A Progress Report on
NIDDK Efforts To Promote

TRANSLATIONAL RESEARCH

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For Administrative Use

National Institute of
Diabetes & Digestive &
Kidney Diseases

Contents

Executive Summary

This Progress Report describes the continuing efforts of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to promote the translation of fundamental discoveries from the laboratory bench of basic scientists into investigations in the clinic, which promise to directly benefit patients. This harnessing of basic research discoveries for clinical testing is one form of what is frequently referred to as "translational research." The NIDDK's ongoing efforts to this end are consonant with an increasing interest in such "translational research" among leaders in the scientific community, public policy makers, and other NIH stakeholders. As noted in a pivotal article in the *Journal of the American Medical Association*: "Medical scientists and public health policy makers are increasingly concerned that the scientific discoveries of the past generation are failing to be translated efficiently into tangible human benefit."[1] The need to enhance translational research has been underscored by the Clinical Research Roundtable of the Institute of Medicine, the Association of American Medical Colleges, and Members of the Congress.

The NIDDK strives to gain the greatest potential clinical benefit from its investment in basic research, and from its many profound contributions to the body of basic scientific knowledge. While the Institute is committed to the continued pursuit of such groundbreaking fundamental work, it likewise recognizes the imperative to translate scientific insights into clinical studies that offer the promise of improving medical care and disease prevention. In recent years, the research enterprise has experienced an explosion of new knowledge and the advent of revolutionary technologic tools. The Clinical Research Roundtable of the Institute of Medicine specifically noted the completion of the human genome project and advances in molecular biology, neuroscience, immunology, biomedical engineering, and functional magnetic resonance imaging—to name a few. Thus, the opportunities for translational research have never been greater.

This Progress Report details the process by which the NIDDK is building on the existing foundation of basic scientific discoveries by leveraging that knowledge to create innovative diagnostics and therapies in an expeditious manner. Highlights are given of the philosophy behind this effort and the mechanisms by which the Institute has identified specific obstacles to overcome and opportunities to pursue in promoting "translational research." Specifically described are the analyses and deliberations of a newly formed Trans-NIDDK Translational Research Working Group, and how it has garnered input from the Institute's National Advisory Council and other sources in devising translational research strategies.

This Progress Report culminates by outlining seven newly developed initiatives to promote translational research. These initiatives focus on:

New Biomarkers: To promote the development of useful biomarkers that can serve as valuable tools for measuring the effects of new candidate therapies and to aid in the design and conduct of clinical trials. Researchers will seek such biomarkers, measured in biological fluids or directly in patients, for well-defined human diseases of interest to the NIDDK for which there are no or very few biomarkers.

New Imaging Methods for the Solid Abdominal Organs and the Urinary Tract: To help stimulate the translation of new methods or imaging reagents from the laboratory to the clinical setting for liver, pancreatic, kidney, and urologic diseases or conditions.

[1] Sung NS, et al. "Central Challenges Facing the National Clinical Research Enterprise." *JAMA* **289**:1278-1287 (2003).

Animal Models for Preclinical Testing in NIDDK-relevant Diseases: To provide support for the development and validation of new animal models to be used as tools for preclinical testing in NIDDK-relevant diseases.

Angiogenesis and Diabetes: To enhance understanding of the effects of type 1 diabetes on new blood vessel growth, in order to exploit its therapeutic potential for diabetic complications and pancreatic islet transplantation.

Preventing Mitochondrial Oxidative Stress in Diabetes and Obesity: To promote the development of therapeutics for preventing the mitochondrial accumulation of reactive oxygen species (ROS) induced by hyperglycemia for the prevention of non-alcoholic steatohepatitis and the complications of diabetes.

Therapeutic Agents for Diseases of Protein Misprocessing and Misfolding: To identify "small interfering RNA" molecules or small molecule reagents that specifically ameliorate protein misprocessing defects in NIDDK-relevant diseases.

RNA Interference Delivery, Processing, Stability and Efficacy in Specific Cell Types, Tissues or Organs: To enhance the practicality of "gene knockdown" technology for pre-clinical and clinical studies relevant to diseases within the NIDDK mission.

Introduction

A pivotal article about challenges facing the national clinical research enterprise appeared in the March 2003 issue of the *Journal of the American Medical Association.* The authors, who were participants in the Institute of Medicine's Clinical Research Roundtable, noted that: "Medical scientists and public policy makers are increasingly concerned that the scientific discoveries of the past generation are failing to be translated efficiently into tangible human benefit." Similar concerns have been expressed by other scientific professional groups, and by public policy makers. For example, the Clinical Research Enhancement Act states: "(1) Clinical research is critical to the advancement of scientific knowledge and to the development of cures and improved treatment for disease. (2) Tremendous advances in biology are opening doors to new insights into human physiology, pathophysiology and disease, creating extraordinary opportunities for clinical research. (3) Clinical research includes translational research which is an integral part of the research process leading to general human applications. It is the bridge and feedback loop between the laboratory and new methods of diagnosis, treatment, and prevention and is thus essential to progress against cancer and other diseases." [2] In an editorial published in the April 3, 2002 issue of the *Journal of the American Medical Association*, Senate Majority Leader William H. Frist, M.D., stated that "today's challenges require a substantially improved ability to translate scientific knowledge and technological capability into daily medical practice…."[3]

Defining Translational Research

Following its inception in 2000, the Institute of Medicine's Clinical Research Roundtable held a series of dialogues and meetings on current issues and problems in clinical research. As part of this process, the Roundtable identified two points on the clinical research continuum—shown in Figure 1—at which impediments constrain the forward movement of scientific discoveries into clinical research, and then further on, into medical practice.

Termed translational research "blocks," these two obstacle points are defined as follows:

> *"The first translational block involves the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans. The second translational block affects the translation of results from clinical studies into everyday clinical practice and health decision making."* [4]

The translation of scientific knowledge and technology into improvements in the practice of medicine is central to the missions of the NIH and NIDDK. The NIDDK is specifically charged to uncover new knowledge leading to the improved prevention, diagnosis, and

[2] Public Law 106-505, Section 202a. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=106_cong_public_laws&docid=f:publ505.106.pdf

[3] Frist WH. "Federal Funding for Biomedical Research: Commitments and Benefits." *JAMA* **287**:1722-1724 (2003).

[4] Sung NS, et al. "Central Challenges Facing the National Clinical Research Enterprise." *JAMA* **289**:1278-1287 (2003).

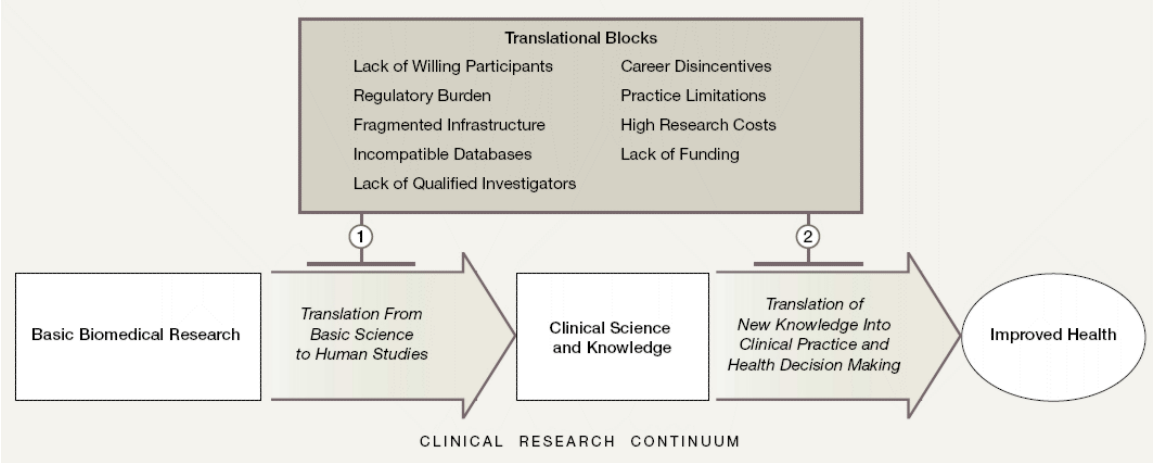


Figure 1: The two translational blocks in the clinical research continuum. Please see the section on this page that describes the importance of the bidirectional flow of new knowledge. Reprinted with permission from *JAMA* **289**:1278-1287, March 12, 2003. *Copyrighted © 2003, American Medical Association.* All Rights reserved.

treatment of diabetes mellitus and endocrine and metabolic diseases; digestive and nutritional disorders; and kidney, urologic, and hematologic diseases. Both the NIH as a whole, and the NIDDK in particular, have taken a series of steps designed to realize the potential of their basic scientific achievements through translational research.

Bidirectional Flow

Although sometimes referred to as "bench-to-bedside" research, translation actually depends on more than the flow of discoveries from basic to clinical researchers and then on to health care providers. The providers likewise contribute vital information to the research endeavor about the responses and needs of patients, and the practical application of new diagnostics and therapeutics. These insights must be conveyed back to researchers in a parallel flow of knowledge from "bedside-to-bench." Thus, translational research is bi-directional.

Importance of Second Translational Research Block

Although this Progress Report will focus primarily on the first block to translational research, the laboratory-clinic bidirectional loop, the NIDDK also makes vigorous efforts to address the second translational block by propelling the results of clinical research into medical practice. Examples of the latter include, but are not limited to:

- *"From Clinical Trials to Community: The Science of Translating Diabetes and Obesity Research."* This meeting was co-sponsored by the NIDDK, the NIH Office of Behavioral and Social Sciences Research, and the Centers for Disease Control and Prevention in January of 2004. The meeting focused on the challenges of determining how to translate findings from the comparatively optimal setting of clinical studies to the more complex situations facing providers caring for diverse communities with limited resources.

- *The National Diabetes Education Program and the National Kidney Disease Education Program.* These are science-based programs for the dissemination of disease- and treatment-related information to patients, their health care providers, and the public.

- *Research Demonstration and Dissemination Project (R18/R34) Grants:* These are designed to

provide support to researchers to develop, test, and evaluate health service activities, and to foster the application of existing knowledge for the control of categorical diseases. For example, the NIDDK is using this grant mechanism to find optimal ways to translate to real-world settings the important prevention message of the Diabetes Prevention Program Clinical Trial; that is, modest weight loss and increased physical activity can prevent or delay the onset of type 2 diabetes in high risk individuals.

Translational Aspects of the NIH Roadmap for Medical Research and Other Cross-Cutting Initiatives

Translational research is featured in the NIH Roadmap for Medical Research in the 21st Century, launched by NIH Director Dr. Elias Zerhouni. The Roadmap is a series of far-reaching initiatives designed to transform the Nation's medical research capabilities and speed the movement of research discoveries from the bench to the bedside. The three major themes of the Roadmap are: (1) New Pathways to Discovery, (2) Research Teams of the Future, and (3) Re-engineering the Clinical Research Enterprise. Of particular note are two translational initiatives included under the third theme:

- Creation of regional translational research centers that will provide sophisticated advice and resources to help scientists master the steps involved in bringing a product from the bench to medical practice.

- Establishment of translational research core services through the NIH Pilot Program for Rapid Access to Intervention Development (RAID). This program will make available, on a competitive basis, certain critical resources needed for the development of new molecule therapeutic agents.

The Roadmap Initiative is NIH-wide in scope, bringing to bear the collective efforts of multiple institutes to address critically important research areas that no single institute could tackle effectively on its own. The NIDDK's contributions to the Roadmap effort include: (1) leadership of a metabolomics initiative that will encourage the development of more powerful technology for analyzing all small molecules found in the body, or other molecules of interest for biomedical research and health; (2) leadership of two interdisciplinary research training initiatives; and (3) development of translational research core resources.

Similarly, the NIDDK leads a trans-NIH translational research initiative, the Type 1 Diabetes Rapid Access to Intervention Development (T1D-RAID) Program. In this case, the NIDDK and the NCI are collaborating to facilitate the development of novel therapies by making available, on a competitive basis, NCI resources for the pre-clinical development of drugs, natural products, and biologics.

NIDDK Strategies

Recognizing the fundamental importance of the translation process, and the critical role that the NIDDK can play, the Institute has developed various strategies for promoting primary translation, and for obtaining and applying the guidance of its Advisory Council and other sources of external expert advice for framing initiatives. The NIDDK has developed approaches to complement other translational efforts in the research community and the NIH, including the NIH Roadmap. This Progress Report serves as a summary of the development and implementation of these translational research initiatives by the Institute.

The Trans-NIDDK Translational Research Working Group

To promote translational research, the NIDDK Director established the Translational Research Working Group in December 2003. The formation of this Working Group built upon findings from an NIDDK Extramural Program Retreat held in the Fall of 2003. The charge to the Working Group was to:

- Identify obstacles to translational research;
- Identify areas where resources would be of general utility (i.e., look for areas where a single infusion of resources would have the potential to advance translation for multiple diseases);
- Adopt or develop mechanisms, where necessary, to address specific obstacles; and
- Develop a consistent process to prioritize translational initiatives;

A roster of the current members of this Trans-NIDDK Working Group is provided in Appendix A.

Paradigms for Translational Research: Learning from Case Studies

Past NIDDK-supported research has led to numerous important advances in medical care. The Trans-NIDDK Translational Research Working Group examined a variety of these translational success stories, and outlined the major milestones in those efforts, and the role of NIH support. The objectives were to identify obstacles to translation, learn how these barriers were or were not overcome, and find common elements that fostered progress from fundamental research toward clinical research on, and application of, diagnostics and therapeutics. The following are selected highlights of some of the case studies reviewed.

Case Study of New Treatments for Hyperparathyroidism: Calcium is not just a key component of bones and teeth, it is also an important regulator of numerous physiological functions in the body. Decades-old research determined that, by releasing parathyroid hormone (PTH), the parathyroid gland stimulates the absorption of calcium from food and the scavenging of calcium from bone as necessary to maintain blood calcium in an optimal narrow range. In “hyperparathyroidism,” the parathyroid gland releases too much PTH, resulting in brittle bones and dangerously high calcium in the blood. Hyperparathyroidism can have a variety of causes, and a form called secondary hyperparathyroidism is common in kidney dialysis patients.

The means by which a healthy parathyroid gland senses calcium and releases appropriate amounts of PTH were unclear until scientists identified the calcium-sensing receptor in 1993. This discovery enabled the development of drugs that can effectively trick the calcium-sensing receptor into perceiving calcium levels as being higher than they actually are. These drugs represent a safer, more effective treatment for secondary hyperparathyroidism than had previously been available.

Case Study of Enzyme Replacement Therapy for Lysosomal Storage Disorders: The lysosome is a structure in which cells employ a group of enzymes to recycle certain substances when they are no longer needed. When any of these enzymes is inactivated by a genetic mutation, toxic waste products accumulate in the lysosome. The accumulation of these toxic compounds results in devastating illnesses called "lysosomal storage disorders" that affect about 1 in 7,700 infants. In the 1960s and 1970s, NIDDK-funded researchers studying one of the enzymes that can be missing in patients with lysosomal storage disorders discovered that healthy cells do not route the enzymes directly to the lysosome immediately after they are synthesized. Instead, the cells secrete and then reabsorb the enzymes before sending them to their final destination in the lysosome.

In principle, this discovery meant that, if these enzymes could be synthesized and purified in sufficient quantity, they could be administered therapeutically to patients with lysosomal storage disorders. The patients' cells would absorb the enzymes and send them to the lysosomes, where detoxification of the cell could then take place. Many years of hard work resulted in development of efficient means to obtain and purify the enzymes. Still more research was required to optimize their administration and prevent the body from mounting an immune response to them. However, the last few years have seen the development and Food and Drug Administration approval of such "enzyme replacement therapies" for several of the more common lysosomal storage disorders, with more such treatments on the way.

Case Study of HbA_{1c} and Glycemic Control for People with Diabetes Mellitus: Patients with diabetes who keep their blood sugar levels within a narrow, optimal window suffer fewer and less serious complications of the disease than those who do not. However, directly measuring blood sugar only provides information at the moment the blood is drawn, not on overall glycemic control (i.e., control of blood sugar). In 1949, scientists first detected certain minor protein components of blood, variants of the oxygen-carrying protein hemoglobin. During the 1960s, researchers discovered that some of these minor components tended to be present in greater quantities in people with diabetes than in the rest of the population. In the 1970s, NIDDK-funded researchers demonstrated that these hemoglobin variants had extra sugar molecules attached to them, and it was hypothesized that the addition of these extra sugar molecules is promoted by elevated blood sugar. Indeed, scientists found that levels of one of the hemoglobin variants fall when diabetic patients carefully control their glycemia. This variant is HbA_{1c}.

The NIDDK-funded Diabetes Complications and Control Trial was designed to test the hypothesis that improving glycemic control in patients with type 1 diabetes would prevent or delay the onset of complications—specifically, damage to the small blood vessels in the kidneys, eyes, and nerves. In addition to validating that hypothesis, the study also established HbA_{1c} as a biomarker for monitoring long-term glycemic control. Both of these results have had profound beneficial effects on the care for the more than 18 million Americans who have either type 1 or type 2 diabetes.

HbA_{1c} has itself become a valuable tool in the quest to develop new therapies for diabetes: as a Food and Drug Administration-accepted endpoint, it provides a means to assess quantitatively a therapeutic's effect on glycemic control. The HbA_{1c} story also serves to underline the value of large trials in the validation of new biomarkers that will stimulate development of new therapies for more than one indication. For these reasons, also, large clinical trial databases should be mined for all possible uses.

All of the case studies indicate that translating a laboratory discovery into a useful clinical tool may require decades of research investment. These research efforts were frequently sustained by a champion who persisted in believing in the potential clinical usefulness of his or her project. Such investigators need access to a source of funding to be able to fulfill the potential promise of their project. Other case studies examined by the Translational

Research Working Group include the development of pegylated adenosine deaminase for treatment of adenosine deaminase deficiency; and the development of Infliximab, Natalizumab, and Anti-IL-12 antibodies for the treatment of Crohn's disease.

Approaches To Promoting Translational Research

As illustrated by the preceding examples, translational research is by no means new to the NIDDK. Research conducted and supported by the Institute has led directly to a large and growing number of innovations in the practice of medicine. As noted previously, in planning new strategies to enhance patient-oriented outcomes of laboratory discoveries the Trans-NIDDK Translational Research Working Group examined several examples of prior efforts in order to learn what steps in successful translation might be reprised in future efforts and what pitfalls might be avoided. The Working Group also selected several diseases and conditions and undertook an analysis of the current status of translation efforts in each of these areas. They garnered expert external input from members of the NIDDK's National Advisory Council and from relevant scientific conferences and workshops.

Translational research was a major focus of all three of the NIDDK's National Advisory Council meetings in 2004:

- During the February 2004 meeting, the Translational Research Working Group asked general priority-setting questions, and obtained input from Council members. The minutes of the February Council meeting may be found at: http://www.niddk.nih.gov/fund/divisions/dea/council/minutes/Feb4-5-04.pdf

- At the May 2004 meeting, the Working Group asked the Council to consider gaps and barriers to translation. The Working Group presented the results of detailed analyses of the research pipelines for several specific disease-oriented translational goals. These included development of: biomarkers, diagnostics, cellular therapies, and drug development. There was a general consensus among the NIDDK and the Council members regarding the following needs: (1) better strategies to assess the biological role of pathways in humans; (2) improved animal models; (3) better methods for early testing in humans, including imaging methods and biomarkers for efficacy and toxicity; and (4) access to resources for pre-clinical development. The minutes of the May Council meeting may be found at: http://www.niddk.nih.gov/fund/divisions/dea/council/minutes/May26-27-04.pdf

- In September 2004, based on its previous analyses and on the input received from Council and from relevant scientific conferences, the Working Group presented seven proposed initiatives to further translational research. The minutes of the September Council meeting may be found at: http://www.niddk.nih.gov/fund/divisions/dea/council/minutes/Sept22-23-04.pdf

The Trans-NIDDK Translational Research Working Group proposed approaches that would either take advantage of specific existing opportunities, or provide research infrastructure to help accelerate the process of translation in several areas. Highlights follow.

Identifying Obstacles to Translational Research

To determine the factors that might represent obstacles to translation, the Translational Research Working Group identified a variety of pathways leading to development of useful translational

endpoints that may be thought of as goals for translational research. These include:

- Drug development;
- Development of biomarkers for gauging disease progression and treatment efficacy;
- Development of diagnostics;
- Development of cellular therapies; and
- Development of behavioral therapies.

With these goals in mind, the Working Group asked what steps in the research pipeline were required to achieve these endpoints, which of those steps were not already being taken through the investment of public or private funds, and what further resources were necessary to overcome the gaps in the translational research process for a variety of diseases within the NIDDK research mission. The pipeline analyses resulted in the production of Gant charts for several of these diseases. Examples are provided in Appendix B.

Creating a Well-defined Plan for Translational Research

The next steps in the planning process were to develop several more narrowly focused program proposals, and to select among them, bearing in mind the guidance of the NIDDK's Advisory Council. The following criteria were deemed useful in determining whether the NIDDK should invest in a particular translational research project:

- The potential for major health impact;
- The availability of specific steps that would lead to measurable translational advances if successfully completed;
- Significant needs that are likely to remain unmet without commitment of NIH resources; and
- Potential application to multiple diseases.

To further maximize the return on investment of research dollars, the following additional selection criteria were considered:

- A strong scientific foundation on which to build a translation effort;
- Likely progress toward a translation goal;
- Partnership opportunities to ensure necessary product development; and
- Scientific teams, clinical samples of patient populations, and infrastructure to carry out specific translation efforts.

February 2004 Advisory Council Presentation and Discussion

To gain expert external advice, the Working Group posed the following questions to Members of the NIDDK's Advisory Council during their meeting in February 2004:

- How can we increase the value of the resources being developed through the NIH Roadmap initiative to the NIDDK investigative communities?
- How can we best identify steps in the translational process where NIDDK resources can serve a critical role that is not served by the private sector?
- Have we chosen the right factors for priority setting? How should we weigh them?
- What steps can we take to encourage more investigator-initiated translational research?
- How can we best encourage broader awareness and knowledge by academic investigators of the intellectual property and regulatory issues important for translational research? Should we consider development of training resources?
- What activities are present in academic medical centers to encourage careers in translational medicine, and are there steps we can take to facilitate these activities?

Council members were asked to address these questions and invited to comment on the Institute's approach to enhancing translational research. In addition to participating in the forum discussion,

members were encouraged to submit questions, concerns, and suggestions regarding the effort during the following weeks. Observations offered by Council members included the following:

Investigator as Translator:

- The gaps along the translational pathway are due not only to a problem with the models, the techniques, and their application, but also to a lack of individuals to perform the work.
- Many Ph.D. researchers are reluctant to leave basic science or to try to refocus their research in a direction up to and including pre-clinical studies.
- Rather than searching for investigators skilled in both the basic and clinical domains, the NIDDK should help to develop a community of translational researchers who would specialize in the application of basic science discoveries to clinical practice.
- Translational research could be conducted under a minority-investigator or training award mechanism.
- A mechanism or strategy could be established for the reverse direction along the translation pathway so that clinicians may contribute their observations for basic science exploration.
- Methods could be developed for facilitating communication between basic research scientists and clinicians.
- NIH-supported pilot studies that require basic and clinical investigators to work together would generate interest and stimulate discussion between them.

Encouraging Careers in Translational Medicine:

- Provide resources to individuals in research training in order to shape the academic environment and encourage research careers in translational medicine.
- Offer to the large pool of Ph.D. scientists various training opportunities that encourage the translational aspect of research and correspond with goals of the NIH Roadmap.
- Build an adequate support system for Ph.D. researchers who have become interested in clinical applications. This could include formal coursework in the principles of medicine.
- Offer very basic hypothesis-driven research opportunities to encourage Ph.D. scientists to undertake work—such as target validation, animal model development, and screening. Reward their efforts.
- In the area of drug development, establish a specific mechanism to recruit analytical chemists and chemical engineers, for example, to help with the screening process and follow up on promising compounds.
- Clarify what resources are available, and ensure that molecular libraries and screening centers are accessible.
- Create well-curated, accessible molecular libraries, and consider developing extensive siRNA libraries for target identification.

Patient-based Translational Research Centers:

- Establish within clinical research centers, such as the NIH-supported General Clinical Research Centers, a means to permit clinical investigators to bring in individual patients with an undiagnosed health problem who may then be studied by other clinicians and basic

researchers to potentially diagnose the condition. This would draw Ph.D. scientists literally to the bedside to study these patients through physical, biochemical, and molecular examination. This bedside access would enable researchers to employ the extraordinary tools currently available to discover the fundamental issues that underlie disease. The interactive setting would foster communication between scientists and physicians, and could ultimately lead investigators to become directly interested in the translational studies. Protection of human subjects would need to be handled meticulously.

Institutional Review Board (IRB), Conflicts-of-Interest, and Intellectual Property Issues:

- Address limitations that restrict basic scientists from participating in more clinically-oriented research and in following up on observations they have made.
- Improve the efficiency of IRB approval by working to balance the need for absolute human subject protection with the desire to streamline the process and remove the barriers for investigators.
- Encourage the development of draft templates for conflict-of-interest and IRB approval which could be used and customized by academic institutions. Such templates could be a major contribution of the NIH to the conduct of clinical research.
- Recognize that barriers to progress include the different state laws involved, the need for a sufficient number of protocols to make the effort worthwhile, and the reluctance of individual institutes to relegate responsibilities to the centralized IRB.
- Note that intellectual property issues are largely handled by the universities.

Opportunities for Possible Research Collaborations with Industry:

- Drug companies and small biotechnology firms frequently are not interested in developing an idea for a product (generated from academic research, for example) for clinical use unless the target is a near-guaranteed success.
- The NIH should encourage translation of basic drug development research to the point at which a potential product might attract industry interest, i.e., lower the threshold for industry collaboration. This consideration also pertains to the area of surrogate marker development for phase I and phase II clinical trial end-points.
- The record of failure in phase III trials (i.e., the low success rate of drug development) relates in part to the lack of surrogate markers that strongly predict the impact of a potential agent on the disease in phase I and phase II trials.
- More meaningful surrogate markers in the smaller and less costly phase I and phase II stages would be much more predictive and could warn against investing additional time and money if the project is not going to work.
- It would be useful to implement an educational process to overcome the lack of knowledge about the decision-making processes for industry's investments.
- A mechanism could be established for the development and clinical testing of inventions that the pharmaceutical industry has decided not to pursue. Proposals for inventions of clinical value could be reviewed through special panels. Successful proposals could be administered through an NIH intramural program, which would take on the responsibility of shepherding the invention through all phases of drug development and clinical trials.

Funding:

- The use of public funds makes NIH investigators accountable for producing valuable results that enhance the public health and welfare.
- The proposed translational efforts need to be balanced with investigator-initiated research efforts.
- Criteria are needed for identifying studies to be conducted, and how the limited available funds will be allocated.

Overall, NIDDK's National Advisory Council Members indicated that they were pleased with the Institute's current and planned efforts to encourage translation research.

Implementing Council Recommendations and Moving the Process Forward

The Trans-NIDDK Translational Research Working Group considered the translational research process from the standpoint of a pipeline for production of a technique, Diagnostic, or therapeutic. One such pipeline is illustrated for cell-based therapies in Figure 2.

The Working Group then highlighted the various stages of the translational research pipeline using Gant charts for biomarkers of acute renal failure, cellular therapies for pancreatic beta cell and liver injury and therapeutics for liver injury, cystic fibrosis, diabetic nephropathy, interstitial cystitis/painful bladder syndrome, inflammatory bowel disease, insulin resistance, intestinal failure, iron overload, obesity, polycystic kidney disease, and type 1 diabetes (See Appendix B). In these

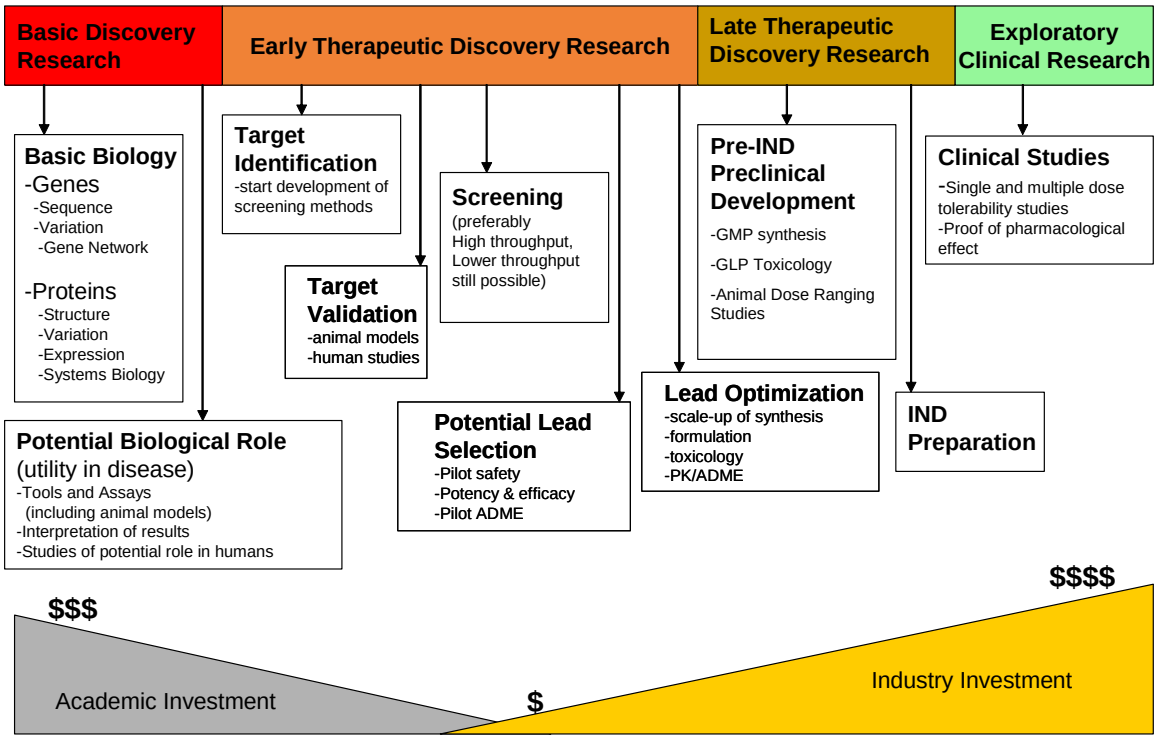


Figure 2: The Path from Discovery Research to Bedside for New Therapeutics.

graphs, bars show the points in the research continuum at which significant efforts and/or progress have been made. Different colors signify whether the work was financed by public or private funds. These graphs serve to highlight the progress that has been made, and, more importantly, the gaps that remain to be filled. After identifying unmet needs, the Translational Research Working Group sought to determine what resources and mechanisms could be targeted to meet them.

May 2004 Advisory Council Presentation and Discussion

The Trans-NIDDK Translational Research Working Group presented analyses and recommendations at the meetings of the disease-oriented subcommittees and to the full Council. In discussions, the Council members identified the following needs:

- Bi-directionality in the "bench-to-beside" model.
- Biomarkers to track progress over a shorter timeframe.
- More and better surrogate outcomes.
- Specific research training programs and other incentives to attract talented individuals to clinical investigation.
- Garnering of industry support, particularly for orphan diseases.
- Promotion of public-private partnerships.
- Better animal models.
- Greater understanding of human disease.
- Assessments of the efficacy of the existing peer-review process.

With these factors in mind, the Working Group and the NIDDK programmatic divisions conducted a portfolio analysis based on disease-specific and cross-cutting research areas that might make attractive targets for pilot translational research initiatives.

Other Sources of External Input

In addition to the extensive interactions with the NIDDK's National Advisory Council mentioned previously, the Working Group has also used a variety of other means to seek expert external input into the efforts to enhance translational research.

For example, in May of 2004, the "Food and Drug Administration (FDA)/National Institutes of Health (NIH) Joint Symposium on Diabetes: Targeting Safe and Effective Prevention and Treatment" helped to identify and discuss therapeutic gaps and hurdles to safe and effective prevention and treatment of type 1 and type 2 diabetes mellitus. The symposium provided assistance to the FDA, the NIH, clinical and basic scientists, and interested representatives of the pharmaceutical industry in their efforts to reduce the burden of diabetes and improve the health of patients.

External input was also garnered from the conference on "Protein Misfolding and Misprocessing in Disease" in May 2004, which was sponsored by the NIDDK and the NIH Office of Rare Diseases. In addition to highlighting the basic clinical and scientific issues associated with these diseases, the meeting helped pinpoint opportunities for new chaperone and small molecule therapeutics to promote proper folding. A new initiative, "Therapeutic Agents for Diseases of Protein Misprocessing and Misfolding" was a direct outgrowth of this meeting, and is detailed in the following section of this Progress Report.

Important insights were gleaned from a workshop held in May, 2004, with investigators in the angiogenesis field. The workshop was planned by the Trans-NIH Working Group on Angiogenesis that included representatives from NIDDK; the National Cancer Institute; the National Heart, Lung, and Blood Institute; the National Institute of Neurological Disorders and Stroke; the National Eye Institute; and the Juvenile Diabetes Research Foundation.

The Special Statutory Funding Program for Type 1 Diabetes, which the NIDDK administers, supports a number of translational research efforts. These include a Type 1 Diabetes-Rapid Access to Intervention Development (T1D-RAID) program, a bench-to-bedside initiative, preclinical research in animal models, and the development of new biomarkers and other methods to assess disease progression. In January, 2005, the NIDDK convened an expert panel to review and perform a mid-course assessment of current efforts supported by the Program, to identify new and emerging opportunities, and to solicit recommendations for future type 1 diabetes research.

NIDDK staff members have been active participants in a planning process for kidney disease research organized by the American Society of Nephrology. Work groups have developed recommendations for translational work in diabetic nephropathy, transplantation, hypertension, acute renal failure, and treatment of uremia. The work of these planning groups was completed in early 2005, and will be used to clarify mechanisms of particular value for nephrology. Translational initiatives were also the focus in a three day strategic planning retreat for pediatric urology, held by the Division of Kidney, Urologic, and Hematologic Diseases, on February 3-5, 2005. The strategic planning group identified a number of critical areas to encourage translational work on urologic disorders of childhood.

Initiatives for Promoting Translational Research

Based on its analyses and external input, the Trans-NIDDK Translational Research Working Group developed several proposals for translational research initiatives and presented them to the Institute's National Advisory Council in September 2004. The following initiative concepts were approved by the Council for funding.

Development of New Biomarkers

Translational Research Objective: To develop biomarkers, measured in biological fluids or directly in patients, for well-defined human diseases of interest to the NIDDK for which there are no or very few biomarkers. These markers are urgently needed as measures of the biological effects of potential new treatments. Especially of interest would be studies designed to test the validity of candidate biomarkers or new technologies to monitor candidate biomarkers in small groups of well-characterized patients. Areas of interest include non-invasive markers of kidney and liver fibrosis; early diabetic neuropathy; inflammation of the kidney, pancreas, adipose tissue; inflammatory bowel disease; hepatitis; and tissue-specific markers of insulin resistance or angiogenesis. New biomarkers would aid in the design and conduct of clinical trials, and might facilitate the development of therapies that could be used at early stages of disease to arrest progression.

Development and Implementation of New Imaging Methods for the Solid Abdominal Organs and the Urinary Tract

Translational Research Objective: To encourage the development and implementation of imaging methods specifically for evaluating diseases and disorders of the solid abdominal organs (liver, endocrine and exocrine pancreas, and kidney) and the biliary and urinary tract. Clinical studies examining the progression of diseases of solid abdominal organs or the urinary tract have been hampered by the lack of reliable non-invasive functional monitoring, or reliable surrogate markers of disease progression. Current clinical endpoints rely on functional markers that vary considerably over short-term studies, and dictate large numbers of patients for adequately powered interventional studies. However, recent observations regarding the natural history of some liver and kidney diseases suggest that some imaging and imaging analysis techniques may provide a reliable non-invasive mechanism for following disease progression. Similarly, it is

becoming increasingly evident that non-invasive imaging techniques, which can detect and quantify specific changes in characteristics of the urinary bladder, are reliable indicators of the extent, prognosis, and progression of disease. Further development of such methods and their specific application to diseases of the liver, endocrine and exocrine pancreas, kidney, and the biliary and urinary tract would have significant impact on the ability to perform interventional trials for these diseases and conditions, utilizing a smaller sample size with validated endpoints.

Animal Models for Preclinical Testing in NIDDK-Relevant Diseases

Translational Research Objective: To provide support for the development and validation of new animal models to be used as tools for preclinical testing in NIDDK-relevant diseases. It is expected that new and/or improved animal models established under this initiative would facilitate preclinical testing of diagnostic, preventive, or therapeutic interventions in a number of NIDDK-relevant diseases. Responsive proposals will address: (1) diseases or conditions for which there are no existing animal models, (2) diseases or conditions where existing models are either insufficient for preclinical testing or fail to duplicate key aspects of the human condition, and (3) comparative analyses of existing models with human clinical data to rigorously establish the model as a valid surrogate for human disease.

Angiogenesis and Diabetes

Translational Research Objective: To enhance understanding of the effects of type 1 diabetes on new blood vessel growth (angiogenesis), in order to exploit its therapeutic potential for diabetic complications and pancreatic islet transplantation. This initiative seeks to facilitate the transfer of scientific discoveries in normal and oncogenic angiogenesis to the clinical problems of excess blood vessel growth in proliferative diabetic retinopathy, and inadequate blood vessel growth in diabetic wound healing, diabetic neuropathy and collateral vessel formation in atherosclerosis. For islet transplantation, the goal is to foster research on improving the revascularization process in the transplanted islets to improve graft survival.

Preventing Mitochondrial Oxidative Stress in Diabetes and Obesity

Translational Research Objective: To develop therapeutics to prevent the mitochondrial accumulation of reactive oxygen species induced by hyperglycemia for the prevention of non-alcoholic steatohepatitis and the complications of diabetes mellitus. Hyperglycemia is the primary cause of microvascular diabetic complications that include end-stage renal failure, blindness, and neuropathy contributing to lower extremity amputations and gastrointestinal dysmotility, and it contributes to the increased risk of myocardial infarction and stroke. Diabetes and obesity can also result in liver failure from non-alcoholic steatohepatitis. Recent advances in understanding the cellular effects of hyperglycemia identify the overproduction of reactive oxygen species by the mitochondrial electron transport chain as the core abnormality that leads to other molecular, cellular and physiological defects. The aim is to translate recent advances in understanding mitochondrial reactive oxygen species production associated with hyperglycemia to therapeutic interventions that would target the accumulation of reactive oxygen species in the mitochondria.

Therapeutic Agents for Diseases of Protein Misprocessing and Misfolding

Translational Research Objective: To identify small interfering RNA (siRNA) molecules or other small molecule reagents that specifically ameliorate a protein misprocessing defect in NIDDK-relevant diseases. The process of identifying potential agents that could be used as biological probes or as the starting point for exploring development of therapeutic agents begins with robust assays, and continues with screening steps and targeted medicinal chemistry, followed by animal testing, and pharmacological optimization. Each disease of interest would require plans that are

appropriate to the state of the research in the specific disease.

This initiative builds upon a May 2004 conference sponsored by the NIDDK and the NIH Office of Rare Diseases. The conference surveyed some of the important progress in applying basic research on protein processing to understanding the molecular defects in numerous diseases. For some diseases, such as cystic fibrosis and nephrogenic diabetes insipidus, there is active screening of small molecule therapeutic agents that has moved into advanced stages of development and testing in the clinic. For others, such as primary hyperoxaluria, there are no reliable assays with which to screen compounds.

RNA Interference Delivery, Processing, Stability, and Efficacy in Specific Cell Types, Tissues, or Organs

Translational Research Objective: To enhance the practicality of gene knockdown technology for pre-clinical and clinical studies. This initiative builds upon an NIH-supported RNA interference (RNAi) workshop in May 2004, which identified gaps in support for RNAi-related basic and applied research, and identified investments that NIH should make in RNAi-related resources. The most significant, rate-limiting roadblock toward enhancing the utility of RNAi in mammalian systems, especially within the therapeutic realm, is delivery. Many issues are yet to be resolved, including understanding the determinants of siRNA stability/half-life, establishing an effective distinction between target and off-target effects, and evaluating risk assessment of pathogenic potential or significant side effects of siRNAs *in vivo*. Variations in delivery to particular organs and tissues may also exist. This initiative would solicit cell-, tissue-, and organ-specific siRNA research projects, with an emphasis on *in vivo* projects, as a prelude to preclinical or clinical studies.
For more information on these initiatives, please see http://www.niddk.nih.gov/fund/crfo/recently-cleared.htm

Other Examples of Current NIDDK Efforts To Promote Translation

NIDDK staff members are collaborating with other government and non-profit agencies to advance specific translational goals such as standardization of insulin assays and the development of biomarkers and surrogates for diabetic nephropathy.

Standardization of Insulin Assays: The American Diabetes Association has taken the lead in re-establishing an effort to develop an internationally standardized insulin assay. Both the Centers for Disease Control and Prevention and NIDDK staff have been actively involved in the planning along with a group of experts in standardization of laboratory tests, biochemistry and measurement of human insulin, and clinical scientists with diabetes expertise. An initial effort was recently completed to compare insulin concentrations across a wide range of values determined by commercial laboratories with their usual reference standards *versus* a reference standard based on recombinant human insulin. The results were encouraging, in that variability between assays was lower with the recombinant human insulin standard compared with the laboratories' regularly used standards. A plan is in place for continuation and optimization of the reference standards, as well as for a self-sustaining system for standardization for research and clinical usage.

The translation impact of these efforts is that, as with HbA_{1c}, a standardized insulin assay would facilitate research and data analysis efforts. Such an assay might also lead to more accurate diagnosis of insulin resistance and identification of patients at very high risk for development of diabetes, and development of clinical guidelines for desirable levels of insulin. Ultimately, these efforts may lead the way for new therapies that specifically target insulin level and insulin resistance.

Proteomic and Metabolomic Approaches to Diagnose Diabetes and Pre-Diabetes: Clinical trials have demonstrated effective interventions for preventing or delaying complications in those with diabetes and for preventing or delaying onset of diabetes in those with pre-diabetes. However, millions of Americans are not receiving effective therapy, in part due to the limitations of current methods of diagnosing diabetes and pre-diabetes. Proteomics technologies can be used effectively in the area of biomarker discovery. An NIDDK initiative solicited proposals to apply proteomic and metabolomic technologies to develop new diagnostic tests and to identify new biomarkers for the diagnosis of pre-diabetes and diabetes. The development of an assay that would not require fasting and glucose administration would allow faster and less expensive screening for these conditions.

Workshop on Drug Screening for Hyperglycemic Cellular Injury: Diabetic complications have been the subject of considerable interest on the part of the pharmaceutical industry, and there have been no successful phase III clinical trials of therapies for microvascular complications to date. In a workshop held in February 2005, leaders in the field of diabetes complications and experts in drug screening discussed possible guidelines for a drug screening program. A goal would be to screen approximately 1,000 FDA-approved agents as potential therapeutics for diabetes complications, including microvascular complications, arising from hyperglycemia. The workshop was jointly sponsored by the NIDDK and the Juvenile Diabetes Research Foundation.

Action Plan for Liver Disease Research: This planning effort aims to advance NIH-supported research on liver diseases, with the ultimate goal of decreasing their burden in the U.S. Among the principles that guided the development of the Plan were the translation of findings from basic research to practical means of diagnosis, prevention, treatment and cure of liver diseases and the reciprocal use of findings from clinical research as a guide for basic research. The Action Plan was developed with broad external input from the research, professional, and patient-advocacy communities. Its development was directed by the Liver Disease Subcommittee of the statutory Digestive Diseases Interagency Coordinating Committee.

Standardization of Serum Creatinine Measurement: Serum creatinine is routinely used to assess kidney function. Serum creatinine reflects the glomerular filtration rate (GFR) in an inverse relationship. The best current means of estimating GFR from serum creatinine employs a prediction equation developed from the database of the Modification of Diet in Renal Disease study (MDRD). Unfortunately, the calibration of serum creatinine varies sufficiently between clinical laboratories that GFR estimates, particularly in the near-normal range, can vary considerably.

A working group of the National Kidney Disease Education Program of NIDDK has begun to address this issue. This working group comprises professional clinical chemistry organizations, instrument makers, commercial laboratories and government agencies including NIDDK, CDC, and the National Institute for Standards and Technology (NIST). A standard reference material is being developed. It will refer back to an isotope dilution mass spectrometry method at NIST and will be validated through the variety of methods in use in the field.

This reference material will improve the accuracy and generalizability of routine application of serum creatinine to estimating GFR. In turn, routine reporting of estimated GFR is expected to allow earlier identification of people with chronic kidney disease and thereby promote effective early therapy.

Translational Efforts to Foster Pre-Clinical Studies in Animal Models of Disease: The Animal Models of Diabetic Complications Consortium (AMDCC) is a cross-disciplinary consortium designed to develop innovative mouse models that closely mimic the human complications of diabetes for the purpose of studying disease pathogenesis, prevention, and treatment. Complications to be examined include diabetic kidney disease, micro- and macrovascular disease, neuropathy, cardiomyopathy, and bladder

function. The Institute also supports four Mouse Metabolic Phenotyping Centers (MMPC) to provide standardized, high quality metabolic and physiologic phenotyping services for mouse models of diabetes, diabetic complications, obesity, and related disorders. A non-human primate cooperative study group is evaluating the safety and efficacy of novel donor-specific, tolerance-induction therapies in non-human primate models of kidney and islet transplantation. The program supports research into the immunological mechanisms of tolerance induction and development of surrogate markers for the induction, maintenance, and loss of tolerance.

Summary

As outlined in this Progress Report, the NIDDK is actively promoting translational research, consistent with concerns expressed by the Institute of Medicine, clinically-oriented professional groups, and public policy makers. During 2004, a Trans-NIDDK Translational Research Working Group conducted extensive case studies of translational research, as well as analyses of the pipeline of research for several disease areas within the Institute's mission. The Working Group presented its findings to the Institute's National Advisory Council at all three Council meetings in 2004 and garnered advice from the Council, as well as from relevant scientific conferences. Based on the analyses performed and expert external input received, the Working Group then framed seven translational research initiatives, the concepts for which have been approved by the National Advisory Council and which will be pursued in FY 2005 and/or FY 2006.

In its thorough analysis of the difficulties associated with accelerating the process of translational research, the Institute of Medicine's Clinical Research Roundtable described four major challenges facing clinical research at present:

1. Public participation;
2. Information systems;
3. Workforce training; and
4. Funding.

The NIDDK has addressed the issue of public participation through programs such as Type 1 Diabetes TrialNet (www.DiabetesTrialnet.org), which seeks to connect interested type 1 diabetic patients with clinical trials in need of participants. More broadly, the NIH Public Trust Initiative seeks to promote public understanding and trust of the NIH and its Institutes and Centers, with a focus on participation in clinical trials; and the NIH clinical trials website (www.clinicaltrials.gov) provides information on the whole array of federally sponsored clinical trials.

To improve on the flow of clinical research information, several efforts are already under way. For example, the NIDDK has created the Collaborative Islet Transplantation Registry (www.citregistry.org) to disseminate the knowledge gleaned from 86 transplantations of pancreatic islet cells. The Institute has also established an NIDDK Repository so that data and samples from past and future NIDDK-funded clinical trials can be appropriately stored and used to gain optimal new knowledge from the investment in these studies. The NIDDK is likewise encouraging ancillary studies to large, ongoing clinical trials so as to maximize the accrual and analysis of clinical data.

With respect to clinical workforce research training, the NIH Roadmap includes cross-cutting initiatives to address this issue. For example, the Multidisciplinary Research Career Development Program will support the early career development of clinical researchers from a variety of disciplines, including patient oriented research, translational research, small and large scale clinical investigation and trials, and epidemiologic and natural history studies. Another initiative, the National Clinical Research Associates program, will create a cadre of qualified healthcare practitioner-researchers who are well trained to ensure the responsible conduct of clinical research.

The fourth issue raised in the Institute of Medicine report—that of funding specific areas in need of special emphasis—is being addressed through the development of several initiatives across the NIH. The NIDDK has contributed to this broader effort through the analyses of the Institute's Translational Research Working Group and through the initiatives it has formulated—as highlighted in this Progress Report.

Appendix A: Members of the Trans-NIDDK Translational Research Working Group

Myrlene Staten, Chair

Kristin Abraham
Beena Akolkar
Josephine Briggs
Francisco Calvo
John Connaughton
Catherine Cowie
Thomas Eggerman
Judith Fradkin
Carol Haft
Frank Hamilton
James Hunter
James Hyde
Stephen James
Teresa Jones
Robert Karp
Chris Ketchum
John Kusek
Maren Laughlin
Ellen Leschek
Catherine McKeon
Rebekah Rasooly
B. Tibor Roberts
Paul Rushing
Salvatore Sechi
Jose Serrano
Philip Smith
Robert Star
Dorothy West
Elizabeth Wilder

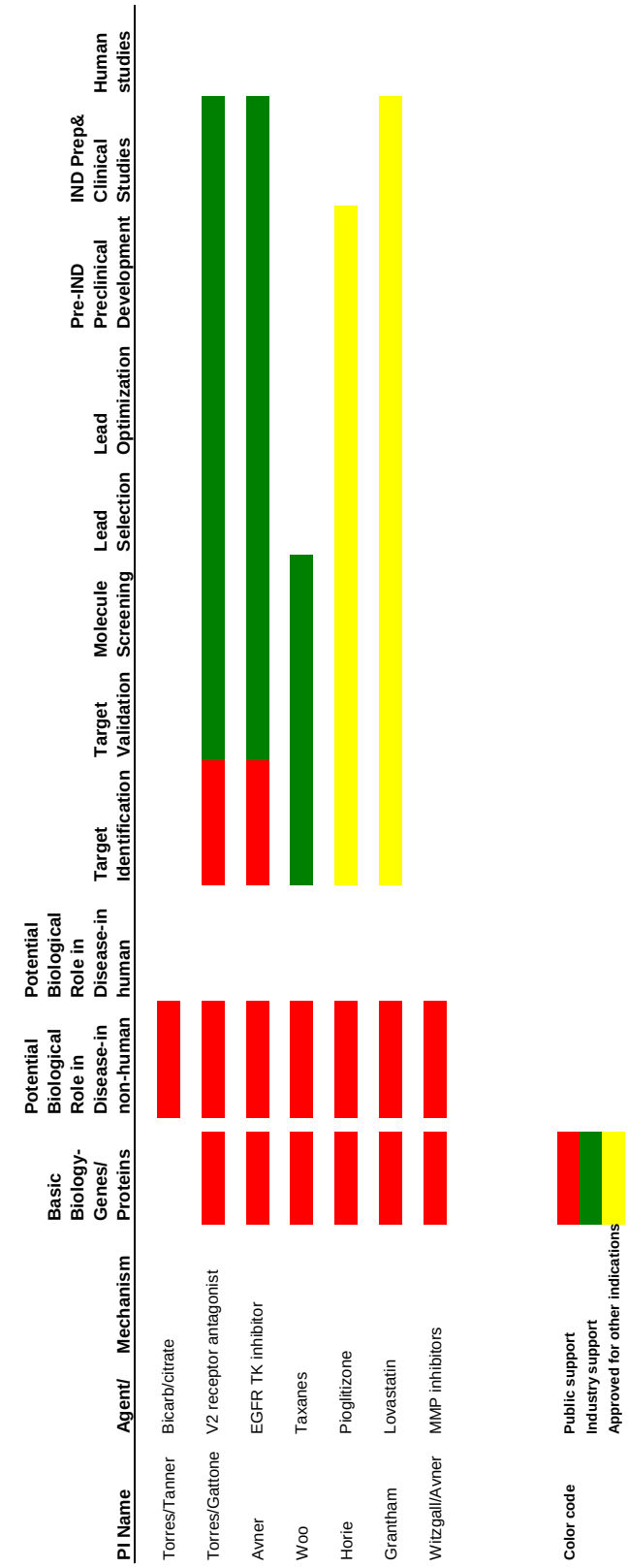
Appendix B: Examples of Gant Charts

Therapeutics development for:

1. Autosomal Dominant Polycystic Kidney Disease
2. Cystic Fibrosis
3. Intestinal Failure

Note: The diseases represented in the following Gant charts are just a few illustrative examples of the approximately 15 disease-specific pipeline analyses performed by the Trans-NIDDK Translation Working Group. The research projects reflected in these Gant charts represent a snapshot of a portion of the NIDDK research portfolio at a particular point in time (April, 2004).

Autosomal Dominant Polycystic Kidney Disease
April 7, 2004



Cystic Fibrosis
April 7, 2004

New Therapeutics Development Cystic Fibrosis
Targeted Disease State 4/7/2004
Date

PI Name	Agent/	Mechanism	Basic Biology-Genes/ Proteins	Potential Biological Role in Disease- human/in vitro	Potential Biological Role in Disease-non-human/in vitro	Potential Biological Role in Disease-Human	Target Identification	Target Validation	Molecule Screening	Lead Selection and Optimization	Pre-IND Preclinical Development
Rubenstein	chaperonine or increased										
Welch	s-nitroglutathione/chaperonine										
Bedwell	Gentamicin/read through										
Egan	Curcumin/ Ca-ATPase inhibitor										
Miller	AAV-CFTR/gene therapy										
Wilson	Adeno-CFTR/gene therapy										
Sorscher	Liposome CFTR/gene therapy										
Davis	Compact DNA-CFTR										
Ramsey	Tobi/antibiotic										
Moran	Insulin/anabolic hormone										
Verkman/Kopito	small molecules/chaperonine										
Naren	small molecules/disrupt syntaxin binding										

Intestinal Failure
April 7, 2004

New Therapeutics Development
Targeted Disease State: Intestinal Failure
Date:

PI Name/Title	Grant #	Agent/Mechanism	Basic Biology-Genes/ Proteins	Potential Biological Role in Disease-non-human/in vitro	Potential Biological Role in Disease-Human	Target Identification	Target Validation	Molecule Screening	Lead Selection and Optimization	Pre-IND Preclinical Development	IND Prep& Clinical Studies
Ziegler, Thomas Diet/Growth Factor Mechs in Gut Adaptation	R01 DK56860	rGH,Glutamine / trefoil factor									
Tappenden, Kelly Short-chained Fatty Acid Enhanced Intestinal Adaptation	R01 DK57682	S-cFAs / GLP-2									
Levin, Marc Nutrient Modulation of Gene Expression in Gut Adaptation	R01 DK50446	Vit A / RARs, PPARs, catenin sig									
Lund, Pauline K. Intestinal Adaptation-Role of Hormones and Growth factors	R01 DK40247	IRS-1, SOCS-2 / IGF-1 signaling									
Yang, Vincent Regulation of Intestinal Epithelial Cell Proliferation	R01 DK52230	Kruppel-like factors/increase transcription									
Hodin, Richard Molecular Mechanisms of Intestinal Atrophy/Hyperplasia	R01 DK47186	Butyrate / IAP gene expression									
Johnson, Leonard GI Hormones and Other Factors in Growth of GI Mucosa	R01 DK16505	Polyamines/Apoptosis, Sig Trans									
Ashley, Stanley Surgery and Intestinal Adaptation	R01 DK47326	GLP-2/ Trophic gene expression									
Evers, Bernard Surgical Studies of Functional Gene Expression in GI Epithelia	R01 DK48498	akt isoforms/ PIK3 pathway									
Sarr, Michael Enteric Physiology of the Transplanted Intestine	R01 DK39337	motilin, somatostatin/ innervation									
Sax, Harry Amino Acid Transport after Small Bowel Resection	R01 DK47989	EGF, GH / EGFR sig transduct									
Slice, Lee Rho-Dependent COX-2 Expression in Intestinal cells	R01 DK061485	PGs, NSAIDs/ COX-2 regulation									
Ney, Denise Total Parenteral Nutrition and Intestinal Adaptation	R01 DK42835	IGF-1,GLP-2 / IGFBP-3 expression									