dr. Cristina Davis, University of California, Davis
Dr. Thomas Diacovo, Columbia University
Dr. Sylvia Frazier-Bowers, University of North Carolina
Dr. Melina Kibbe, Northwestern University
Dr. Andreas Klein, Tufts University
Dr. Smita Nair, Duke University
Dr. Andrew Wilson, Boston University

10:10 – 10:30: panel discussion, audience comments
10:30 – 10:45: Wrap up (session chair)

10:45– 11:00: Break

11:00 – 12:00: Panel of panels (Workshop and Session chairs, Chair of the CTSA Translational Key Function Committee)
Conclusions and Recommendations
Moderator: Dr. Matrisian
Participants: Drs. Frazier-Bowers, Gibbons, Tarantal, Toga and Tromberg

12:00 – 12:30: Wrap up; Workshop chairs: Drs. Matrisian and Tromberg