National Cancer Institute

Report of the Translational Research Working Group of the National Cancer Advisory Board

Transforming Translation—

Harnessing Discovery for Patient and Public Benefit

Executive Summary

Full report available at:

http://www.cancer.gov/aboutnci/trwg/finalreport.pdf

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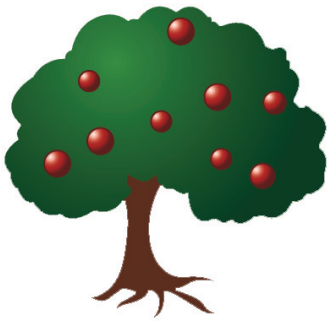


June 2007

Proposed TRWG Initiatives

Coordinated Management

A1 Establish a coordinated NCI-wide organizational approach to manage the diverse early translational research portfolio, reduce fragmentation and redundancy, and ensure that resources are focused on the most important and promising opportunities.

A2 Designate a specific portion of the NCI budget for early translational research to facilitate coordinated management, long-term planning, and prioritization among opportunities and approaches as well as to demonstrate NCI's commitment to translational research.

A3 Develop a set of award codes that accurately captures the nature and scope of the early translational research portfolio to enable a complete, shared understanding of NCI's total investment, help identify gaps and opportunities, and demonstrate the extent of translational activity to the public.

A4 Create a transparent, inclusive prioritization process to identify the most promising early translational research opportunities based on scientific quality, technical feasibility, and expected clinical or public health impact.

Tailored Funding Programs

B1 Modify guidelines for multiproject collaborative early translational research awards to focus research on advancing specific opportunities along a developmental pathway toward patient benefit, and to reward collaborative team science.

B2 Improve processes and mechanisms for review and funding of investigator-initiated early translational research to incentivize researchers to propose such studies.

B3 Establish a special funding program to advance a select number of especially promising early translational research opportunities identified through the newly created prioritization process.

B4 Establish a program for joint NCI/industry funding of collaborative early translational research projects that integrate the complementary strengths of both parties to pursue opportunities that are more attractive as a combined effort.

B5 Integrate access to GMP/GLP manufacturing and other preclinical development services more effectively with high-priority, milestone-driven early translational research projects to better address this often rate-limiting step in moving a product forward to early human testing.

Operational Effectiveness

C1 Build a project management system involving staff both at NCI and at extramural institutions to facilitate coordination, communication, resource identification and access, and management of milestone-based progress for multidisciplinary, early translational research projects.

C2 Coordinate core services essential for early translational research to reduce duplication and ensure that high-quality services are readily accessible to all projects and investigators.

C3 Improve standardization, quality control and accessibility of annotated biospecimen repositories and their associated analytic methods to strengthen this key translational resource.

C4 Develop enhanced approaches for negotiation of intellectual property agreements and agent access to promote collaborations among industry, academia, NCI, and foundations.

C5 Increase NCI interaction and collaboration with foundations and advocacy groups to capitalize upon their complementary skills and resources for advancing early translational research.

C6 Enhance training programs and career incentives to develop and maintain a committed early translational research workforce.

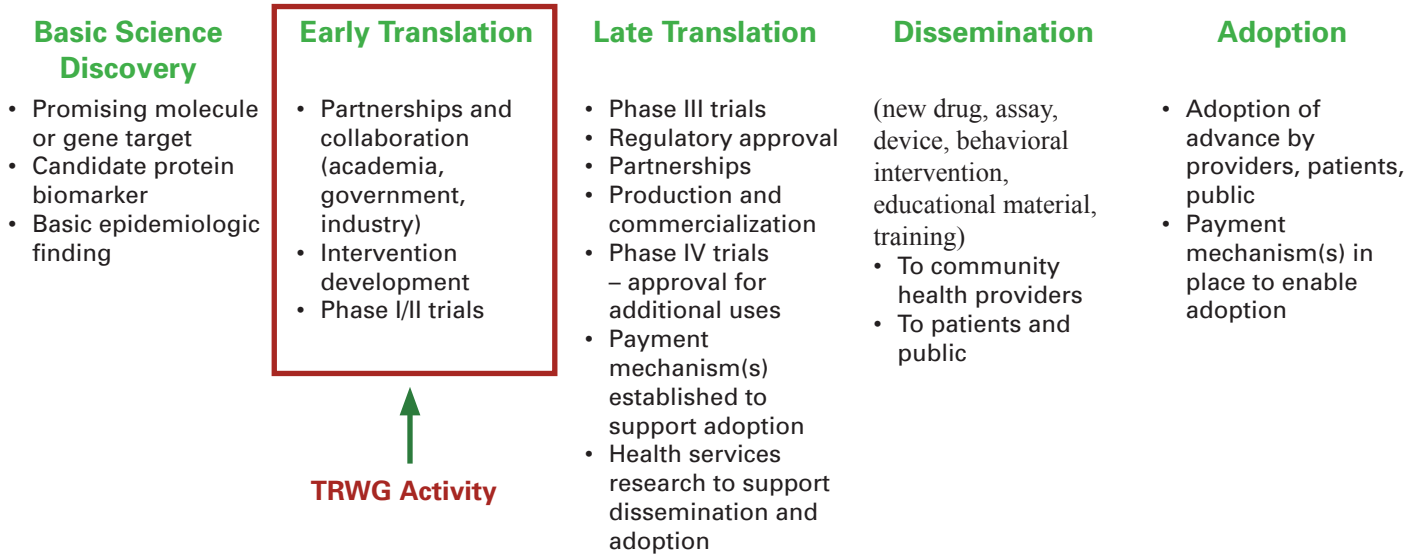
Executive Summary

In June 2005, the Translational Research Working Group (TRWG) was established under the auspices of the National Cancer Advisory Board (NCAB) to advise the National Cancer Institute (NCI) on the future course of NCI-supported translational research, a critical link in realizing the promise of molecular oncology for patient and public benefit. The TRWG was constituted as a broad and inclusive panel of translational research experts, including academic scientists and clinicians, representatives from industry and foundations, patient advocates, and NCI staff.

The TRWG first reached consensus on an operational definition of translational research as "research that transforms scientific discoveries arising in the lab, clinic, or population into new clinical tools and applications that reduce cancer incidence, morbidity, and mortality." For the focus of its deliberations, the TRWG further selected the "early translational research" portion of the President's Cancer Panel Translational Continuum, which is situated between fundamental discovery research and Phase III clinical trials (see Figure 1). The TRWG thus intentionally did not seek to change any aspect of discovery research—the largest component of the NCI extramural research funding portfolio—and also focused on complementing and extending, but not duplicating, the initiatives of the Clinical Trials Working Group, which concentrated its attention on clinical trials. The TRWG also viewed the areas of dissemination and adoption, while critically important to the overall success of the continuum, to be outside the scope of its deliberations.

The TRWG next drafted six developmental pathways to clinical goals, defining the overall course of early translation for each of six key domains—biospecimen-based risk assessment devices, image-based risk assessment agents/techniques, agents, immune response modifiers, interventive devices, and lifestyle alterations. The TRWG also conducted an analysis of NCI's current portfolio in translational research, which revealed a wide range of activities supported through many different mechanisms including both investigator-initiated and solicited programs. In addition, a process analysis involving 20 recent translational "successes" was conducted to identify the NCI programs, individuals, organizations, etc., involved in achieving translational progress within the current system. Finally, in an attempt to learn from others' experiences and recommendations, the TRWG reviewed 11 prior reports and planning documents relevant to translational research that had been generated over the previous several years.

Figure 1. TRWG Scope of Activity: The Translational Continuum*



* From the President's Cancer Panel's 2004-2005 report Translating Research Into Cancer Care: Delivering on the Promise.

In assessing the rationale for change, the TRWG recognized from the outset that the NCI-supported translational research enterprise is not keeping pace with the enormous opportunities presented by advances in knowledge and technology over the past 40 years of cancer research. Based on these opportunities, public expectations for significant advances in cancer prevention, treatment, and care are rising, yet resources devoted to cancer research have reached a plateau. Given this climate, the TRWG asked how NCI could best ensure that the most promising basic research concepts enter the developmental pathways and are advanced rapidly and efficiently either to translational success or to a productive failure that usefully informs further translational or discovery research.

To meet this challenge, the TRWG identified four critical objectives for a national early translational research enterprise that can advance discoveries more effectively toward early human testing of a new drug, biologic, diagnostic/screening test, or other therapeutic, diagnostic, or preventative intervention. The first objective was to improve coordination and collaboration and instill a culture of active, goal-oriented management for both individual projects and the enterprise as a whole. The second objective was to improve identification of the most promising early translational research opportunities across all disease sites, populations, and pathways to clinical goals through a transparent, inclusive process involving all relevant stakeholders and driven by: a) the strength of the scientific rationale, b) the technical feasibility of the development approach, c) the expected clinical or public health impact, and d) the risk that the opportunity would not be taken forward by industry. The third objective was to tailor both new and existing funding programs to facilitate early translational research progress and incentivize researcher participation. The fourth objective was to enhance the operational efficiency and effectiveness of early translational research projects and the many supporting activities essential to the enterprise, including the participation of patients and advocacy groups.

In addressing these objectives, the TRWG proceeded through a consensus-building process involving three sequential stages. First, the TRWG identified those specific aspects of the current NCI-supported early translational research enterprise in need of improvement. The second stage was to develop recommendations for targeted enhancements in each of those aspects, some of which were presented to the NCAB on June 14, 2006. In the third stage, the TRWG defined specific initiatives based on those recommendations and designed implementation plans for their practical realization. In each of these stages, the TRWG obtained substantive and valuable input from the broader cancer research community through both Internet-based public forums and invited Roundtable Meetings.

This transparent, inclusive, and strategically driven process, involving all the critical stakeholder groups in the cancer early translational research community, resulted in the 15 initiatives detailed in this report on "Transforming Translation—Harnessing Discovery for Patient and Public Benefit." The proposed initiatives cover the full breadth of the current and future early translational research enterprise, and each addresses one of the common themes derived from the TRWG goals: Coordinated Management, Tailored Funding Programs, or Operational Effectiveness. Taken together, these initiatives will strengthen and transform the NCI-supported early translational research enterprise into a national effort that integrates the individually strong components of the current system into a coordinated and collaborative endeavor focused on the distinctive needs and characteristics of early translational research and optimized for its success.

The initiatives, which are described in detail in the report, are summarized below.

Coordinated Management

- Establish a coordinated NCI-wide organizational approach to manage the diverse early translational research portfolio, reduce fragmentation and redundancy, and ensure that resources are focused on the most important and promising opportunities.
- Designate a specific portion of the NCI budget for early translational research to facilitate coordinated management, long-term planning, and prioritization among opportunities and approaches as well as to demonstrate NCI's commitment to translational research.

- Develop a set of award codes that accurately captures the nature and scope of the early translational research portfolio to enable a complete, shared understanding of NCI's total investment, help identify gaps and opportunities, and demonstrate the extent of translational activity to the public.
- Create a transparent, inclusive prioritization process to identify the most promising early translational research opportunities based on scientific quality, technical feasibility, and expected clinical or public health impact.

Tailored Funding Programs

- Modify guidelines for multiproject, collaborative early translational research awards to focus research on advancing specific opportunities along a developmental pathway toward patient benefit, and to reward collaborative team science.
- Improve processes and mechanisms for review and funding of investigator-initiated early translational research to incentivize researchers to propose such studies.
- Establish a special funding program to advance a select number of especially promising early translational research opportunities identified through the newly created prioritization process.
- Establish a program for joint NCI/industry funding of collaborative early translational research projects that integrate the complementary strengths of both parties to pursue opportunities that are more attractive as a combined effort.
- Integrate access to GMP/GLP manufacturing and other preclinical development services more effectively with high-priority, milestone-driven early translational research projects to better address this often rate-limiting step in moving a product forward to early human testing.

Operational Effectiveness

- Build a project management system involving staff both at NCI and at extramural institutions to facilitate coordination, communication, resource identification and access, and management of milestone-based progress for multidisciplinary early translational research projects.
- Coordinate core services essential for early translational research to reduce duplication and ensure that high-quality services are readily accessible to all projects and investigators.
- Improve standardization, quality control, and accessibility of annotated biospecimen repositories and their associated analytic methods to strengthen this key translational resource.
- Develop enhanced approaches for negotiation of intellectual property agreements and agent access to promote collaborations among industry, academia, NCI, and foundations.
- Increase NCI interaction and collaboration with foundations and advocacy groups to capitalize upon their complementary skills and resources for advancing early translational research.
- Enhance training programs and career incentives to develop and maintain a committed early translational research workforce.

For each of these initiatives, the TRWG developed an implementation plan to realize its goals. The individual plans were developed through many hours of iterative discussion and deliberation by the TRWG, first within the subcommittee that generated the initiative and then in plenary session. While complete consensus was not achieved on all specific points, there was widespread support for all of the proposed plans. The plans presented in the report thus represent the combined wisdom of the 62 TRWG members concerning how each of the initiatives might be implemented in an effective and innovative, yet feasible, manner. The goal was to develop implementation plans that would build on the best of the current NCI early translational research system while proposing specific new action steps designed to achieve the improvements

envisioned by the initiatives. The TRWG recognizes that actual implementation may well proceed along a different course. The plans detailed in the report are offered as an approach which the TRWG believes could achieve the goals of the proposed initiatives.

The implementation plan proposed for each initiative includes an associated timeline and budget. The TRWG estimates that implementation of all the initiatives, according to the proposed plans, would require 4 to 5 years to complete, with the full impact on routine NCI operational practices expected to require at least 2 to 3 additional years. In this timeline, all initiatives are targeted to begin implementation by the end of year three. The implementation effort as outlined is projected by the TRWG to cost $94M over 5 years. Estimated expenses increase from approximately $4M each in FY08 and FY09 to $13.5M in FY10, $28.5M in FY11, and $44M in FY12. The increased expenditures in FY10-12 are due entirely to direct support for the extramural community associated with the new tailored early translational research funding programs. Of the annual $4M in nonextramural funding, 50% is to operate the project management system, 25% is to support the prioritization process, and 25% is for the NCI management and administrative structure necessary to implement the remaining initiatives and effectively guide the transformed enterprise.

Major changes in an ongoing enterprise, such as the TRWG proposes for NCI-supported early translational research, should be undertaken only if there is a plan to evaluate the success of those changes. Therefore, if the initiatives are implemented, the TRWG proposes that a formal evaluation system be established to determine the impact of the initiatives. The proposed evaluation system would include measures that address three important dimensions of success. The first are program management measures to evaluate the effectiveness with which the initiatives are implemented. The second are system performance measures to determine whether the new structures, processes, and programs are achieving the objectives of a more coordinated, collaborative, transparent, efficient, and goal-oriented early translational research enterprise that is better managed and prioritized. The third are system outcome measures to assess whether the combined changes result in advancing an increased number of early translational research opportunities to middle- and late-stage human studies.

Implementation of the TRWG initiatives, whether as outlined in the report or by other means, will require considerable additional effort by the cancer translational research community, as well as a focused, but modest, financial investment by NCI. The TRWG believes that this commitment and investment are essential to ensure that the much larger ongoing national investment in early translational research is appropriately managed and targeted to help realize the promise of molecular oncology by moving important new discoveries effectively toward early human testing. By embracing these initiatives, NCI and the cancer research community will demonstrate their strong commitment to harnessing the advances in cancer biology achieved through the last 40 years of progress for patient and public benefit.

TRWG Initiatives Summary Timeline

Initiatives	FY08	FY09	FY10	FY11	FY12
A1: Integrated NCI Management					
A2: Budget Designation					
A3: Translational Research Coding					
A4: Prioritization Process					
B1: Modify Translational Research Award Guidelines					
B2: Improve Investigator-Initiated Translational Research Awards					
B3: STRAP Awards					
B4: Academia/Industry Collaboration Awards					
B5: Develop Integrated Services					
C1: Project Management					
C2: Core Services Coordination					
C3: Enhance Biorepositories					
C4: Improve Intellectual Property Negotiations					
C5: Enhance Foundation/Advisory Group Collaborations					
C6: Enhance Training Programs and Career Incentives					
Evaluation					

TRWG Initiatives Summary Budget

Initiatives	FY08	FY09	FY10	FY11	FY12
A1: Integrated NCI Management	$800K	$800K	$850K	$850K	$850K
A2: Budget Designation	—	—	—	—	—
A3: Translational Research Coding		$150K	$150K	$150K	$150K
A4: Prioritization Process	$950K	$750K	$750K	$750K	$750K
B1: Modify Translational Research Award Guidelines	—	—	—	—	—
B2: Improve Investigator-Initiated Translational Research Awards	—	—	—	—	—
B3: Special Translational Research Acceleration Project (STRAP) Awards	—	—	$10M	$20M	$30M
B4: Academia/Industry Collaboration Awards				$5M	$10M
B5: Develop Integrated Services	—	—	—	—	—
C1: Project Management	$1.35M	$1.3M	$1.55M	$1.75M	$2M
C2: Core Services Coordination	$200K	$370K	—	—	—
C3: Enhance Biorepositories	—	—	—	—	—
C4: Improve Intellectual Property Negotiations	$100K	$530K			
C5: Enhance Foundation/Advisory Group Collaborations	—	—	—	—	—
C6: Enhance Training Programs and Career Incentives	$300K	$100K	—	—	—
Evaluation	$350K	—	$350K	—	$350K
TOTAL	**$4.05M**	**$3.99M**	**$13.65M**	**$28.5M**	**$44.1M**

Summary Vision

Build a focused, collaborative, multidisciplinary enterprise, tailored to the distinctive requirements of early translational research, which transforms and strengthens this essential link from discovery to patient and public benefit.

Advances in understanding the molecular and cellular events underlying cancer offer an unprecedented opportunity to translate discoveries into tangible benefits for patients and the public. However, development of targeted, molecular approaches to therapy, prevention, prediction, detection, diagnosis, and prognosis requires not only an effective clinical trials system but also a dynamic early translational research enterprise that can transform fundamental discoveries from the lab, clinic, or population into specific products, interventions, or lifestyle alterations ready for human testing.

In particular, early translational research has enormous potential to improve the outcome of clinical trials directed at new therapies by both establishing reliable molecular markers of therapeutic response and clearly identifying the patients most likely to respond based on the molecular characteristics of their disease. Clinical trials informed by such molecular understanding will be more efficient and put fewer patients at risk than the empiric approaches used in the past.

Early translational research poses three primary challenges. The first is to ensure that the most promising and important discoveries are identified and moved forward into development. The second is to ensure that these discoveries advance through the complex, multidisciplinary, goal-oriented development process as efficiently and effectively as possible. The third is to ensure a smooth, timely transition between early translational research and late-stage human trials, product commercialization, and community dissemination.

Meeting these challenges will require a coordinated and collaborative national enterprise focused on the distinctive needs and characteristics of early translational research and optimized for its conduct. Such an enterprise is needed because translational research has only recently emerged as a focused endeavor, distinct from discovery or clinical research, due at least in part to the enormous array of discoveries on which scientifically driven development of a broad range of new cancer interventions can be based. This enterprise will also improve the National Cancer Institute's (NCI) ability to ensure that all Americans benefit from the Nation's investment in cancer research. This includes patients afflicted with rare cancers, which may not be attractive targets for industry-supported early-stage development, and populations that are disproportionately affected by certain cancers or underserved by current approaches to research, prevention, and treatment.

Building a more effective and coordinated NCI early translational research enterprise will require a shared definition of what constitutes early translational research, an accurate and comprehensive understanding of the scope of ongoing activity, and a commitment to adequate funding. Given that early translational research is distributed across virtually all NCI Divisions, Centers, and Offices, an integrated, cross-NCI approach is needed to adequately analyze the portfolio of current awards and address any identified gaps, overlaps, or inefficiencies in allocation of resources. A comprehensive, coordinated approach is also required to ensure that scarce resources are equitably balanced across disease sites, affected populations, and the developmental pathways to clinical goals, and are focused on projects with the greatest potential for both translational success and impact on patients and the public.

The accumulating number of early translational research opportunities, coupled with finite resources, requires a transparent, inclusive, and fact-based process for identifying those opportunities that are most promising for development. Scientific quality, the gold standard for discovery research, is an essential criterion for such a process. However, early translational research must also be judged by the technical feasibility of a focused development effort, the potential impact on a critical unmet clinical or public health need, and the likelihood that the opportunity will not be taken forward by private industry without NCI involvement. Once a comprehensive and inclusive process to identify the most important opportunities is in place, the translational research effort can be enhanced in two complementary ways. The first is to

establish a proactive, highly facilitated funding program to advance a select number of the highest priority opportunities through the development process as efficiently and effectively as possible. The second is to use the identified priorities to inform funding decisions and the development of new initiatives within the broader translational research portfolio across the Institute.

For enhanced early translational research coordination and prioritization to be optimally effective, funding programs must be structured to advance projects down a developmental pathway in a focused, milestone-driven, and goal-oriented fashion. Such programs must have guidelines, incentives, and award structures designed to facilitate timely developmental progress toward a specific clinical goal rather than to advance scientific knowledge or identify new research opportunities. These latter goals are central to discovery research, and remain important ancillary goals for translational research, but the primary purpose of translational progress is patient and public health benefit. Moreover, because of their complex, multidisciplinary nature, early translational research projects need more active management to ensure that needed resources are available and that diverse participants and activities are coordinated across the various stages of development. Efficient translational progress will also require integration between award programs that fund different portions of the developmental pathways and timely handoff to late-stage clinical trials.

Enhancing early translational research productivity will also require improvements in several aspects of operating efficiency. High-quality, cost-effective core services, from molecular analysis to manufacturing, must be readily accessible to all projects and investigators. This is especially true for standardized, annotated biospecimens, which are an essential foundation for key elements of translational progress. Improved training and career incentives will be essential to ensure a workforce committed to early translational research that is continually refreshed by new generations of clinical and laboratory researchers. Collaboration, not only among NCI-funded researchers but with other key players such as industry, research foundations, health care practitioners and other health care professionals, patients, and patient advocates, is central to the success of the early translational research endeavor, particularly in the transition to later-stage development. Successful collaboration among all parties will depend on enhanced communication and outreach, broad participation in NCI management and prioritization processes, more joint funding opportunities, and streamlined processes for establishing relationships.

To achieve these objectives, the Translational Research Working Group (TRWG) of the National Cancer Advisory Board (NCAB) has developed a detailed blueprint for "Transforming Translation—Harnessing Discovery for Patient and Public Benefit." The TRWG strategy is to build on the strengths of existing early translational research endeavors by enhancing coordination, prioritization, and operational effectiveness while tailoring funding programs to facilitate translational progress. The strategy recognizes the key role of cancer centers in providing a stable translational research infrastructure, the strong early translational research conducted through the Specialized Centers (P50) and various cooperative agreement and contract-based programs, and the many excellent early translational research projects supported through investigator-initiated Program Project (P01), R01, and Z01 awards. The proposed TRWG initiatives preserve and strengthen each of these existing components while creating new organizational structures and processes that will enable them to work together in a more integrated and cooperative way. The proposed initiatives are also intended to complement and extend the work of the Clinical Trials Working Group, which focused its initiatives on the clinical trials enterprise, especially late-stage trials, and the enabling informatics infrastructure and applications currently being developed by the NCI Center for Bioinformatics as part of the cancer Biomedical Informatics Grid (caBIG™).

Extramural investigators and NCI staff from throughout the Institute will be asked to collaborate in ensuring that the NCI early translational research portfolio is appropriately balanced across disease sites, affected populations, and developmental pathways to clinical goals with appropriate attention to projects targeted at rare cancers and minority/underserved populations. They will also be asked to participate in identifying especially promising early translational research opportunities and to incorporate identified priorities into their research programs. Milestone-based, goal-oriented progress will become the standard for rewarding early translational research, and investigators will be expected to collaborate openly, sharing resources, handing off projects to new teams of experts as development warrants, and making team science a reality.

Implementing these changes will require a strong, committed effort by all stakeholders as well as a modest, focused financial investment. But this investment of both time and money is well justified to ensure that the much larger ongoing national investment in early translational research achieves the goal of moving important discoveries more effectively toward successful human testing. By embracing these initiatives, NCI and the cancer early translational research community will enhance the Nation's effectiveness and competitiveness in meeting the needs and opportunities of cancer research as it evolves into a global priority. Perhaps more importantly, the NCI's commitment to these initiatives will also demonstrate a strong dedication to harnessing the advances in cancer biology achieved through the last 40 years of research progress for patient and public benefit.

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