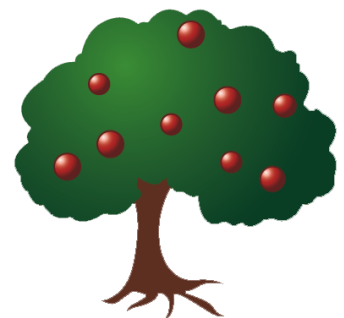


**Transforming Translation—  
Harnessing Discovery  
for Patient and Public Benefit**



## 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.

## 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
<b>TOTAL</b>	<b>\$4.05M</b>	<b>\$3.99M</b>	<b>\$13.65M</b>	<b>\$28.5M</b>	<b>\$44.1M</b>

## Acknowledgments

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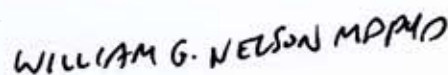
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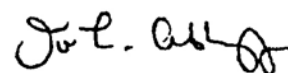
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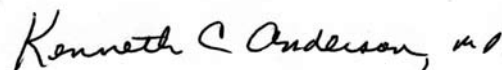
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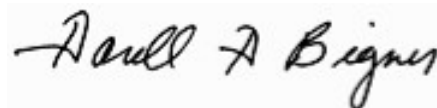
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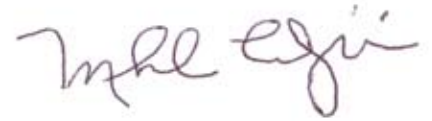
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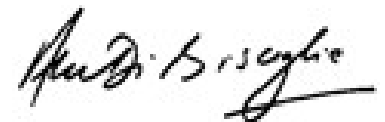
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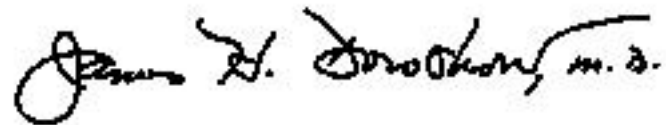
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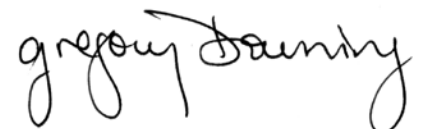
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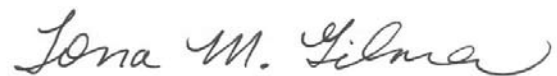
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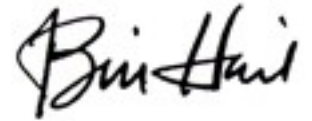
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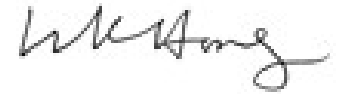


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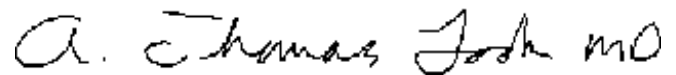
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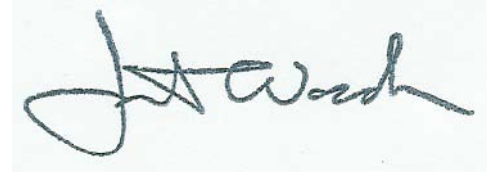
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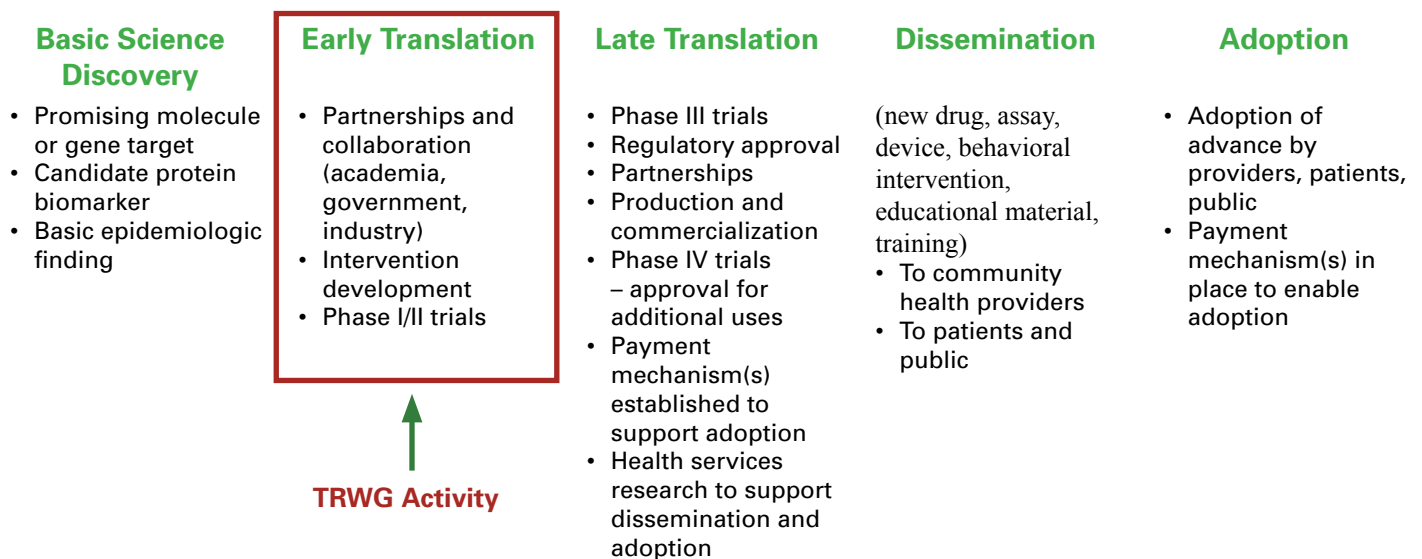
## Executive Summary

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, interventional 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.

## 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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## Introduction

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 this key component of NCI's research portfolio. The charge to the TRWG was to evaluate the current status of NCI's investment in translational research, envision its future, and develop recommendations and implementation plans to realize that vision. This effort followed—and was intended to complement and extend—the work of the Clinical Trials Working Group, which had just completed a similar process related to clinical trials. The TRWG is a broadly constituted panel of academic translational researchers, representatives from industry and foundations, patient advocates, and NCI staff. The membership of the TRWG is provided at the front of this report.

In order to fully understand the context for its charge, the TRWG began its work with a detailed review of 11 prior analyses and recommendations for improving translational research. This included the President's Cancer Panel 2004-2005 Annual Report; the NCAB 1994 Cancer at a Crossroads Report; the NCAB P30/P50 Ad Hoc Working Group Report; the NCAB Clinical Trials Working Group Report; several NCI Progress Review Reports; the NIH Roadmap for Medical Research; and the Food and Drug Administration Critical Path Initiative Report (see Appendix A for citations). The TRWG also reviewed several published articles on the promise and challenges of translational research.

To further guide and inform its deliberations, the TRWG developed an operational definition of translational research and selected the “early translational research” portion of the President's Cancer Panel Translational Continuum as the focus for its deliberations (see Appendix B). Based on the definition of early translational research as extending from a credentialed discovery in the lab, clinic, or population to the point of early human testing, the TRWG drafted six developmental pathways to clinical goals: biospecimen-based risk assessment devices, image-based risk assessment agents/techniques, agents, immune response modifiers, interventional devices, and lifestyle alterations (see Appendix C). By clearly defining the steps involved in early translational research and distinguishing it from discovery research, these pathways served as a valuable tool for understanding barriers and challenges in the current system and for identifying areas in need of improvement.

To understand the nature and scope of NCI's current translational research activity, the TRWG commissioned a comprehensive analysis of the FY04 award portfolio, including investigator-initiated, solicited, and infrastructure awards (see Appendix D). This portfolio analysis revealed that translational research awards are currently distributed over most Divisions, Centers, and Offices and funded by a range of programs. However, the analysis also revealed that awards are not currently categorized in a manner that provides an accurate assessment of translational content. The TRWG also commissioned an analysis of 20 NCI-supported translational research successes to determine whether there were common elements or themes that contributed to those successes (see Appendix E). These analyses demonstrated that successful translation occurs through a diverse range of funding programs and stakeholder interactions.

The TRWG conducted seven face-to-face meetings from December 2005 through January 2007. To accomplish its work, the TRWG organized itself into subcommittees responsible for different aspects of translational research. During the plenary meetings, each subcommittee reported on the progress of its work and solicited comments from the TRWG as a whole. Between plenary meetings, the subcommittees conducted a substantial number of conference calls among themselves and with non-TRWG experts to develop and refine their proposals. Furthermore, during this process, the external community provided substantive, real-time input into the development of the TRWG recommendations through two important venues—Internet-based public forums and invited Roundtable Meetings.

During the first Internet forum, conducted December 2005 through January 2006,<sup>1</sup> the TRWG sought public input on various translational research issues including barriers, incentives, prioritization, funding, system organization, facilities/technologies, and manpower/training. At the initial Roundtable Meeting, held in February 2006, the TRWG solicited input from a broad array of cancer community stakeholders on issues in translational research and recommendations for

<sup>1</sup> Meeting dates are listed in Appendix F.

improvement from three different perspectives: a) the TRWG pathways to clinical goals; b) populations served; and c) cross-cutting themes such as funding, organization, coordination, facilities/technologies, workforce/training, and industry interactions. An Industry/Society/Foundation Roundtable, held in April 2006, provided an opportunity for the TRWG to gather input from pharmaceutical, biotechnology, and device companies as well as cancer societies and foundations. The discussions at this Roundtable focused on issues of resources, collaboration, and management in translational research as well as the utility of the TRWG pathways as tools for developing and guiding research plans. During the second Internet forum in October 2006, the TRWG requested public comment on the draft initiatives and implementation concepts. During the final Roundtable Meeting, also held in October 2006, the TRWG requested comments and discussion concerning the draft initiatives and their associated implementation concepts, again from the perspective of the different TRWG developmental pathways and populations served.

In addition to the Internet forums and Roundtable Meetings, the TRWG also received valuable input from the American Association for Cancer Research, the American Society of Clinical Oncology Translational Research Task Force, the Oncology Nursing Society, the Cancer Biology Training Consortium, the UK Medical Research Council, the National Institute of Neurological Diseases and Stroke, and the Directors of the Specialized Programs in Research Excellence, the Early Detection Research Network, and the cancer centers.

In its deliberations, the TRWG reached consensus through four sequential stages. The first stage was to define the following list of current challenges to the success of early translational research:

1. Insufficient coordination and integration results in a fragmented translational research effort that risks duplication and may miss important opportunities.
2. Absence of clearly designated funding and adequate incentives for researchers threatens the perceived importance of translational research within the NCI enterprise.
3. Absence of a structured, consistent review and prioritization process tailored to the characteristics and goals of translational research makes it difficult to direct resources to critical needs and opportunities.
4. The multidisciplinary nature of translational research and the need to integrate sequential steps in complex developmental pathways warrant dedicated project management resources.
5. Translational research core services can be duplicative and inconsistently standardized, with capacity poorly matched to need.
6. Inadequate collaboration with industry delays appropriate developmental handoffs.
7. Extended negotiation on intellectual property issues delays or prevents potentially productive collaborations.
8. Inadequate collaboration with foundations/advocacy groups risks missing important opportunities for patient outreach and integration of translational research efforts.
9. Insufficient collaboration and communication between basic and clinical scientists and the paucity of effective training opportunities limits the supply of experienced translational researchers.

The TRWG then defined specific improvements in the current NCI-supported early translational research enterprise to address these obstacles.

The second stage was to develop recommendations addressing the most important improvements. An initial group of recommendations concerning organization and funding, prioritization, core services, and project management were presented to the NCAB on June 14, 2006. During the third stage, additional recommendations were developed, focusing on external integration and workforce/training. Finally, during the fourth stage, specific initiatives and implementation

plans were developed addressing the various recommendations. The goal was to develop proposed implementation plans that would be innovative, yet practical, and would build on the best of the current NCI early translational research system.

This consensus-building process resulted in the 15 initiatives detailed in this report, “Transforming Translation—Harnessing Discovery for Patient and Public Benefit.” These initiatives are not intended to address NCI efforts in other areas of the Translational Research Continuum as defined by the President’s Cancer Panel, including basic science discovery, late translation (Phase III trials), dissemination, and adoption.

The proposed initiatives are organized into three categories: Coordinated Management, Tailored Funding Programs, and Operational Effectiveness. The Coordinated Management Initiatives establish an integrated organizational approach across NCI to coordinate and prioritize early translational research, designate a specific portion of the NCI budget for early translational research, and improve the coding of early translational research awards. The Tailored Funding Programs Initiatives establish new funding programs tailored to the distinctive characteristics of early translational research and modify existing programs to enhance translational productivity. The Operational Effectiveness Initiatives improve the conduct of early translational research by establishing a formal project management system, coordinating core services, improving biospecimen resources, facilitating industry and foundation collaborations, and enhancing workforce development. Each initiative also has a proposed implementation timeline and budget presented in a consolidated Timeline and Budget section.

Each of the initiatives presented in this report was created to address a critical issue for translational progress and represents an essential goal about which there is strong consensus among the TRWG membership. For each initiative, the TRWG developed a rationale that supports the goal of the initiative and served as a premise for the implementation strategy. The TRWG then gave careful consideration to developing constructive ideas for implementation steps that could most effectively achieve the stated goals. These proposed implementation plans attempt to balance the requirements of the initiatives against the realities and constraints of current structural, functional, economic, and political environments. The TRWG hopes these ideas will be given careful consideration; they are not intended to constrain NCI’s options for achieving the goals but, rather, to enhance its success in doing so.

No major modification to an ongoing enterprise, such as that recommended by the TRWG, should be undertaken without establishing a mechanism for evaluating its success. Accordingly, this report includes a section on Evaluation and Outcomes that outlines the process recommended by the TRWG for evaluating the implementation and impact of the proposed initiatives.

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## Coordinated Management

### Introduction

The TRWG portfolio analysis revealed that early translational research is supported by a wide variety of programs managed through virtually all NCI Divisions, Centers, and Offices. Coordination of translational research activities across these programs and organizational structures is currently informal and project or issue specific, which can result in duplication, missed opportunities, and lack of synergy. A more integrated management approach has the potential to develop a shared vision for the goals of the overall enterprise and increase the efficiency, productivity, and transparency of NCI-supported early translational research.

A more coordinated NCI organizational structure for early translational research will take better advantage of the respective scientific and managerial strengths of the existing Divisions, Centers, and Offices and facilitate comprehensive extramural advice and oversight. A key management tool will be a shared understanding of the nature and scope of the early translational research portfolio at both the program and award level. Such an understanding is essential to identify potential gaps, redundancies, and synergies across projects and programs. Coupled with a budget target for early translational research, it also will facilitate long-term planning and the balancing of investments across disease sites, populations, and the six TRWG developmental pathways.

Another key management tool will be a systematic prioritization process drawing on input from all NCI Divisions, Centers, and Offices and the broad extramural community, including a wide range of health care professionals, patient advocates, and the other government agencies and foundations active in cancer research. The process will be designed to identify translational opportunities most promising for development based upon scientific quality, technical feasibility, and expected clinical or public health importance, including the needs of those with rare cancers and medically underserved populations.

To build a coordinated management approach that incorporates these elements, the TRWG proposes four initiatives.

- A1. Establish a flexible, integrated organizational approach that coordinates early translational research across the National Cancer Institute.**
- A2. Designate a specific portion of the National Cancer Institute budget for early translational research.**
- A3. Develop a set of award codes that accurately capture the nature and scope of the early translational research portfolio.**
- A4. Establish a distinctive prioritization process for early translational research.**

## **Initiative A1: Establish a flexible, integrated organizational approach that coordinates early translational research across the National Cancer Institute.**

### **Rationale**

Translational research is intended to move a discovery or set of discoveries through a focused development process to the point of early human testing (see the six TRWG developmental pathways in Appendix C). Because of the complex, multidisciplinary, goal-oriented, fast-paced, and time-sensitive nature of this development process, translational research requires a more integrated and coordinated management approach than would be appropriate for discovery research.

Currently, NCI-funded translational research projects are managed by individual programs distributed across virtually all Divisions, Centers, and Offices. Coordination across programs and organizational structures is generally informal and situational, which results in the potential for overlap, duplication, missed opportunities, and other inefficiencies. This distributed approach can make it challenging to identify potential synergies and to redirect energies and resources to emerging opportunities in a timely manner, and can lead to a lack of focus in translational research goals and programs. While the scientific quality of the individual research projects and programs is very high, integrating the programs more formally and substantively would enhance the efficiency and productivity of the enterprise as a whole.

Many of the TRWG initiatives are designed to improve coordination and integration of translational research across projects and programs, both among investigators, institutions, and NCI, and with external stakeholders such as industry, foundations, and advocacy groups. However, to fully realize their potential, these initiatives must be guided by a cohesive and coordinated NCI organizational structure that is focused specifically on the needs of translational research and dedicated to its vitality. Such a coordinated structure is necessary to effectively manage the overall translational research portfolio; reduce fragmentation and redundancy; ensure that rare cancers, medically underserved populations, and historically lower-resourced pathways to clinical goals are appropriately addressed; and allocate resources across the enterprise for maximum overall benefit. This comprehensive coordination is especially important today given the anticipated rapid pace of cancer discoveries and the resulting need for adaptive structures and functions to manage and guide the overall enterprise.

To realize the goals of this initiative, the TRWG proposes the implementation plan described below.

### **Implementation Plan**

#### ***Overall Approach***

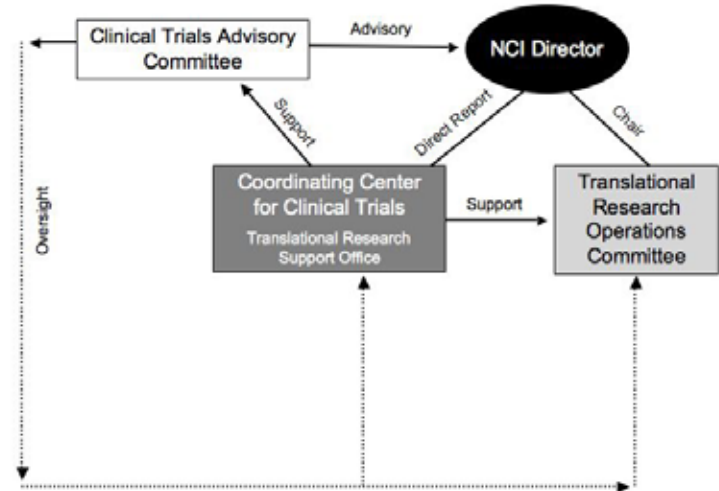
In order to establish a more integrated and coordinated management approach for translational research across NCI, three critical organizational elements will be established. The first is formal extramural advice and oversight specifically for translational research, which the TRWG recommends be vested in the new Clinical Trials Advisory Committee established as a result of the Clinical Trials Working Group Report. The second element is a Translational Research Operations Committee involving the Directors (or designees) of all NCI Divisions, Centers, and Offices with responsibility for translational research programs in a matrix management structure responsible for coordinating and integrating translational research activities across the Institute. The third element is a Translational Research Support Office within the new Coordinating Center for Clinical Trials established as a result of the Clinical Trials Working Group Report. This Support Office will be responsible for supporting the Translational Research Operations Committee and facilitating and coordinating implementation of all of the TRWG initiatives. This coordinated management structure is depicted in Figure 2, page 15.

#### ***Leadership Focus***

A strong focus for translational research within the Office of the Director is essential to provide clear direction for the future of NCI-funded translational research and ensure that issues related to translational research have a dedicated, coordinated voice within the NCI senior leadership team. This leadership role for translational research will be either

assumed by the NCI Director or delegated by the Director to a senior translational researcher who is at the level of a Division Director and serves on the Executive Committee. To ensure commitment to the broad translational mission of the Institute rather than any single component, this individual ideally would not be a standing Director of a Division, Center, or Office. If the NCI Director elects to delegate this responsibility, the designee should have a nationally recognized scientific reputation in translational research and experience managing organizations carrying out translational research. The individual should also have experience with NCI operations, possibly through serving on NCI advisory committees (e.g., National Cancer Advisory Board (NCAB), Advisory Committee of the Director (ACD), Board of Scientific Advisors (BSA), Board of Scientific Counselors for Basic Sciences, Board of Scientific Counselors for Clinical Sciences and Epidemiology).

**Figure 2. Coordinated NCI Organizational Structure**



The NCI Director or designee will serve as Chair of the Translational Research Operations Committee (discussed below). The Chair will be responsible for ensuring that the Committee functions as a cohesive team to advance translational research in a coordinated and balanced manner across NCI. A particularly important responsibility will be to guide the Committee through an annual review of the NCI translational research portfolio in order to achieve a consensus recommendation on an integrated program and budget across all Divisions, Centers, and Offices.

### **Translational Research External Advisory Oversight**

As a result of the initiatives recommended by the Clinical Trials Working Group, a new external advisory committee, the Clinical Trials Advisory Committee, has recently been established to advise the NCI Director on the conduct of clinical research across the Institute. The TRWG is keenly aware that the benefits of a similarly focused and informed oversight group for translational research must be balanced against the potential costs and complexities of such an undertaking. Therefore, the TRWG recommends that the responsibilities of the new Clinical Trials Advisory Committee be extended to include oversight of translational research and that NCI consider changing the name of this committee to the Clinical and Translational Advisory Committee. (Hereafter in this report, the Committee will be referred to simply as the “Advisory Committee” when discussing its translational research responsibilities.) Although several newly appointed members of the Advisory Committee are experienced translational researchers, the TRWG recommends that the membership be reviewed and expanded as necessary to ensure that at least 50% of the members have translational research expertise.

The rationale for this approach is fourfold. First, the new Advisory Committee already has oversight responsibility not only for late-stage clinical trials, but also for early-stage trials, which are an integral part of early translational research. Second, the Advisory Committee has responsibility for certain correlative science studies, which may inform nonclinical discovery and translational research activities. Third, integrated oversight will facilitate coordination of the prioritization processes for early translational research and later-stage clinical trials.

The fourth, and most important, rationale is that rapid advances in cancer biology, which enhance our understanding of the genetic and cellular mechanisms underlying specific cancers, are making possible the scientifically driven development and clinical testing of novel interventions targeted at the specific characteristics of a patient’s tumor or underlying genetic profile. Capitalizing on these advances will require close collaboration among translational scientists and the clinical researchers responsible for both early- and late-stage trials. The dedicated high-level attention provided by a coordinated

extramural oversight body is needed to ensure that these advances in molecular medicine move forward through development and clinical trials in a coordinated and efficient fashion.

Investing oversight responsibility for translational research in the Advisory Committee rather than NCI's other advisory committees (e.g., NCAB, ACD, BSA, the Boards of Scientific Counselors) is recommended because these other committees are charged with advising the Director on all aspects of cancer research, rather than focusing specifically on individual components of the enterprise. In contrast, merging oversight responsibility for early translational research with that for clinical trials will provide efficient, focused oversight for both critical components of the overall translational research continuum across both the intra- and extramural communities.

The Advisory Committee will have the following responsibilities with regard to early translational research:

1. Advise the Director on the effectiveness of NCI's translational research management and administration across all Divisions/Centers/Offices in meeting demands and opportunities across disease sites, patient populations, the six TRWG developmental pathways, and the range of molecular mechanisms responsible for cancer development, and make recommendations for needed improvements and future directions.
2. Advise the Director on the operations and activities of the Translational Research Operations Committee (described below).
3. Advise the Director and Executive Committee on the appropriate magnitude for the dedicated translational research budget target (see Coordinated Management Initiative A2) and recommend allocation of translational research funding across organizational units, programs, disease sites, populations, developmental pathways, and molecular mechanisms.
4. Ensure that appropriate emphasis is placed on identifying research needs and priorities for rare cancers, medically underserved populations, and historically lower-resourced pathways to clinical goals (e.g., immunotherapy, interventional devices, lifestyle interventions).
5. Recommend to the Director translational research priorities based on the new, system-wide translational research prioritization process (see Coordinated Management Initiative A4).

### ***Translational Research Operations Committee***

Given the number, breadth, and pace of early translational research activities under way across NCI Divisions, Centers, and Offices, it is essential to create an internal management structure that can coordinate and integrate these activities and respond to emerging opportunities. To that end, a Translational Research Operations Committee will be established that includes the Directors (or designees) of all NCI Divisions, Centers, and Offices with responsibility for substantial early translational research programs. The Committee will be chaired by the NCI Director or the individual designated by the Director to lead translational research across NCI (see above).

As with the external advisory role, the TRWG considered the advantages and disadvantages of tasking an existing body, such as the Executive Committee, with the responsibilities envisioned for this new committee. In this case, however, a new, dedicated committee seemed the most effective approach given the requirement for active management and the operational challenges to be addressed. Such a new Operations Committee will constitute an efficient management tool and forum to ensure that translational research issues are addressed with a dedicated time and agenda that cannot be diverted to other pressing matters.

**Membership.** Given NCI's current translational research portfolio, initial membership of the Translational Research Operations Committee will be the Directors (or designees) from the following NCI organizational units:

- Division of Cancer Prevention
- Division of Cancer Treatment and Diagnosis

- Division of Cancer Biology
- Division of Cancer Control and Population Sciences
- Division of Cancer Epidemiology and Genetics
- Office of Centers, Training, and Resources
- Center for Cancer Research
- Office of Technology and Industrial Relations
- Center for Bioinformatics
- Division of Extramural Activities.

Other NCI entities—such as the Office of Science Planning and Assessment, the Office of Legislative Affairs, and the Technology Transfer Branch—will be represented on the Operations Committee on an ad hoc, nonvoting basis.

**Coordination of Translational Research Portfolio.** The Translational Research Operations Committee will, on an annual basis, review and prioritize the translational research portfolio proposed by each Division, Center, and Office with the goal of balancing, coordinating, and integrating translational research across NCI. Prioritization of new initiatives and guidance to program staff concerning R01 and P01 priorities will be based on the priorities resulting from the new prioritization process (see Coordinated Management Initiative A4), as well as equitable balance across disease sites, populations, and the TRWG developmental pathways, along with special attention to the needs of rare cancers and minority or underserved populations. The Committee will review and approve all translational research Program Announcements (PAs) and Requests for Applications (RFAs) prior to submission to the Executive Committee.

**Development of an Integrated Translational Research Program Budget.** The Operations Committee will develop an integrated translational research program budget that will be recommended to the Executive Committee and the NCI Director for use in NCI-wide budget deliberations. This “translational research budget” will represent a matrix of the portion of each Division, Center, and Office budget devoted to translational research.

The matrix translational research budget will initially involve all RFA- and PA-directed programs identified by the Operations Committee as focused on early translational research. These will likely include the Specialized Programs of Research Excellence (SPORE), Early Detection Research Network (EDRN), *In Vivo* Cancer Molecular Imaging Centers (ICMIC), National Cooperative Drug Discovery Groups (NCDDGs), Rapid Access to Intervention Development (RAID)/Rapid Access to Preventive Intervention Development (RAPID)/Development of Clinical Imaging Drugs and Enhancers (DCIDE) programs, and projects funded through PAs and RFAs identified as “translational.” The Phase I and Phase II clinical trial contracts will either be included in this budget or as part of the clinical trials budget managed by the Clinical Trials Operations Committee formed in response to the Clinical Trials Working Group Report.

While this initial group of projects will not define the complete translational research budget, it will represent a core set of translational research activities. This will allow the Operations Committee to make an initial evaluation of the translational research budget with regard to the following:

- Overall size relative to the total NCI research budget
- Allocation across Divisions, Centers, and Offices
- Percentage of funding from each Division, Center, and Office designated for translational research
- Allocation across funding programs
- Allocation across disease sites



- Allocation across populations
- Allocation across prevention, therapy, risk assessment, etc.
- Allocation across the six TRWG developmental pathways
- Allocation across topics of interest (e.g., exploration of specific mechanisms of cancer development, specific technologies, core facilities).

As the coding system and portfolio analysis techniques improve (see Coordinated Management Initiative A3), the integrated budget will be expanded to include R01 and P01 and Z01 awards that are coded as translational, training awards from programs identified as applicable to translational researchers (e.g., K12, K23, K24), and awards from other mechanisms identified by the TRWG portfolio analysis as being more than 50% translational (e.g., Small Business Innovation Research Program [SBIR]/Small Business Technology Transfer Program [STTR]). This will allow the Operations Committee to further refine its management of translational research funding across NCI.

Once the integrated translational budget and its associated portfolio analysis are available in a comprehensive fashion, the Operations Committee will be able to identify gaps, overlaps, and opportunities. These can then be used as the basis for developing and sustaining a 5-year rolling plan and budget to guide the future of translational research. Such a plan will allow NCI to chart future obligations associated with already-funded translational research awards as well as analyze tradeoffs that may be required among funding existing programs, funding new TRWG-recommended programs (see Tailored Funding Programs Initiatives B3 and B4), and funding other new programs.

**Additional Responsibilities.** In addition to the major responsibilities described above, the Translational Research Operations Committee will be responsible for the following tasks in consultation with the Advisory Committee:

1. Evaluate organizational infrastructures and operating budgets for translational research program support across all Divisions, Centers, and Offices, and make recommendations as necessary to improve cost-effectiveness and reduce duplication and overlap.
2. Refine the TRWG operational definition of “translational research,” as distinguished from discovery or clinical research, and approve a new coding system that will allow the NCI translational research portfolio to be identified and tracked accurately.
3. Identify future opportunities for programmatic improvement, whether through new partnerships (industry, foundations, trans-NIH), new collaborations across NCI grantees, new intramural-extramural partnerships and collaborative activities, or identification of emerging barriers/roadblocks to translational success.
4. Oversee and coordinate implementation of the TRWG initiatives.

### ***Translational Research Support Office***

To manage implementation of the TRWG initiatives and support the Translational Research Operations Committee and the Advisory Committee, a Translational Research Support Office (TRSO) will be created within the Coordinating Center for Clinical Trials (CCCT) recently established in the Office of the Director as a result of the Clinical Trials Working Group process. Such an expansion of the CCCT’s responsibilities will require creating two distinct but integrated offices under management of a center director. One office will have primary responsibility for clinical trials issues and the other will have primary responsibility for translational research issues.

This organizational structure will have several benefits. First, it will ensure that activities at the intersection of translational and clinical research (e.g., early-stage trials) are well integrated. Second, it will facilitate creation of a cadre of professionals who are cross-trained and able to contribute both operationally and strategically to activities that impact



either translational or clinical research, regardless of their primary focus of responsibility. Finally, it will allow more efficient use of administrative support and organizational services.

**Staffing.** The Support Office staff, which will be phased-in over time to support implementation of the TRWG initiatives, will be primarily professional staff. The head of the Office will be a translational researcher and manager, preferably with experience in both the extramural community and at NCI. He or she will be responsible for management of the Office and its integration with overall activities of the expanded Coordinating Center. The professional staff will have translational research experience in either academia or industry as well as experience in NCI extramural program management or review. The Support Office will also include individuals with translational research project management experience in either industry or academia (see Operational Effectiveness Initiative C1). Many Support Office responsibilities will be implemented with the assistance of contractors and other NCI staff; however, those activities will be directed and coordinated by Support Office staff.

**Responsibilities.** The TRSO will have the following responsibilities:

1. Manage operation of the new translational research prioritization system (see Coordinated Management Initiative A4), including gathering and analyzing input from the broad cancer research community and overseeing the portfolio analysis of ongoing NCI-funded activities.
2. Provide support for the Translational Research Operations Committee, especially in overseeing portfolio analyses and developing the integrated translational research budget.
3. Serve as program officers and project managers for the Special Translational Research Acceleration Project (STRAP) program and the academic/industry collaboration program (see Tailored Funding Programs Initiatives B3 and B4).<sup>2</sup>
4. Provide project management support and coordination to project managers and program officers in the Divisions/Centers/Offices in executing their project management responsibilities for multiproject collaborative awards, including P50 and U-series awards.
5. Manage implementation of the remaining TRWG initiatives in consultation with NCI leadership and program staff:
  - New coding system for translational research awards
  - Modifications of guidelines for multiproject collaborative translational research awards
  - Collaboration across NIH to create new R-series and P-series mechanisms tailored to translational research
  - Integration of funding programs for pharmacology, toxicology, and manufacturing services with funding programs for other steps in translational research
  - Core services coordination and creation of regional centers of excellence
  - Collaboration with the Office of Biorepositories and Biospecimen Research on enhanced quality and accessibility of biospecimen repositories
  - Improved practices for negotiation of intellectual property matters in translational research
  - Enhanced integration and collaboration with foundations and advocacy groups
  - Improved training and career incentives for the translational research workforce.

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<sup>2</sup> For each award, TRSO staff will work closely with a designated Divisional program staff member who has the relevant scientific expertise and experience. As the programs expand, program officer/project manager responsibilities may be shifted to the relevant Divisional staff at time of award.

### ***Minority and Underserved Populations Working Group***

To facilitate the focusing of translational research resources on unmet cancer research needs associated with minority and underserved populations, the TRWG recommends that the Advisory Committee establish a Translational Research Minority and Underserved Populations Working Group charged with making recommendations with regard to the following areas:

1. Identify initial targets of translational research need and opportunity with regard to these special populations, using prioritization approaches similar to those described in Coordinated Management Initiative A4.
2. Develop a programmatic strategy for addressing the identified targets, including the appropriate mix of intramural and extramural activities, the funding vehicles best suited to facilitating the extramural component, and approaches for obtaining new funds or reprogramming existing funds over time to support this effort.
3. Design research-linked training opportunities that will engage young researchers from underrepresented populations as well as researchers interested in addressing the unmet needs of minority and underserved populations.
4. Develop a strategy for networking and collaboration with industry, foundations, advocacy groups, community organizations, etc., in support of the objectives of this effort, and for dissemination of its priorities, strategies, and results.

The TRWG recommends that the Working Group include the following members:

- Advisory Committee members with translational research expertise relevant to minority and underserved populations
- Representatives from the Director’s Consumer Liaison Group
- Directors (or designees) of all intramural and extramural Divisions, Centers, and Offices with programs relevant to minority and underserved populations
- Director of the NCI Center to Reduce Cancer Health Disparities
- Chief of the Comprehensive Minority Biomedical Branch in the NCI Office of Centers, Training, and Resources
- Cancer disparities experts
- Intramural translational researchers focused on the needs of minority and underserved populations
- Extramural translational researchers focused on the needs of minority and underserved populations
- Leaders of existing cancer research initiatives, networks, and consortia in the areas of minorities and underserved populations
- Advocates representing patients from minority and underserved populations
- Community leaders representing minority and underserved populations.

### ***Rare and Pediatric Cancers Working Group***

To facilitate the focusing of translational research resources on unmet needs associated with rare cancers and pediatric cancers, the TRWG recommends that the Advisory Committee establish a Translational Research Rare and Pediatric Cancers Working Group charged with making recommendations with regard to the following areas:

1. Identify initial targets of translational research need and opportunity with regard to these cancers, using prioritization approaches similar to those described in Coordinated Management Initiative A4.

2. Develop a programmatic strategy for addressing the identified targets, including the appropriate mix of intramural and extramural activities, the funding vehicles best suited to facilitating the extramural component, and approaches for obtaining new funds or reprogramming existing funds over time to support this effort.
3. Design research-linked training opportunities that will engage young researchers interested in addressing the unmet needs of rare and pediatric cancers.
4. Develop a strategy for networking and collaboration with industry, foundations, advocacy groups, etc., in support of the objectives of this effort, and for dissemination of its priorities, strategies, and results.

The TRWG recommends that the Working Group include the following members:

- Advisory Committee members with translational research expertise relevant to rare cancers and pediatric cancers
- Representatives from the Director’s Consumer Liaison Group
- Directors (or designees) of all intramural and extramural Divisions, Centers, and Offices with programs relevant to rare cancers and pediatric cancers
- Intramural translational researchers focused on the needs of patients with rare cancers and pediatric cancers
- Extramural translational researchers focused on the needs of patients with rare cancers and pediatric cancers
- Leaders of existing cancer research initiatives, networks, and consortia in the areas of rare cancers and pediatric cancers
- Advocates representing pediatric cancer patients and patients with rare cancers.

### ***Potential Translational Research Consortia***

As the translational research process evolves, an additional level of coordination around organ-specific disease sites may be beneficial in enhancing synergy and reducing redundancies. The TRWG therefore recommends that the Advisory Committee evaluate the benefits of establishing organ-specific, multi-institutional, multidisciplinary, multiproject consortia integrating all aspects of early translational research across the TRWG developmental pathways. These consortia are envisioned to include the following elements:

- Significant translational and clinical research experience in the relevant organ system
- Linkage to relevant discovery laboratories for identification of new approaches
- Expertise in the technologies required for the relevant TRWG developmental pathways
- Access to cross-cutting technologies such as imaging, animal models, high-throughput screening, and assay validation
- Experience with molecular mechanisms known to be relevant to the organ system
- Access to significant numbers of tissue samples and expertise in the standardized collection, storage, and annotation of relevant biospecimens
- Access to toxicology, pharmacology, and manufacturing facilities and expertise
- Experience in the conduct of early-stage, tissue-driven Phase I and Phase II trials in relevant patient populations and access to those patient populations
- Integration with the late-stage clinical trials infrastructure for relevant patient populations.

In determining whether such consortia would be valuable and feasible, the TRWG recommends that the Advisory Committee consider a variety of models. For example, one model would be to establish specific requirements and supplemental funding in order to integrate existing funding programs and projects into consortia. Another model would involve creating a new multi-institutional, multidisciplinary consortium funding mechanism by consolidating several current funding mechanisms, at least in part.

The TRWG recommends that the Advisory Committee address the benefits of creating for the common cancers (e.g., breast, prostate, lung, colorectal) two or more consortia focused on specific aspects of the disease (e.g., therapy versus prevention) and also identify organ systems that might be especially appropriate for piloting of such an approach (e.g., rare cancers). In addition, the TRWG suggests that there would be substantial benefit in configuring these consortia in a matrixed manner, not just for organs but also for cross-cutting themes, such as molecular mechanisms or specific technologies (e.g., imaging, biospecimens, mouse models, molecular diagnostics) that would interact with the organ-specific consortia. Finally, the Committee should determine whether seed grants would be beneficial in encouraging the extramural community to develop approaches for building such consortia.

## **Initiative A2: Designate a specific portion of the National Cancer Institute budget for early translational research.**

### **Rationale**

Currently, the NCI “translational research budget” is not well defined. An integrated budget comprising identifiable translational research components (i.e., intra- and extramural research infrastructures, projects, personnel, etc.) and their missions does not exist. Although certain NCI programs are clearly translational, identifying all “translational research awards” and understanding their contribution to the translational research budget currently requires the development of ad hoc inclusion/exclusion criteria and labor-intensive portfolio analyses of individual translational research awards. Moreover, no target has been established for the portion of the NCI budget that should be devoted to translational research. Thus, even if the total translational research budget were known with accuracy, it would still be the result of a large number of individual decisions as opposed to a coordinated process to achieve an agreed-upon budget allocation.

The portfolio analysis commissioned by the TRWG (see Appendix D) revealed that half of the research identified as translational was funded through investigator-initiated R01 and P01 awards (\$662M of \$1.33B, or 49.8%).<sup>3</sup> Given this prominence of unsolicited investigator-initiated research within NCI’s translational research portfolio, without a budget target the actual amount of translational research funding could vary widely over time depending upon the fortunes of individual proposals within the NIH-wide peer review system.

Designating a specific portion of the NCI budget for translational research will have two critical benefits. The first is that NCI will be able to manage its investment in translational research in a coordinated fashion, facilitating long-term planning and allowing prioritization among programs and approaches. The second benefit is that a designated budget target will demonstrate NCI’s recognition of and commitment to the importance of translational research that is essential to achieve its core mission of improving the health of patients and the public. Moreover, achieving consensus on a designated budget target is a vital complement to the creation of a coordinated management structure for translational research across NCI. It is also in keeping with the NIH Director’s commitment to devote approximately 35% of the overall NIH budget to translational research.<sup>4</sup>

To realize the goals of this initiative, the TRWG proposes the implementation plan described below.

### **Implementation Plan**

The Advisory Committee (see Coordinated Management Initiative A1) will be responsible for recommending the desired percentage target for NCI’s annual spending on translational research. Based on the TRWG translational research portfolio analysis (see Appendix D), it appears that approximately 30% of the total NCI budget (\$1.33B relative to a total of \$4.4B) was devoted to translational research in FY04. Although a more detailed assessment of a subset of the awards indicated that this number may be high by as much as 20-40%, it is reasonable to assume that current translational research funding is in the range of 20-30% of the total NCI budget. Therefore, the TRWG recommends that the initial target be in the 25%-35% range, which is in line with Dr. Zerhouni’s recommendation. The Translational Research Operations Committee and the Advisory Committee will use this budget target to manage translational research across NCI, while the Office of the Director will use the budget target as a component in managing NCI-wide research funding.

The translational research budget target will be expected to encompass four components. The first is the solicited (i.e., RFA/PA-directed) programs already identified as translational in the portfolio analysis. These programs provide critical infrastructures, projects, and personnel to advance translational research. The second is the unsolicited, investigator-

3 Although the portfolio analysis did not assess funding by individual Program Announcements or Requests for Application, it is likely that the vast majority of the R01 and P01 awards identified as translational are investigator-initiated. When funding mechanisms such as K-series career development awards, R37 Method to Extend Research in Time (MERIT) awards, and Small Business Innovation Research/Small Business Technology Transfer Research awards are added to the R01 and P01 awards, nearly 60% of the identified translational research occurs through investigator-initiated mechanisms not necessarily specifically designed by NCI to foster translation.

4 *NIH at the Crossroads: Myths, Realities and Strategies for the Future.*

initiated awards identified as translational by the new coding system (see Coordinated Management Initiative A3). The third is the awards resulting from the new solicited funding programs proposed by the TRWG (see Tailored Funding Programs Initiatives B3 and B4). The fourth is the operational expenses associated with implementing and sustaining the TRWG initiatives.

Once a complete picture of translational research funding is obtained based on the new coding system, the Translational Research Operations Committee will compare the budget target, on an annual basis, with the actual translational research funding activity through both solicited and investigator-initiated awards. If the target funding level is not being achieved, funding priorities will be adjusted and/or new directed programs created to bring actual funding in line with the target.

## Initiative A3: Develop a set of award codes that accurately capture the nature and scope of the early translational research portfolio.

### Rationale

Currently, there is no set of NCI-specific award codes that accurately and explicitly characterizes translational research, making it nearly impossible to determine the nature and scope of NCI translational research funding. Translational research is not specifically identified by any of the codes applied to grants, such as the Common Scientific Outline (CSO),<sup>5</sup> Special Interest Category, or NIH Clinical Aspect (NIHCA)<sup>6</sup> codes, although translational activities would clearly be included, along with other types of research, in certain categories. Therefore, in order for the TRWG to characterize the NCI translational research portfolio, an ad hoc coding system had to be employed (see Appendix D). This was not only labor-intensive, but it produced results that are open to criticism because of their dependence on ad hoc inclusion/exclusion criteria regarding the translational nature of various projects and infrastructure components.

Managing translational research more effectively in the future will require a logistically straightforward and precisely defined method for coding awards as translational. A unified set of codes will have a number of advantages. It will enhance understanding of NCI's overall investment in translational research and help to identify gaps and opportunities in a more timely and effective manner. It will also enable NCI staff, leadership, and advisory committees to better monitor the nature and scope of NCI's translational research portfolio over time. And finally, the establishment of meaningful award codes will allow NCI to better communicate translational research activities, opportunities, and progress to the public. This is essential to build and sustain the public's commitment to and participation in translational research.

To realize the goals of this initiative, the TRWG proposes the implementation plan described below.

### Implementation Plan

#### Overall Approach

The Translational Research Support Office, under guidance from the Translational Research Operations Committee, and in association with the Research Analysis and Evaluation Branch (RAEB), will develop a new set of codes, based on the six TRWG developmental pathways, that operationalize the TRWG functional definition of early translational research. These new codes will be incorporated into the existing NCI coding system operated by RAEB.

#### Integration with Current NCI Coding System

Currently, coding of all NCI awards is performed by RAEB in the Division of Extramural Activities, which has a large coding group of professional indexers. The new translational research codes will be incorporated into this established system in the following manner. First, an award will be classified as “translational,” based on its relevance to one or more of the TRWG developmental pathways. The degree of translational relevance (e.g., 25%, 50%, 75%, or 100%) will also be coded. Once a translational research code has been applied, an additional group of codes will be considered to further characterize the exact nature of the translational research activity (see below). A similar approach to detailed coding is being employed for trans-NIH AIDS-related and nanotechnology-related research, which may serve as useful models. The implementation of the new translational research codes will also be coordinated, as appropriate, with the new portfolio analysis tools being investigated by the NIH Office of Portfolio Analysis and Strategic Initiatives.

5 The Common Scientific Outline is a classification system that divides cancer research into seven categories: Biology; Etiology; Prevention; Early Detection, Diagnosis and Prognosis; Treatment; Cancer Control, Survivorship and Outcomes Research; and Scientific Model Systems. Full information is available at: <http://researchportfolio.cancer.gov/crp/cso.jsp>.

6 NIHCA codes are quartile-based measures, assigned by NCI's Research Analysis and Evaluation Branch, of the relevance of projects to the NIH definition of clinical research. NIH defines human clinical research as follows: 1) Patient-oriented research—research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: a) mechanisms of human disease, b) therapeutic interventions, c) clinical trials, or d) development of new technologies. 2) Epidemiologic and behavioral studies. 3) Outcomes research and health services research.



### ***Coordination with Other Organizations***

In developing the new codes, the Translational Research Support Office will seek input from other Federal agencies that have developed their own coding and tracking systems. For example, the Department of Defense (DOD) has worked to generate a taxonomy system to code and track all funded research from the initial stages up to public delivery. The system is now being used for portfolio analysis and monitoring, reporting of “success,” and ongoing tracking of projects. Although a system of this type might be too comprehensive to be implemented throughout NCI, the DOD has developed some best practices that could prove useful. The Support Office will also work with the Food and Drug Administration to ensure consistency between the efforts of these two agencies and to adopt common language and classification systems.

### ***Coding Categories***

The new codes will incorporate a range of categories related to translational research. The RAEB already codes grants based on organ site and target populations (rare cancers, pediatrics, minorities, underserved populations, etc.). Additional categories specifically relevant to translational research might include the following:

- Mechanism of cancer development
  - Tissue/cellular level (e.g., apoptosis, proliferation, angiogenesis)
  - Molecular level (e.g., p53 alterations, APC alterations, Her-2 alterations)
  - Primary TRWG developmental pathway
  - Agent (drug or biologic)
  - Immune response modifier
  - Biomarker risk assessment device
  - Imaging risk assessment device
  - Interventive device
  - Lifestyle intervention
- Region of the relevant TRWG developmental pathway
  - Early development/testing (target validation, assay development, prototype development, etc.)
  - Optimization/validation
  - Preclinical development (process/device development, pharmacology, toxicology, manufacturing, etc.)
  - Early-stage human studies
- Population
  - Average risk/unscreened
  - Elevated risk
  - Local disease
  - Regional disease
  - Advanced disease
  - Palliative.



TRWG representatives, NCI program staff, Translational Research Support Office staff, and representatives from the NCI Center for Bioinformatics (NCICB), RAEB, and Office of Science Planning and Assessment will be convened to define the codes and determine how they can be most efficiently and rapidly incorporated into the coding system. The new codes will be expressed using enterprise vocabularies and Common Data Elements developed by NCICB.

### ***Coding of Awards***

Once the new translational research codes are incorporated into the coding system, RAEB staff will code all newly funded awards based on those codes. This will ensure that coding is consistently and objectively applied across all translational research projects. It currently is not possible to code individual subprojects for grants with multiple components (e.g., Specialized Programs of Research Excellence, P01s), although NCI and NIH are actively working to incorporate such capability. As coding of subprojects is essential for accurate portfolio analysis, incorporating such capability should be a high priority for both NCI and NIH. Until coding of subprojects is implemented coding will be applied to the parent grant only, although all relevant codes will be included from the subprojects. Once coding has been assigned by RAEB, it will be forwarded to the relevant program officer for concurrence that the codes have been applied correctly. In order to gain a complete picture of the NCI translational research portfolio in a timely manner, RAEB will be asked to assign translational research codes retrospectively to all active awards soon after the codes have been implemented for new awards.

Once the new coding system is in place, the Translational Research Operations Committee will evaluate the option of investigator-assigned codes that are then confirmed during peer review and by program and RAEB staff. If feasible, the TRWG considers this latter option to be highly preferable, as it would encourage a more comprehensive understanding on the part of investigators of the role of their individual research projects to the overall translational research process.

## Initiative A4: Establish a distinctive prioritization process for early translational research.

### Rationale

In funding discovery research, NCI's primary objective is to enable qualified researchers to freely explore new ideas in fundamental cancer science and pursue new lines of inquiry in whatever directions seem most promising. In funding translational research, on the other hand, NCI's obligation is to deploy its scarce resources so as to maximize the effectiveness, speed, and efficiency with which promising new insights from discovery research are transformed into tangible products,<sup>7</sup> interventions, or lifestyle alterations that can impact patient care or public health.

Mechanisms for allocating resources should be tailored to the respective characteristics of these different types of research. For discovery research, selection mechanisms focus on identifying the best scientific ideas proposed by investigators qualified to pursue them. For translational research, selection mechanisms need to consider not only the strength of the scientific hypothesis, but also identify concepts especially ripe for development and targeted at important unmet clinical or public health needs unlikely to be advanced by industry.

Existing approaches to selection of research projects for funding evolved primarily to support discovery research. As translational research is appreciated as a distinct part of NCI's research portfolio, it is important that appropriate selection mechanisms be developed to optimize that portion of our Nation's investment in cancer research as well. By creating a prioritization process distinctive to translational research, it will be possible to identify and prioritize emerging translational research concepts and opportunities and ensure that they are advanced via appropriate NCI translational research support mechanisms, without compromising the function of existing selection processes and funding tailored to the different needs of discovery research.

To realize the goals of this initiative, the TRWG proposes the implementation plan described below.

### Implementation Plan

The intent of the prioritization process will be to identify, on an annual basis, a small number of specific clinical or product development goals to be designated as priorities based on their ripeness for development and their potential clinical significance for defined patients or populations. This new prioritization process will be managed by a Prioritization Working Group of the Advisory Committee (see Coordinated Management Initiative A1, page 14, and Figure 3).

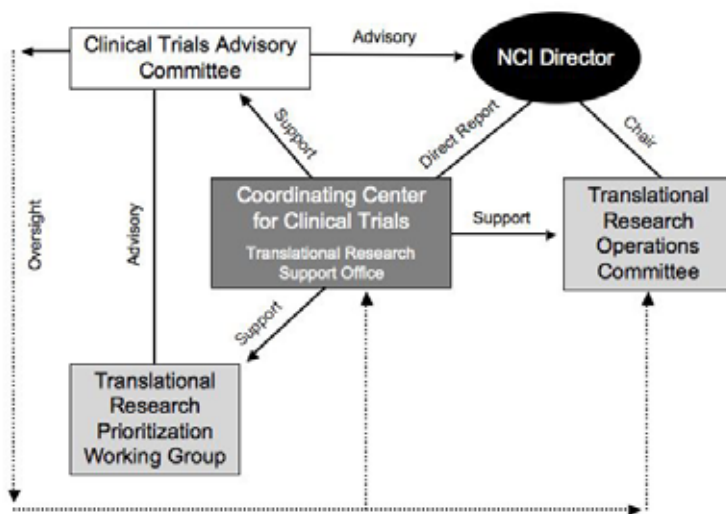
### Prioritization Working Group

**Membership.** The Prioritization Working Group will include 15-20 members, drawn in part from members of the parent Advisory Committee and in part from the larger cancer research community. Membership will encompass a range of key stakeholders, including:

- Extramural translational researchers, as well as discovery, clinical, and population researchers experienced in the conduct of translational research

<sup>7</sup> "Products" includes new or repurposed drugs, biologics, devices, and other tangible products that can be used for therapeutic, diagnostic, prognostic, preventive, or population risk assessment purposes.

**Figure 3. Relationship of Prioritization Working Group to Coordinated NCI Organizational Structure**



- NCI program and intramural research staff experienced in the conduct or coordination of translational research
- Patient advocates
- Nonacademic health professionals
- Representatives from a foundation active in translational research funding
- Representatives from industry.

In addition to representing these stakeholder groups, the Prioritization Working Group will include expertise across the following domains:

- Disease sites
- Mechanisms of cancer development
- TRWG developmental pathways to clinical goals
- Prevention
- Therapy
- Population sciences
- Rare cancers
- Minority/underserved populations.

To promote dynamism and adaptability of the prioritization process and ensure that the Working Group is continually refreshed with new perspectives, a new Working Group will be formed each year with 30-50% new members. No individual will serve on more than three successive Working Groups.

**Responsibilities.** Each year the Prioritization Working Group will have the following responsibilities, which are explained in greater detail below.

1. Identify translational research opportunities that warrant the highest priority for advancement.
2. Identify gaps in the NCI translational research portfolio (i.e., infrastructures, projects, personnel, resources) relative to these opportunities.
3. Recommend a subset of these high-priority opportunities for Special Translational Research Acceleration Project funding solicitations (see Tailored Funding Programs Initiative B3).
4. Issue a report to the community on the identified priorities.

### ***Prioritization of Opportunities***

Each year the Prioritization Working Group will use the six-step process outlined below to identify the most important translational research opportunities for that year. All of these steps will be supported, facilitated, and implemented through the Translational Research Support Office with the assistance of other NCI staff and/or contractors.

**Information Gathering.** The Prioritization Working Group, with the assistance of the Support Office, will systematically gather, review, and analyze information from the published literature, including reviews and state-of-the-science reports. The goal will be to identify concepts that potentially warrant a focused effort to advance them down the relevant TRWG developmental pathway.

The Prioritization Working Group will also convene, as needed, “Translational Needs and Opportunities” symposia to obtain expert input from discovery, translational, and clinical researchers; manufacturing and regulatory specialists; management experts; industry representatives; patient advocates; and NCI program and intramural research staff. These symposia will be organized by the Support Office and conducted as focused sessions during existing professional society, foundation, or advocacy group meetings, and/or as part of existing program meetings (e.g., Specialized Programs of Research Excellence, Early Detection Research Network) or “state-of-the-science” meetings conducted by the disease-specific Scientific Steering Committees formed as part of the Clinical Trials Working Group Report implementation.

If deemed appropriate by the Prioritization Working Group (or the parent Advisory Committee), the Support Office will convene targeted subgroups of key investigators and NCI program staff to provide needed input. The focus of such subgroups may be organ/disease systems (e.g., breast cancer, leukemia/lymphoma), TRWG developmental pathways (e.g., immune response modifiers, imaging), mechanisms of cancer development or progression (e.g., protein kinases, angiogenesis), or other organizing principles. In particular, the TRWG recommends that such subgroups be convened to provide input on priorities for rare cancers, minority/underserved populations, and lifestyle interventions.

**Solicitation of Ideas.** The Prioritization Working Group will, through the Support Office, issue a Request for Information (RFI) soliciting ideas for important translational research opportunities that are ripe for development. The RFI will include a submission template specifying the following key elements that must be addressed in order for a submitted concept to be evaluated by the Prioritization Working Group:

- Key results of discovery research that support the opportunity proposed
- Key factors supporting the technical feasibility of a focused development effort
- Importance of clinical or public health need
- Likelihood that the need will be met, or the opportunity advanced, by private industry without NCI involvement.

Concepts may be submitted by the research and advocacy communities at large, by ad hoc groups focused on translational research, or by any other intra- or extramural source. All concepts submitted will be subject to a common review process.

**Analysis of Input.** Based on the information gathered from the literature, the output of the Translational Needs and Opportunities symposia, and the concepts proposed in response to the RFI, the Support Office will prepare brief concept packages for those opportunities that have the following attributes:

- A strong and validated body of knowledge supporting the potential of the discovery to lead to meaningful impact on cancer prevention, detection, diagnosis, or therapy
- A feasible series of steps for advancing the discovery into early human testing
- A demonstrated clinical or population health need that is not adequately addressed by either existing approaches or those already in development.

Concept packages summarizing the information supporting each of these attributes will be presented to the Prioritization Working Group for review and prioritization of up to 10 of the most promising translational research opportunities. In selecting priorities, the Prioritization Working Group will ensure that appropriate emphasis is placed on the needs of patients with rare cancers and medically underserved populations.

**Portfolio Analysis.** For each selected opportunity, the Support Office will analyze the current NCI grant portfolio to determine the scope of ongoing translational activity relevant to that opportunity. This analysis will identify what additional research activities are required to complete a focused, coordinated, and facilitated translational research effort to move the identified concept into early human testing. The portfolio analysis will also attempt to identify relevant research under way with foundation, industry, or other Government agency support. This will allow NCI to avoid

duplication of ongoing efforts and identify opportunities for synergy. Based on this analysis, the Prioritization Working Group will select the five highest priority opportunities.

**Public Comment.** The Prioritization Working Group will publish the concept packages for the five most promising opportunities, present them for discussion at a special annual Translational Research Needs and Opportunities symposium reserved especially for this purpose, and solicit public comment more generally. All comments received will be analyzed and used to refine and further prioritize the selected opportunities.

**Selection of Prioritized Opportunities.** Taking into account all of the input received and the analysis conducted as well as its own collective knowledge and expert judgment, the Prioritization Working Group will rank order the identified opportunities. In preparing the ranking, the Prioritization Working Group will ensure that appropriate emphasis is placed on the needs of patients with rare cancers and medically underserved populations. The Prioritization Working Group again will select two or three of the opportunities as subjects for STRAP solicitations (see Tailored Funding Programs Initiative B3). The prioritized opportunities plus the recommendations for STRAP solicitations will be forwarded to the Advisory Committee for review and approval. The Advisory Committee will then forward the priorities and STRAP recommendations that they approve to the Executive Committee and the Board of Scientific Advisors for final review and approval. Upon final approval, the priorities will be published and used to form the basis for STRAP solicitations and to guide translational research across NCI.

### ***Application of Priorities Across NCI***

The Translational Research Operations Committee will develop policies and procedures for integrating the designated priorities, as appropriate, into Special Emphasis Panel review criteria and into funding decisions by program staff for the overall NCI translational research portfolio, including P50, U-series, P01, and R01 awards, as well as for stimulating the creation of new initiatives by program staff on specific priorities. The Operations Committee will also inform other standing committees, such as the Investigational Drug Steering Committee and the disease-specific Scientific Steering Committees, about the identified priorities, so that they can be incorporated, as appropriate, into their respective activities.

### ***Annual Report***

Following completion of its deliberations for that year, the Prioritization Working Group will issue a report covering the following topics:

- Description of the Working Group's activities
- List of prioritized opportunities, including rationale for selection
- Summary of other opportunities proposed but not selected for prioritization
- Summary of STRAP solicitations proposed.

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## Tailored Funding Programs

### Introduction

Funding programs tailored to the distinctive needs and characteristics of translational research are essential to advance promising concepts to the point of initial testing of a specific drug, biologic, device, procedure, or other intervention in the clinic or community. However, the major NCI funding mechanisms, especially R01s and P01s, are designed primarily to enable researchers to explore new ideas in fundamental science and pursue new lines of inquiry in response to their results. While ideal for discovery research, these mechanisms are not well matched to the goals of translation.

As a result, several targeted funding programs have been developed over the last several years, especially the P50 and various U-series programs, to address the translational research opportunities emerging from recent advances in cancer biology. The future vitality of translational research depends at least in part on continued refinement of these current programs to reflect evolving best practices in the management of translational research. Management best practices of particular importance include a project plan covering all the activities up to and including early-stage clinical trials, project milestones with associated dates and funding requirements, and development/commercialization strategies describing likely approaches for late-stage human testing and eventual commercialization.

In addition to refining existing programs, NCI's translational research portfolio should be augmented by two new programs that exemplify these best practices and address important translational opportunities not captured by existing efforts. For supporting emerging opportunities selected by the new prioritization process (see Coordinated Management Initiative A4), a new type of funding program is needed that can assemble an optimal mix of resources, investigators, and institutions to conduct a large, integrated, multidisciplinary effort to accomplish a prioritized translational goal. In addition, although NCI has several programs that encourage industry involvement, it would be advantageous to develop a new program that requires industry resource and cost sharing. Such a program would incentivize industry involvement in projects they would not take forward independently. And finally, it is important to integrate successful, milestone-driven early translational research projects seamlessly with NCI-funded development resources in order to prevent unnecessary delays in moving projects toward human testing.

To achieve the desired improvements in funding programs to facilitate and promote translational research, the TRWG proposes five initiatives.

- B1. Modify multiproject collaborative award guidelines, as appropriate, to facilitate early translational research.**
- B2. Improve processes and mechanisms for funding investigator-initiated early translational research.**
- B3. Establish a special translational research funding program to advance prioritized early translational research opportunities.**
- B4. Establish a funding program for early translational research that requires academic/industry collaboration involving resource sharing and/or co-funding.**
- B5. Integrate access to GMP/GLP manufacturing and other preclinical development services more effectively with milestone-driven early translational research projects.**



## Initiative B1: Modify multiproject collaborative award guidelines, as appropriate, to facilitate early translational research.

### Rationale

NCI has created a diverse portfolio of Program Announcement/Request for Application-directed translational research funding programs that support multiproject, collaborative awards. These include center/multiproject awards (P50 programs) and a variety of cooperative-agreement based programs (U01, U19, U24, and U54). In addition, using an RFA approach, NCI can establish P01 programs specifically focused on translational research. Because of the differing circumstances under which they were created and the different models on which they are based, these programs utilize a range of management practices, program guidelines, and review approaches.

Through its deliberations, the TRWG identified a number of management best practices that if uniformly incorporated into program guidelines for multiproject collaborative awards would facilitate translational progress. The purpose of these proposed modifications is not to homogenize all translational research programs or force them into a common model. Rather, the goal is to enhance productivity across the enterprise by consistently implementing best practices for management elements shared by all translational research programs, while maintaining the variation in research design and scientific approach that is essential to innovation and problem solving.

These common management elements include:

- Focus research projects on accomplishing specific milestones along the TRWG developmental pathways in order to move discoveries efficiently forward into human testing.
- Reward projects that have a defined development and commercialization strategy.
- Reward inter-institutional collaboration and network formation, including with industry.
- Incentivize participation by increasing budgetary authority and responsibility and rewarding success with greater funding stability.

To realize the goals of this initiative, the TRWG proposes the implementation plan described below.

### Implementation Plan

Guidelines for the Specialized Centers P50 programs (e.g., SPORE, ICMIC)<sup>8</sup> and cooperative agreement-based programs (e.g., Early Detection Research Network [EDRN], Network for Translational Research: Optical Imaging [NTROI], National Cooperative Drug Discovery Groups [NCDDGs])<sup>9</sup> will be reviewed and modified as described below. Since these are NCI-specific programs reviewed by NCI-chartered Special Emphasis Panels, they can be flexible in incorporating translational research principles into the design of their RFAs or PAs and their program guidelines.<sup>10</sup> Any new translational research-oriented, multiproject/collaborative programs, including RFA-directed P01 programs, will also incorporate these principles.

<sup>8</sup> The P50 center/multiproject awards fund several independent research projects and supporting cores, organized around a common theme such as an organ site. The center principal investigator coordinates the overall effort and has discretion to reallocate funds among projects and to terminate projects as necessary. Unlike cooperative agreement-funded networks, there is no formal program-wide governance structure or Steering Committee. Discretionary funds held at the program level are disbursed by the NCI program officer through a supplement process.

<sup>9</sup> Cooperative agreement programs such as EDRN and NTROI are structured such that each award acts as a component of a common research network. The network has a Steering Committee consisting of award principal investigators and NCI program officers that directs network-wide research activities and disburses funds held at the network level. Other cooperative agreement programs, such as NCDDG, fund multiple inter-related projects within each award but do not coordinate the awards.

<sup>10</sup> All guideline changes will be subject to NIH-wide review. P01 guideline changes, especially, may require NIH-wide input to ensure that modifications remain within the boundaries of the P01 program project concept.



The Translational Research Operations Committee, with support from the Translational Research Support Office, will review the guidelines of other U-series programs identified as “translational” but which contribute model systems (e.g., Mouse Models Consortium), core resources (e.g., Cooperative Human Tissue Network), or specific services (e.g., Phase I/II consortia) to determine which, if any, of the translational research principles delineated below should be incorporated into their program guidelines.<sup>11</sup>

### ***Incorporation of Milestones***

The guidelines for P50 and translational U-series programs, as well as RFA-directed translational P01 programs, will be modified to require the inclusion of milestones in proposed project plans. Milestones will be developed by the investigator on a project-specific basis, but will be based on the steps in the TRWG developmental pathways (see Appendix C for pathways).

For P50 programs, each individual research project will be required to propose a set of milestones to be achieved over the 5-year grant period. The milestones would set out the starting point of the project, the projected pathway steps that would be completed by the end of the 5-year funding period, and specific milestones that would be reached during the award period, including dates by which such milestones are expected to be achieved. The reasonableness of the proposed milestones in terms of charting efficient, timely, and yet realistic progress will be an important element in initial review of the application. Each research project proposed should have early human testing as the final milestone. However, not all projects will be able to meet that milestone in 5 years. Therefore, proposing a reasonable set of interim milestones with the goal of entering human testing in a subsequent grant period will be acceptable for certain projects.

Each project will be subject to rigorous formal review at the time of each projected milestone. In programs that are governed by a program-wide Steering Committee (e.g., EDRN, Centers of Cancer Nanotechnology Excellence [CCNE]), the milestone review will be performed by the Steering Committee. In programs where awards have external advisory groups (e.g., many SPOR awards, some P01 awards), these advisory bodies will participate in milestone review. Results of the milestone review will be used by the principal investigator to make a decision on continuation, modification, or termination of the specific project. When appropriate, milestone review will be integrated with review by the RAID, RAPID, or DCIDE programs (see Tailored Funding Programs Initiative B5). In addition, whenever projects reach the stage of Phase II clinical trial design, milestone reviews and design activities will be coordinated with the ongoing clinical trial prioritization efforts of any relevant disease-specific Scientific Steering Committees established as a result of the Clinical Trials Working Group Report implementation.

Annual progress reports will require an account of the status of proposed milestones. If for a given project a milestone has not been achieved by the projected date, the report will include an analysis of the problems encountered and a recommendation as to whether there should be continued efforts to reach the milestone or whether the project should be terminated.

Success in achieving the proposed milestones and effective action to terminate or modify projects that are not achieving their milestones will be key review criteria at the time of competitive renewal. Moving existing projects forward according to a milestone-based plan will be more important in competitive renewal than generation of data on which to base new, future projects. For network programs, progress in achieving milestones will be taken into account in evaluating individual awards within the network for renewal. For P50 and P01 awards, success in achieving milestones throughout the various research projects and acting to modify or terminate unsuccessful projects will be a critical element at the time of competitive renewal of the entire award.

### ***Development/Commercialization Strategies***

Because translational research projects are intended to result in drugs, biologics, devices, procedures, or other interventions that ultimately benefit patients, guidelines for translational research P50, U-series, and RFA-directed

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<sup>11</sup> Certain clinical research U-series programs (e.g., Phase I U01 trialists, American College of Radiology Imaging Network [ACRIN], the cooperative groups, and Community Clinical Oncology Programs [CCOPs]) are not intended to be covered by this initiative.

P01 programs will be modified, as necessary, to include a requirement to present a proposed development and commercialization strategy for each project proposed.<sup>12</sup> The strategy will describe not only the envisioned approach for proceeding along the relevant TRWG developmental pathway into early human testing but also an analysis of the requirements and potential options for later-stage human studies and eventual product commercialization and/or dissemination to the larger community.

If the ultimate goal is a commercial product, whether for testing, therapy, or prevention, the strategy will include a description of the optimal stage for industry handoff and potential commercialization partners. The strategy will also include a plan for protecting and licensing inventions and describe any license or material transfer agreements already in place. The strength and feasibility of the development strategy will be an important criterion in initial review, and progress toward establishing the relationships necessary to implement the strategy will be an important criterion in recompeting review. The NCDDG program already includes guidelines and review criteria for development plans that may serve as a starting point.

### ***Promotion of Collaborations***

SPORE guidelines currently encourage interinstitutional collaborations both with other SPOREs and with other NCI/NIH programs. This will be strengthened by making evidence of meaningful interinstitutional collaboration an important element in both initial and recompeting review. Comparable requirements for collaboration will be incorporated into all new and existing P50 and translational RFA-directed P01 programs. Because industry collaborations can be critical for the ultimate value of translational research for patients, guidelines will be modified to encourage industry collaborations and reward them in review. Such collaborations may include co-funding of projects, in-kind provision of materials or technical assistance, industry advisory roles, or handoff of projects reaching maturity. Industry collaborations will not, however, serve as a precondition for award or renewal.

Networks supported by cooperative agreements such as EDRN and NTROI currently incentivize and reward collaborations with other academic institutions and industry by providing collaborators with associate memberships and allocating network funds to facilitate collaborations. Collaborations with industry are explicitly incorporated into EDRN review criteria and encouraged by the NCDDG program. Similar incentives and rewards for interinstitutional and industry collaboration will be incorporated into the guidelines of all other new and existing U-series translational research programs.

NCI terms and conditions of award require sharing of research resources (e.g., research tools, cell lines, model systems), and plans to share resources are required and used in review for all P50, U-series, and RFA/PA-directed programs. However, given the importance of collaboration in translational research, guidelines will be modified to specify not only that plans are required, but also that sharing of resources during the award period will be an important criterion during recompeting review.

### ***Budgetary Flexibility***

Maximizing the benefit of milestone-driven project reviews will require that principal investigators and/or steering committees have the ability to reallocate or redirect funds when projects are completed or terminated early. This could involve providing additional funds to accelerate existing projects or providing funds for the startup of new projects. Such budgetary flexibility, which is already incorporated into SPORE awards and certain U-series network awards, will be expanded to all P50, RFA-directed P01, and U-series translational research programs. Effective use of this budgetary flexibility to keep the overall program on track despite events in individual projects will be an important review criterion for competing renewals. If ongoing peer review of these decisions is warranted, external advisory boards associated with the program should be charged with providing this service.

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<sup>12</sup> Commercialization plans will be tailored to the needs of the individual application. For example, if a set of projects combine to produce a single translational product, or if an individual project within a translational mechanism is not intended to produce a specific translational product, applicants will not be required to propose a development plan for each project.

### ***Review Panels***

P50, U-series, and RFA-directed P01 applications are reviewed by Special Emphasis Panels convened by NCI rather than through the NIH-wide Center for Scientific Review. For award programs focused on translational research, and in light of the proposed guideline changes discussed above, involvement by industry scientists, nonacademic health professionals, program managers at foundations funding cancer research, and patient advocates, in addition to academic translational researchers is especially important. As guideline changes are implemented, the rosters of these panels, including the P01 Discovery and Development Special Emphasis Panel, will be examined by the Division of Extramural Activities Research Programs Review Branch to determine whether additional reviewers may be needed. Should the evaluation identify potential gaps or limitations in roster membership, the Research Programs Review Branch will coordinate with the Translational Research Support Office and relevant program staff in identifying and recruiting additional members. As translational research programs become more collaborative—both among academic researchers and between academic and industry researchers—recruiting qualified reviewers free of conflict of interest may require a focused and proactive effort on the part of NCI.

### ***Rolling Review***

Once milestones have been incorporated into project plans as objective criteria for evaluating the success or productive failure of translational research programs, the Translational Research Operations Committee will, in consultation with the Division of Extramural Activities (DEA), consider whether a 3+3 rolling review system for selected awards is feasible and, if so, how it might be structured.<sup>13</sup> Such a review system would involve conducting a full program review (comparable to a competitive review) after 3 years of a 5-year award, with one of two results. If the award is going well and meeting most if not all of its project milestones, the award would be renewed for another 5 years with, again, a full program review after 3 years. If the award has experienced difficulty in meeting milestones and redirecting project funds, it would be subject to termination at the end of the remaining 2-year period unless significant positive progress were made.

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<sup>13</sup> Any such changes would be subject to NIH-wide review.

## **Initiative B2: Improve processes and mechanisms for funding investigator-initiated early translational research.**

### **Rationale**

The TRWG portfolio analysis found that more than half of the identified early translational research awards were funded through mechanisms designated for unsolicited, investigator-initiated research, predominantly R01s and P01s (see Appendix D). The programmatic guidelines for these mechanisms are set NIH-wide, and they were developed primarily for the support of discovery research. As a result, they do not incorporate important translational research concepts, including milestones, collaboration, development plans, etc. Moreover, although several oncology study sections have been recently established that are focused on translational research, there is still a perception that translationally oriented R01s and P01s fare worse in peer review than do discovery-oriented proposals.

Improvements in the process for review and funding of translationally oriented R01 and P01 applications, as distinct from discovery-oriented applications, are thus necessary to incentivize investigators to propose such projects by assuring that their applications will be judged by review criteria tailored to translational research. Such improvements will assist NIH in achieving the second component of its mission—“...application of (that) knowledge to extend healthy life and reduce the burdens of illness and disability”<sup>14</sup> and are especially important given the prominence of the Research Project Grant (RPG) pool in the overall NCI, and NIH, funding portfolio.

To realize the goals of this initiative, the TRWG proposes the implementation plan described below.

### **Implementation Plan**

#### ***Translational Research Study Section Analysis***

Recent efforts by the NIH Center for Scientific Review (CSR) and NCI resulted in creation of the Oncological Sciences Integrated Review Group, which includes six study sections specifically oriented toward translational research. To determine whether these new study sections are providing adequate and equitable review of translational research applications, the Translational Research Support Office will coordinate with the NCI DEA and CSR to conduct an analysis of current study sections. The analysis will have three components. The first is to examine whether there are any gaps in study section coverage for specific areas of translational research (e.g., immunotherapy, imaging, lifestyle). The second is to evaluate referral guidelines for the study sections and perceptions of study section members concerning whether they receive an appropriate portfolio of grants to review. The third is to examine membership on the study sections to identify any gaps in the translational research expertise represented.

If any gaps in study section coverage are identified, the Support Office will work with DEA and CSR staff to expand the mandate of existing study sections or suggest the creation of new study sections to fill those gaps. If deficiencies in study section operations are identified, the Support Office will coordinate with DEA and CSR to refine procedures and referral guidelines. Where there appear to be gaps in reviewer expertise, the Support Office will identify additional translational researchers qualified for service on study sections. As collaboration in translational research increases, Support Office staff will coordinate with CSR to develop strategies for identifying and recruiting qualified reviewers who are free of conflicts of interest. The Support Office will also work with CSR to encourage the involvement of patient advocates in study sections oriented toward translational research.

A related activity will be to work with the DEA Research Programs Review Branch to assess the review of translational P01s through NCI-chartered Special Emphasis Panels. This assessment will include: a) determining the effectiveness of the pilot single-tier P01 structure as applied to translational P01 applications; b) assessing the treatment of P01 applications identified as “translational” as they are assigned to the five standing panels (Molecular Biology; Cellular and

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14 National Institutes of Health: <http://www.nih.gov/about/index.html#mission.htm>.

Tissue Biology; Prevention, Control, and Population Sciences; Discovery and Development; and Clinical Studies); and c) identifying potential improvements to the P01 review process within the boundaries of the NCI-wide P01 guidelines.

### ***Exploration of Translational R-Series and P-Series Mechanisms***

NIH has a dual mission of scientific discovery and translational development to benefit human health. R01 and P01 mechanisms, which serve as the foundation of NIH's grant-based efforts to achieve these goals, are governed by NIH-wide guidelines that are not specific to the translational mission, nor to the needs of any individual Institute or Center. However, because the challenges of translational research are critically important to all NIH Institutes and Centers, NIH should evaluate whether its overall grant program properly incentivizes and supports translational research.

Because NCI's perspectives on translational research needs and opportunities may be shared by and useful to other Institutes and Centers, NCI will pursue an NIH-wide initiative to examine the value of creating distinctive R-series and P-series mechanisms for supporting unsolicited, investigator-initiated translational research. These mechanisms would incorporate characteristics desirable for translational research (e.g., milestone-based review, team-based science, project management, device/intervention development) and ensure that review of translational research proposals reflects these criteria.

Members of the Translational Research Operations Committee, with support of the Translational Research Support Office, will begin a dialogue with other NIH Institutes and Centers concerning the potential value of new R-series and P-series mechanisms focused on the needs of translational as opposed to discovery research. One opportunity would be to work with the NIH Office of the Director/Office of Portfolio Analysis and Strategic Initiatives to develop a Roadmap initiative.

### **Initiative B3: Establish a special translational research funding program to advance prioritized early translational research opportunities.**

#### **Rationale**

The primary objective of early translational research is to advance promising concepts either to initial testing in the clinic or population or to the point where results indicate that an alternate approach should be pursued. In many situations, existing funding programs, which advance knowledge incrementally by supporting portions of a developmental pathway, likely constitute an optimal use of resources. However, in certain instances, opportunities arise that are especially promising, both because of their apparent readiness for development from a scientific and technical perspective and because of their potential clinical and/or public health impact. The new translational research prioritization process proposed by the TRWG (see Coordinated Management Initiative A4) is intended to identify just such opportunities, especially those that are unlikely to be pursued by private industry because they may not be justifiable on business grounds. This is especially likely to be true of opportunities related to rare cancers, minority/underserved populations, immunotherapies, and lifestyle alterations.

While it might be possible to advance these prioritized opportunities through existing programs, progress along a specific developmental pathway is likely to be slow if different steps are supported via multiple, uncoordinated funding vehicles subject to separate peer review. Even under ideal circumstances, such fragmented funding will impose burdens of time, logistical complexity, and cost that can impede progress. Accordingly, NCI should develop an innovative funding program that is designed to advance certain prioritized early translational research opportunities efficiently along the appropriate TRWG developmental pathway in a coordinated and highly facilitated fashion.

To realize the goals of this initiative, the TRWG proposes the implementation plan described below.

#### **Implementation Plan**

##### **Overall Approach**

NCI will establish a new funding program entitled the Special Translational Research Acceleration Project (STRAP) program. This program will be designed to fund the advancement of specific opportunities, identified by the new translational research prioritization process, along one of the TRWG developmental pathways through early human testing of a specific drug, biologic, diagnostic/screening test, or other therapeutic, diagnostic, or preventive intervention. This program is not intended to develop new scientific knowledge, research methodologies, or infrastructure except when necessary for and linked to the development of specific products or interventions.

STRAP awards will support an integrated research and development program designed to achieve a specific clinical or product development goal. The initiation of a STRAP can occur at a variety of points at the beginning of, or early in, a TRWG developmental pathway. However, the project plan and proposed budget will extend through the end of the development pathway (i.e., to the point of early human testing) and encompass a substantial portion of the pathway. STRAP awards are intended to support a larger scope of integrated activity and have a higher degree of NCI-facilitation than would be feasible under any of the funding programs currently in existence.

The size and duration of a STRAP award will be determined on a project-specific basis, via negotiation between NCI and the principal investigators, in light of the needs of the particular research and development plan. It is understood that in certain cases, the goals of a STRAP may entail an effort lasting more than 5 years.

##### **Structure**

By definition, a STRAP award is intended to support a translational research opportunity that has been prioritized because of a combination of scientific credibility, technical feasibility, clinical or public health impact, and the likelihood that the opportunity will not be pursued by another funding agency (i.e., private industry, foundation, other governmental agency).



In many cases, the scientific credibility and technical feasibility of a concept will be based on the results of one or more existing research efforts along the relevant TRWG developmental pathway. In such situations, it may be appropriate for NCI to implement a STRAP by integrating existing awards and making new awards to cover the missing components of the developmental pathway.

In other situations, a substantially new scope of work may be optimal for achieving the objectives of a STRAP. Accordingly, the STRAP program will also provide for entirely new awards covering the entire developmental pathway for a concept just emerging from discovery research that is deemed sufficiently compelling and its development path conceptualized with sufficient clarity to justify a focused, prioritized development effort.

Because of the diverse requirements and multidisciplinary character of the developmental pathways, STRAP awards may use any or all of the following strategies whenever they will facilitate timely and efficient achievement of the goals of the STRAP:

- Participation of multiple, collaborating principal investigators, including investigators from the NCI intramural research program
- Collaboration of multiple academic institutions
- Collaboration with industry to access complementary human, infrastructure, and/or financial resources
- Contracts with the private sector for appropriate activities (standard analyses, manufacturing, etc.)
- Collaboration and coordination with existing foundation-supported efforts relevant to the goals of the STRAP.

### **Funding**

Approximately \$10 million will be allocated to new STRAP awards each year, up to a steady state of approximately \$50 million in annual funding after 5 years. If STRAP funding for certain projects can be assembled by integrating existing awards, this level of annual funding could be reduced or additional projects could be pursued. It is anticipated that funding for a complete STRAP would typically require \$5-10 million over a multiyear period averaging about \$2 million per year. However, funding for each STRAP will be determined by the specific needs of the approved development program, and funding for any particular STRAP may vary considerably from program averages.

Projects will generally be funded in annual increments based on the proposed budget, subject to successful achievement of agreed-upon milestones (see below). Upon a recognized need to terminate a STRAP due to the inability to reach the translational goal as determined by the milestone review group, investigators will be permitted, depending on the reason for milestone failure, to negotiate up to 75% of the current budget for 1 more year.<sup>15</sup> This will assist in promoting the stability of established translational research teams.

Industry or foundation co-funding will not be a requirement for a STRAP proposal. However, industry financial or in-kind support or foundation financial support that accelerates achievement of STRAP goals will be viewed favorably. Where appropriate, NCI will engage the assistance of the Foundation for NIH in identifying potential external collaborating funders for STRAP awards, and will assist STRAP principal investigators in negotiation of such support.

### **Solicitation and Award Process**

Topics for each year's STRAP solicitation will be determined through the new prioritization process (see Coordinated Management Initiative A4). A single solicitation will be issued, identifying the prioritized concepts for the year. The solicitation will be prepared by the Translational Research Support Office with the active involvement of Divisional program staff who have scientific expertise relevant to the prioritized concepts.

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<sup>15</sup> The TRWG recognizes that implementation of such a funding strategy may be complex and will require NIH-level review.



Awards will be made from a single pool of funds, rather than reserving specific funding for each prioritized concept. However, awards will not necessarily be limited to one per prioritized concept. Guidelines will allow for the funding of two or more awards for projects pursuing alternate approaches to the same early translational research goal if the competing proposals are equally meritorious. Conversely, issuance of the solicitation will not imply a commitment to fund proposals for every prioritized concept. Funding might not be granted if proposals responsive to a particular concept are judged not to be competitive with those for other concepts or if the required budgets are too large to fund projects for all solicited concepts.

For STRAPs that involve a complete, *de novo* program of activity, a cooperative agreement mechanism is likely to be most appropriate, although a contract mechanism could be used as well. For STRAPs that are constructed via integration of existing awards, a supplemental funding mechanism will be required to fill in the missing components of the developmental pathway, and procedures will be needed to integrate existing grants into a coordinated endeavor subject to the required milestone-based review and other appropriate requirements (see below).

STRAP proposals will be reviewed by a Special Emphasis Panel convened for review of proposals in response to a given solicitation. To ensure appropriate expertise for evaluation of the proposals, the panels will include members who are experienced in preclinical development and manufacturing, project management, and academic-industrial collaboration, in addition to encompassing scientific domains relevant to the prioritized concepts targeted by the solicitation. There will also be an extramural standing oversight committee to provide continuity and a broader perspective on overall program objectives. Once the reviews are complete, the Translational Research Operations Committee will recommend a set of awards to the Executive Committee for funding.

### **Management**

Each STRAP proposal will include a complete project plan, addressing activities through early-stage clinical or population trials. In addition to addressing the research and development activities to be conducted and the resources required, each project plan must include a well-developed management plan addressing the following: a) governance, organizational structure, and project management; b) approaches to communication and coordination; c) the process for making decisions on scientific direction, allocation of resources, publications, and intellectual property issues; and d) procedures for resolving conflicts. As described in Operational Effectiveness Initiative C1, NCI project management resources will also be available for STRAP awards and the projects will be highly facilitated by NCI staff.

Each STRAP award will be governed by a Steering Committee comprising the senior investigator from each component of the award and the Translational Research Support Office staff member serving as the STRAP program officer and project manager.<sup>16</sup> This Steering Committee will have oversight responsibility for the entire project including allocation of resources, participation in review of progress against milestones, and overall coordination of the project. Each STRAP project will also have an external advisory committee, composed of scientific, clinical, and product development experts relevant to the specific project, as well as a patient advocate with prior advisory experience within the NCI system. The advisory committee will participate in milestone reviews (see below) and ideally will include at least some members of the review panel that recommended the particular STRAP award.

### **Milestones**

Each STRAP proposal will include a specific set of development milestones, defined by reference to the relevant TRWG developmental pathway(s), including dates by which such milestones are expected to be achieved. The reasonableness of the proposed milestones for charting efficient, timely, yet realistic progress will be an important element in initial review of the application. Definitive milestones and dates will be established at the time of award through negotiation between NCI and the principal investigators.

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<sup>16</sup> Initially, Translational Research Support Office staff will serve as the official STRAP program officer and project manager, but with active involvement of a designated Divisional program staff member who has the relevant scientific expertise and experience to guide the specific project in question. As the STRAP program expands, it may be preferable to transfer the program officer/project manager responsibilities to relevant Divisional staff at the time of award.

A secondary objective of the STRAP program is to improve the likelihood that any failure of a development effort will be “productive” or “informative”; i.e., that knowledge gained will be of substantial value in focusing future research. In evaluating project proposals, NCI will take into account the degree to which such knowledge acquisition is built into the design of milestones.

Each STRAP award will be subject to ongoing informal monitoring by the Steering Committee, as well as a rigorous formal review by the Steering Committee and the external advisory committee at the time of each projected milestone. Ongoing informal monitoring will have several purposes, including to:

- Ensure that the perception of project progress on the part of both the principal investigator(s) and the responsible NCI project manager is consistent, accurate, and up-to-date.
- Ensure that problems are identified and addressed in a timely manner and that no major problem first becomes apparent at the time of a formal milestone review.
- Anticipate forthcoming formal milestone reviews and facilitate timely generation of needed documentary support.
- Enable formal milestone reviews to be moved forward whenever progress warrants.
- Anticipate foreseeable failures to reach milestones and develop contingency plans.

Formal milestone reviews involving the project Steering Committee and the external advisory committee will be used to make a recommendation to NCI on continuation, modification, or termination of the project. When appropriate, STRAP milestone review will be integrated with review by the RAID, RAPID, or DCIDE programs (see Tailored Funding Programs Initiative B5). In addition, whenever projects reach the point of Phase II clinical trial design, the STRAP Steering Committee will coordinate milestone reviews and design activities with the ongoing clinical trial prioritization efforts of any relevant disease-specific Scientific Steering Committee established as a result of the Clinical Trials Working Group Report implementation.

Annual STRAP reports will include a description of progress toward appropriate milestones. If progress toward a milestone is behind schedule, the report will include an analysis of the problems encountered and a recommendation as to whether there should be continued efforts to reach the milestone or whether the project should be modified or terminated. Such recommendations would be the result of Steering Committee and external advisory committee deliberations.

### ***Development/Commercialization Strategy***

Each STRAP proposal will include a proposed late-stage development and commercialization strategy. The strategy will describe the requirements and potential options for both later-stage human testing and eventual product commercialization and/or dissemination to the larger community. If the ultimate goal is a commercial product, whether for testing, therapy, or prevention, the strategy will include a description of the optimal stage for industry handoff and potential commercialization partners. The strategy will also include an intellectual property plan for protecting and licensing potential inventions and will describe any license or material transfer agreements already in place. The strength and feasibility of this late-stage development and commercialization strategy will be an important criterion in initial review of STRAP proposals.

### ***Investigator Credit for Participation***

Investigators who participate in STRAPs will be credited not only for successful handoff of a new product or intervention to late-stage trials, but also for conduct of STRAP activities in a way that maximizes the development of scientific insight and the timely recognition of development failure for projects that are not able to achieve the intended goal.

***Program Evaluation***

The Translational Research Support Office will develop a plan for evaluation of the STRAP program, including the identification of both process and outcome measures. Continuation of the program after the first 5 years will be subject to an evaluation of the effectiveness of its implementation and of preliminary evidence concerning translational impact. Continuation or expansion of the program after 10 years will be subject to an evaluation that addresses the impact and productivity of the program. As with all NCI programs, long-term continuation will be subject to external peer review and to weighing of priorities in light of needs, opportunities, and budget conditions.

## **Initiative B4: Establish a funding program for early translational research that requires academic/industry collaboration involving resource sharing and/or co-funding.**

### **Rationale**

Advancing most NCI-funded cancer discoveries into products of broad utility for patients or the community requires the eventual participation of industry. Therefore, NCI has developed several programs that encourage industry collaboration in the development of new agents, devices, and other interventions. However, NCI does not have a program specifically focused on joint industry/NCI funding of collaborative early translational research projects that integrate the complementary skills and expertise of academic institutions and pharmaceutical and biotechnology companies to pursue specific early-stage product development opportunities.

The Academic Public-Private Partnership Program (AP4), which was recently eliminated due to budget constraints, focused on assembling multidisciplinary teams involving academic research centers, pharmaceutical and biotechnology companies, nonprofit agencies, and government organizations. Each AP4 center was to develop a broad scope of research projects rather than pursue a single, focused project to achieve a specific product development goal. Similarly, although the Network for Translational Research: Optical Imaging (NTROI) program requires industry collaboration, it supports broad research programs rather than a targeted development effort. The Division of Cancer Treatment and Diagnosis funds investigator-initiated grants that support drug discovery, but this program does not focus on early-stage product development or handoff to industry. The Molecular Targeted Drug Discovery (MTDD) program provides funding to an academic research center or a small business for identification of new therapies, and the National Cooperative Drug Discovery Groups (NCDDGs) program funds research for discovery of new anticancer drugs. However, neither program requires collaboration between academic and industrial researchers. Finally, although the goal of the Centers of Cancer Nanotechnology Excellence (CCNE) program is the development of new therapies and industry collaboration is required, this program only funds nanotechnology research.

A new funding program that specifically requires academic/industry collaboration has the potential to speed the pace and productivity of early translational research in several ways. First, it will capitalize on the complementary strengths of industry and academia. Second, it will facilitate the transfer of academic early translational research successes to later-stage development by industry. Third, it will encourage industry to pursue promising opportunities that they would not undertake on their own, including projects focused on pediatric and rare cancers or minority/underserved populations. Finally, it will allow NCI to leverage industry funding to pursue opportunities that have a higher potential to be taken forward by industry.

Both industry and academia have demonstrated interest in the types of collaborative relationships envisioned by such a new program. This is evidenced by the success participants in the AP4 Planning Grant program experienced in structuring relationships with industrial partners and the establishment of similar state programs, such as the University of California Discovery Grant program, which funds collaborative relationships between University researchers and California-based companies.

To realize the goals of this initiative, the TRWG proposes the implementation plan described below.

### **Implementation Plan**

#### **Overall Approach**

NCI will establish a new program designed to fund investigator-initiated academic/industry collaborative early translational research projects via a U-series mechanism. The program will fund projects that advance a discovery or set of discoveries along one of the TRWG developmental pathways through early human testing of a specific drug, biologic, diagnostic/screening test, or other therapeutic diagnostic or preventative intervention. The program will be designed to encourage projects that focus on rare cancers, pediatric cancers, or issues involving minority/underserved populations that

are less likely to attract the interest and investment of industry without NCI involvement. This program is fundamentally different from the STRAP program (see Tailored Funding Programs Initiative B3) in that industry participation and co-funding are required, not optional, and because the projects are proposed by investigators rather than being driven by system-wide priorities, as is the case for STRAP awards.

The program will require active participation and co-funding by at least one industry partner. The Translational Research Support Office will work with NIH's Program on Public-Private Partnerships within the Office of the Director, as appropriate, in developing this initiative and will also work with the Office of Liaison Activities and the Foundation for NIH to investigate opportunities for joint funding by foundations for specific projects. The size and duration of the awards will be determined on a project-specific basis, via negotiation between NCI and the principal investigator(s), in light of the requirements of the specific project plan. Thus, a project could be funded for 6 months to pursue a very specific short-term goal or for 5 or more years to pursue a more complex, involved development plan.

### ***Industry Relations Working Group***

In order to lay the groundwork for negotiation of the joint funding arrangements underlying these new academic/industry collaboration awards, NCI will establish an Industry Relations Working Group under the auspices of the Advisory Committee and with logistical support from the Translational Research Support Office. The membership will be composed of 8-10 individuals from industry and NCI representing:

- A large biotechnology/pharmaceutical company
- A small biotechnology/pharmaceutical company
- Device development
- Imaging agent development
- Drug development
- Biologics development.

The Working Group will review past examples of interactions between NCI and industry, drawing from several use cases, such as intellectual property licensing, access to agents, and Cooperative Research and Development Agreements. The Working Group will be asked to report within 1 year on the findings and recommendations derived from its investigation, consultation, and consensus-building in the following areas:

- Actions NCI can take to improve NCI-industry interactions
- New approaches NCI can implement for NCI-industry interactions
- Actions NCI can take to eliminate barriers to effective NCI-industry interactions.

The findings of the Working Group will be shared, as appropriate, with NIH's Program on Public-Private Partnerships within the Office of the Director for dissemination in support of efforts to foster industry relationships across NIH.

### ***Funding***

Approximately \$5 million will be allocated to new academic/industry collaborations each year, up to a steady state of approximately \$25 million in annual funding after 5 years. It is anticipated that funding for a complete project (including both NCI and industry components) would require \$5-10 million over a multiyear period, averaging \$1-2 million per year. However, funding will vary with the nature and size of the project. For example, smaller, more narrowly focused projects could be funded for \$500,000 or less, while larger, more complex projects could be funded for more than \$10 million.

Project funding will be distributed in accordance with the milestones provided in the development plan (see below). Upon award, the research team will be provided with the funding required to meet the first milestone, plus additional funding to support 6 months of work following the milestone due date. This will ensure continued funding for the research while the milestone review is completed. If the milestone review is positive, funding will be provided for reaching the next milestone (plus the 6-month extension).<sup>17</sup>

### ***Solicitation and Award Process***

NCI will issue a Request for Applications with multiple annual submission dates, soliciting proposals for jointly funded academic/industry collaborative projects. Proposals will be reviewed by a Special Emphasis Panel composed of translational experts drawn approximately equally from industry and academia,<sup>18</sup> with additional input from the advocacy community. To ensure appropriate expertise for review and evaluation of these projects, the review panel will include members with expertise in project management, drug development, and intellectual property in addition to appropriate scientific expertise and academic or industrial experience.

### ***Management***

Each proposal will include a complete project plan, covering all activities through the projected handoff of the product, device, or intervention to further development by the industry partner. In addition to addressing the research and development activities to be conducted and the resources required, each project plan must also include a well-developed management plan addressing the following: a) governance, organizational structure, and project management; b) approaches to communication and coordination; c) the process for making decisions on scientific direction and allocation of resources; and d) procedures for resolving conflicts. As described in Operational Effectiveness Initiative C1, NCI project management resources will be available for these projects. A project manager may be one of the resources that the industrial partner contributes to the project.

Each project will be governed by a Steering Committee composed of the senior investigator from each component of the project (including industry investigator(s)) and the Translational Research Support Office staff member serving as the Program Officer and project manager.<sup>19</sup> The Steering Committee will have oversight responsibility for the entire project, including allocation of resources, review of progress against milestones, and overall coordination of the project. Each project will also have an external advisory committee, composed of scientific, clinical, and product development experts relevant to the specific project, drawn equally from industry and academia, as well as a patient advocate with prior advisory experience within the NCI system. The advisory committee will participate in milestone reviews (see below) and ideally will include at least some members of the review panel that recommended the award.

### ***Industry Participation***

Participation and cost-sharing in the research project by at least one company will be required. Multiple industrial partners will be permitted if there is a strong scientific or technical rationale. Industrial partners will generally be expected to fund 50% of the total direct project costs plus applicable indirect costs. Some or all of that funding can be in-kind provision of materials, services, or research work. A co-investigator from industry will be required, and the proposal will describe the nature of the interaction between the academic institution and the industrial partner, the time commitment of the industrial researcher(s), the nature of the work to be performed by industry, and the cost- or resource-sharing plan. Collaborations involving more than one academic partner will also be permitted but not required.

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17 The TRWG recognizes that implementing such a funding strategy may be complex and will require NIH-level review.

18 The TRWG recognizes that it may be challenging to recruit individuals from industry for these review panels due to potential conflicts of interest.

19 Initially, Translational Research Support Office staff will serve as the official program officer and project manager, but with active involvement of a designated Divisional program staff member who has the relevant scientific expertise and experience to guide the specific project in question. As the program expands, it may be preferable to transfer the program officer/project manager responsibilities to relevant Divisional staff at the time of award.



### ***Intellectual Property***

As part of the proposal development process, the industrial and academic collaborators will negotiate an intellectual property agreement, including publication and patent rights, that will be included with the proposal. A draft agreement will be required at the time of proposal submission, with the signed agreement required at the time of award.

As part of the intellectual property agreement, the industrial partner(s) will have a “right of first refusal” for any intellectual property developed under the project. However, if the industrial partner declines to further develop the technology or product, the academic investigators and NCI will have the right to pursue further development and negotiate licenses with other industrial partners. The intellectual property agreement will address compensation to the original industry partner if a product is successfully commercialized by such a follow-on partner.

### ***Milestones***

Each proposal must include a detailed timeline and development plan with appropriate milestones defined by reference to the relevant TRWG developmental pathway. The reasonableness of the proposed milestones for charting efficient, timely, and realistic progress will be an important element in initial review of the application. Definitive milestones and dates will be established at the time of award through negotiation between NCI and the principal investigator(s).

Each project will be subject to ongoing informal monitoring by the Steering Committee, as well as a rigorous formal review by the Steering Committee and the external advisory committee at the time of each projected milestone. Ongoing informal monitoring will:

- Ensure that the perception of project progress on the part of both the principal investigator(s) and the responsible NCI project manager is consistent, accurate, and up to date.
- Ensure that problems are identified and addressed in a timely manner and that no major problem first becomes apparent at the time of a formal milestone review.
- Anticipate forthcoming formal milestone reviews and facilitate timely generation of needed documentary support.
- Enable formal milestone reviews to be moved forward whenever progress warrants.
- Anticipate expected failures to reach milestones and develop contingency plans.

Annual reports will address progress toward appropriate milestones. If progress toward a milestone is behind schedule, the report will include an analysis of the problems encountered and a recommendation as to whether there should be continued efforts to reach the milestone or whether the project should be modified or terminated. Such recommendations would be the result of Steering Committee and external advisory committee deliberations.

### ***Milestone Review***

Formal milestone reviews involving the project Steering Committee and the external advisory committee will be used to make a final recommendation to NCI on continuation, modification, or termination of the project. If a milestone is achieved ahead of schedule, the review will occur when the milestone is achieved and funding can be accelerated.

Upon determination of the Steering Committee and the external advisory committee that a milestone has been met successfully, the next round of funding, sufficient to complete the next milestone plus 6 months of work, will be released to the research team. This funding process will continue until either a milestone has not been met or the project is completed. If the Steering Committee and the external advisory committee determine that the milestone has not been met, no additional funding will be released and the award will be terminated. The ongoing informal monitoring process should anticipate this situation and allow the investigators to plan for termination of the project.



***Program Evaluation***

The Translational Research Support Office will develop a plan for evaluation of the academic/industry collaboration funding program, including the identification of both process and outcome measures. Continuation of the program after the first 5 years will be subject to an evaluation of the effectiveness of its implementation and preliminary evidence concerning translational impact. Continuation or expansion of the program after 10 years will be subject to an evaluation that addresses the impact and productivity of the program. As with all NCI programs, long-term continuation will be subject to external peer review and weighing of priorities in light of needs, opportunities, and budget conditions.

## **Initiative B5: Integrate access to GMP/GLP manufacturing and other preclinical development services more effectively with milestone-driven early translational research projects.**

### **Rationale**

Availability of preclinical development services, especially manufacturing of clinical-grade materials, is perceived to be among the biggest bottlenecks in bringing discoveries from the laboratory to the clinic. Despite the success of NCI-funded manufacturing and preclinical development resource programs such as RAID, RAPID, and DCIDE, access to these development capabilities is still a rate-limiting step for translational research in general. Integrating access to these services with the new tailored translational research funding programs proposed by the TRWG will enhance the productivity of NCI investments in translational research and the development services required to bring products to the clinic. It will also ensure that development resources are readily available for high-priority, milestone-driven early translational research projects.

To realize the goals of this initiative, the TRWG proposes the implementation plan described below.

### **Implementation Plan**

#### **Overall Approach**

Currently, the review of translational research projects is not coordinated with the reviews conducted by NCI-supported preclinical development resource programs. An application for development resources requires a separate investigator-initiated application and review process that is independent of the review and approval of projects covering earlier steps in the translational pathway. This lack of integration is perceived by investigators to cause a significant additional delay for projects that have reached the stage where development services are needed.

Under the modified P50/U-series guidelines and the new STRAP funding program for prioritized projects (see Tailored Funding Programs Initiatives B1 and B3), all major translational research projects will be subject to objective, formal, milestone-based review. For these projects, access to the development capabilities represented by RAID, RAPID, and DCIDE will not occur via the standard application and review processes, although these processes will continue to be required for investigator-initiated projects not subject to milestone-based review. Rather, the review processes established by RAID, RAPID, and DCIDE will be integrated with the new translational research milestone-based review processes. Such an integrated review will ensure that when a project has achieved all of the required milestones and is ready for toxicology/pharmacology testing and clinical grade manufacturing, it will need to undergo only one coordinated review to move forward. This integrated review is not intended to affect or compete with the review and funding of traditional, investigator-initiated RAID, RAPID, and DCIDE applications.

#### **Integrated Review**

The integrated review process will be implemented as follows. When a successful translational research project is nearing the stage where preclinical development resources are needed, the relevant program officer will contact staff from either RAID, RAPID, or DCIDE, as appropriate, to organize a coordinated review. This coordinated review will involve the individuals and committees involved in the standard development resources review process as well as the external advisory committees, steering committees, principal investigators, project managers, program staff, etc., that were involved with previous milestone reviews for the translational research project in question.

For example, RAID now uses a two-tiered review process—an oversight committee and an initial review committee that is a subcommittee of the oversight committee. The initial review committee is composed of members of the oversight committee plus, if necessary, additional experts in the science and production technology relevant to the application in question. The oversight committee is composed of individuals from NCI, academia, and industry who have experience

in developing new anticancer agents.<sup>20</sup> The oversight committee recommends funding based on review of the applications given a sufficiently high priority score by the initial review committee. These recommendations are based on scientific merit, feasibility, practical development considerations, and NCI priorities. The oversight committee also conducts periodic reviews of funded projects to evaluate achievement of milestones and adherence to timelines as well as to decide on continuation.

For milestone-based translational research projects relevant to RAID, a RAID initial review committee will be involved in the coordinated review, and the RAID oversight committee will prioritize the recommended projects for funding. Thus, the new NCAB-approved RAID review process will constitute the integrated “back-end” of the new milestone-based “front-end” review process for these translational research projects.

The integrated review process will evaluate the following criteria:

- Scientific quality
- Importance of clinical need
- Fit with NCI-wide translational research priorities
- Strength and feasibility of the preclinical development plan, including appropriateness of milestones
- Strength and feasibility of the envisioned clinical development plan
- Projected cost of the development program
- Experience of the principal investigator and the institution in drug development, including Investigational New Drug Application (IND) submissions
- Strength of intellectual property protection and resolution of any intellectual property issues.

### ***Project Management***

As a translational research project proceeds through preclinical development, it will be overseen by the program and project management staff involved in earlier stages of the project (see Operational Effectiveness Initiative C1) and by project management and/or program staff from the relevant development resources program. The project will be reviewed at predetermined milestones by the same integrated process described above, with funding for each stage contingent on successful completion of the milestone.

### ***Funding***

Because the cost of manufacturing and other preclinical development services is substantial, funds for these services will not be included in specific translational research awards. Rather, each year, the Translational Research Operations Committee will recommend reserving a portion of the dedicated translational research budget in a set-aside pool of contract funds for preclinical development. These funds will be allocated by the Executive Committee based on recommendations from the Operations Committee concerning which projects, approved through the integrated review process described above, are the highest priority for use of these preclinical contract development funds. These recommendations will be based on available funds, fit with NCI-wide translational research priorities, estimated costs of completing development, and competing needs and opportunities across disease sites, TRWG pathways, patient populations, etc. As many projects will require more than 1 year to complete all preclinical work, some portion of the set-aside each year likely will be required to fulfill ongoing commitments. This contract funding will be in addition to current RAID, RAPID, and DCIDE funding for independent investigator-initiated projects. TRWG members believe this is a critically underresourced area of translational services. The new portfolio coding and coordinated translational

<sup>20</sup> Report of the Workshop to Review the National Cancer Institute’s Rapid Access to Intervention Development (RAID) Program, November 2005. Available at: <http://dtp.nci.nih.gov/docs/RAID/RAIDFinalReport061406.pdf>.

research management system is envisioned to make this more apparent and provide the system-wide credibility necessary to warrant increased investment.

### ***Involvement of Development Experts in Translational Research Review***

Development experts involved in the RAID, RAPID, and DCIDE review processes will be incorporated, as appropriate, in earlier stages of reviewing milestone-based translational research projects funded through the modified P50 and U-series programs and the new STRAP funding program. Involvement of drug, biologics, or imaging agent development experts earlier in the process will help ensure that projects are not advanced that have a high probability of encountering serious road blocks in toxicology, pharmacology, or manufacturing. Moreover, these experts can share lessons learned and best practices with investigators at the initial phases of a project to better inform the approach taken. This type of early involvement and collaboration will ensure that RAID, RAPID, and DCIDE program staff and external reviewers become more integrated with the overall translational research effort.

### ***Molecular Analysis Assay/Device Preclinical Development Resource Program***

The Translational Research Support Office will work with the Division of Cancer Treatment and Diagnosis and the Division of Cancer Prevention to evaluate the need for and potential benefits of an NCI development resources program to develop and validate biomarker molecular analysis assays and devices for use in NCI-supported projects. The evaluation will also address the technical and financial requirements of such a program and the potential that industry might license certain of the developed devices.

### ***Use of Industry Excess Capacity***

It may be possible to take advantage of excess capacity at pharmaceutical and biotechnology companies if the services are not available through NCI development programs. The Translational Research Support Office will investigate whether such excess capacity exists, for what services it exists, and the interest of industry in making these services available at a reasonable cost to NCI-funded academic researchers.

## Operational Effectiveness

### Introduction

In addition to improving management coordination across NCI and strengthening funding programs, the TRWG identified a number of specific opportunities to enhance the overall operational effectiveness of translational research.

One key improvement would be the availability of critical project management resources to assist large, multiproject, collaborative translational research programs in achieving their goals. Industry has long used formal project management approaches to facilitate their development programs by ensuring communication across project teams, efficiently identifying resources, coordinating transitions between developmental stages, and solving problems. Many of the more complex NCI-supported translational research programs would benefit from such facilitation.

A second critical area for improvement is in core services. Enhanced coordination across institutions and programs is needed to ensure that resources are not invested in duplicative infrastructures and that services operate in a cost-effective manner. In particular, increasing demand for high-quality, annotated biospecimens requires enhanced standardization, dedicated funding, and approaches for efficient and equitable sharing of available specimens.

Collaborations among NCI, academic institutions, industry, and foundations are fundamental to the success of translational research. Such collaborations should be promoted by streamlining legal negotiations and building partnerships that leverage complementary skills and resources. Finally, the need for a continuing flow of qualified translational researchers challenges the current system, which is designed primarily to train either laboratory scientists or clinicians. A critical evaluation of training programs and career incentives is needed to chart a clear education and career development path for translational research professionals and others engaged in multidisciplinary translational research teams.

To achieve this diverse set of objectives for improving the operational effectiveness of NCI-supported translational research, the TRWG proposes six initiatives.

- C1. Establish a formal project management system for early translational research.**
- C2. Establish a system to coordinate core services essential for early translational research.**
- C3. Enhance quality and accessibility of annotated biospecimen repositories and associated analytic methods.**
- C4. Develop enhanced approaches for negotiation of intellectual property agreements and agent access.**
- C5. Enhance interactions and collaborations with foundations and advocacy groups to advance early translational research.**
- C6. Enhance training and career incentives for early translational research.**

## **Initiative C1: Establish a formal project management system for early translational research.**

### **Rationale**

The multidisciplinary nature of translational research and the need to integrate sequential steps along complex developmental pathways warrants the provision of dedicated project management resources. Creation of a formal project management system at NCI, incorporating specific management competencies and clarifying responsibility for key functional roles, would speed the translational research process by addressing several important management tasks that are not consistently realized under current, informal arrangements.

These tasks include:

- Identifying and accessing specialized resources and expertise such as manufacturing capabilities and regulatory support
- Coordinating and communicating between the project scientific leads and the multidisciplinary project team to ensure that project plan modifications are implemented smoothly and that problems are identified and addressed in a timely fashion
- Coordinating the transition of projects across development stages, disciplines, and programs
- Ensuring efficient progress and adhering to a milestone-based project plan.

Project management has long been used by various industries, including pharmaceutical and biotechnology companies, to efficiently move research and development projects toward tangible products. In addition, several academic institutions have established project management positions to assist with their local translational research programs. Implementation of an NCI project management system would bring these benefits consistently to all major NCI-funded translational research programs.

To realize the goals of this initiative, the TRWG proposes the implementation plan described below.

### **Implementation Plan**

#### ***Scope of Projects Covered***

Project management resources will be provided for the following categories of translational research projects:

- Multiproject collaborative translational research awards (i.e., P50, U-series, and RFA-directed P01 awards)<sup>21</sup>
- Projects funded via the new STRAP program (see Tailored Funding Programs Initiative B3)
- Research projects funded via the new program that requires academic/industry collaboration (see Tailored Funding Programs Initiative B4)
- Phase I and II clinical trial contracts.

The project management system will be implemented by including project management in the guidelines for P50, U-series, and P01 awards as well as Phase I and Phase II clinical trial contracts and the new STRAP and academic/industry collaboration programs. These projects may also request and allocate funds to support the services of an institutionally based project manager.

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<sup>21</sup> Note that the project management system will only be required for P50 and RFA-directed P01 awards if guidelines can be modified to require the use of NCI project management resources. If modifying the guidelines to include this requirement is not possible, investigators for these awards will be strongly encouraged to utilize NCI project management resources for their projects.

## Overall Approach

The Translational Research Support Office will be responsible for ensuring that the project management functions described below are provided for all designated projects. For P50, P01, and U-series awards and Phase I and II clinical trial contracts, the proposed project management functions will be performed primarily by current program staff in conjunction with a new project management position within each appropriate Division, Center, or Office. These project managers will serve as a resource for program staff requiring guidance or assistance in fulfilling project management functions. The project managers will also work closely with the Translational Research Support Office project management staff in implementing and coordinating project management functions.

Project management will be implemented initially for P50, U-series, and RFA-directed P01 awards and Phase I and II clinical trial contracts as those guidelines will be revised before the initial STRAP and academic/industry collaboration awards are made. For the new STRAP and academic/industry collaboration awards, Support Office staff will serve as both program officers and project managers. The Support Office will also provide certain project management functions (e.g., overview and inventory of resources) for all applicable projects. Most importantly, Support Office staff will serve as the coordinating focus of responsibility for ensuring that the distributed project management system described above functions effectively. This will include coordinating the activities of project management staff in the Divisions, Centers, and Offices; communicating with the extramural community concerning the value provided by the NCI project management system; and communicating with NCI leadership concerning progress and any issues that may arise.

Following 2 years of implementation, the project management system will be evaluated. One aspect of the evaluation will be to determine if the distributed model, with most project management functions vested in the Divisions, Centers, and Offices, has been effective, or whether a more centralized model should be considered. If the conclusion is that project management has provided significant value, a decision will be made whether to expand the availability of NCI project management resources to include investigator-initiated R01s and P01s that primarily involve translational research as identified by the newly established translational research award codes (see Coordinated Management Initiative A3).

## Project Management Staffing

**Translational Research Support Office.** The Translational Research Support Office professional staff will include individuals with skills and experience relevant to project management (e.g., industry interaction, regulatory compliance, interaction with academic institutions). At least one Support Office senior professional will have a doctoral degree in a relevant scientific field, or equivalent experience, as well as direct project management experience, preferably within an industry environment. Additional staff with project management expertise will be added as project demands grow. Cross-training will be provided so that other Support Office staff members have skills in certain aspects of project management.

**Divisions/Centers/Offices.** At least one project management position will be established within each Division, Center, and Office to assist program staff in providing project management services. These project managers will have direct project management experience, preferably within an industry environment, and will work closely with Translational Research Support Office staff to ensure development and operation of a coordinated, well-functioning project management system. To drive successful implementation of project management responsibilities by program staff, such responsibilities, including coordination with the Translational Research Support Office, will be included in their performance plans.

## Project Management Roles and Responsibilities

**System-Wide Roles and Responsibilities.** Translational Research Support Office staff will be responsible for coordinating the formal project management system and directly providing the following project management functions for all applicable translational research projects.

1. **Cross-NCI Coordination and Communication.** The Support Office will maintain an overview and inventory of translational research projects across all NCI organizational units and programs and facilitate coordination between programs where increased synergy and/or decreased redundancy could be realized. In addition, the Support Office



will arrange regular forums with project management and program staff from the relevant Divisions, Centers, and Offices to discuss programmatic project management needs. Support Office staff will also interact with extramural investigators and institutionally based project managers to discuss project management needs.

2. Resource Inventory and Database. The Support Office will maintain an inventory and database of the following resources, often needed by translational research projects, which are currently available across NCI, academic institutions, and industry:

- High-throughput screening
- Biospecimen repositories
- Research tools (e.g., cell lines, animal models)
- Biomarker assay systems
- Imaging capabilities
- Agents, devices, or other materials/information from industry
- Development capabilities, including manufacturing, toxicology, and pharmacology
- Biostatistical analysis services
- Patient populations.

Support Office staff will coordinate assembly of the inventory and work with the NCI Center for Bioinformatics (NCICB) to design and build the database. This database will be an expansion of the NCI-supported core services database developed as part of Operational Effectiveness Initiative C2. Program staff and project managers will use this inventory to direct investigators to needed resources. This inventory also will be available to investigators preparing proposals in response to translational research solicitations to assist them with developing fully responsive proposals.

3. Oversight Role. Support Office staff will be available for consultation with principal investigators who have concerns regarding project management functions provided by program staff.

**Project-Specific Roles and Responsibilities.** Program staff will be responsible for providing project-specific project management functions for the applicable P50, P01, and U-series awards and Phase I and II clinical trial contracts in consultation with their unit project management staff. For the STRAP and academic/industry collaboration awards, these functions will be provided by Translational Research Support Office staff, who will serve as program officers and project managers for those awards.

1. Resource Identification. Program officers will work proactively with principal investigators to identify resources needed at each stage of a translational research project. This includes facilitating contacts and collaborations through which principal investigators can obtain access to resources such as those listed in the Translational Research Support Office database.
2. Regulatory Filings. Program officers will assist with regulatory filings, as necessary, working with principal investigators and other NCI program staff. Any Investigational New Drug (IND) applications will be prepared in cooperation with the Regulatory Affairs Liaison from the Cancer Therapy Evaluation Program and other relevant intramural or extramural parties.
3. Coordination and Communication. Program officers will assist principal investigators in ensuring consistent and meaningful communication among all members of a multidisciplinary, multiproject translational research team. This will include organizing regular meetings for discussion and planning, identifying points of communication breakdown, and coordinating the transfer of project tasks between groups that may be from different institutions.

4. **Monitoring Progress and Problem Solving.** Program officers will work with principal investigators to monitor continued progress of translational research projects according to established project milestones (see the sections on milestones within the Tailored Funding Programs Initiatives B1, B3, and B4) and to assist with solving any problems that arise. They will organize appropriate milestone-based reviews and provide input to the steering or external advisory committees that are charged with deciding whether a project should be continued, modified, or terminated.
5. **Collaboration with Institutionally Based Project Managers.** Program officers will collaborate with institutionally based project managers (see below), as needed, to facilitate the research program. This may include coordination concerning which project management functions will be fulfilled by each project manager and assisting in solving day-to-day management issues for the project.

### ***Institutionally Based Project Managers***

Although the NCI project management system will provide valuable assistance for major long-term management issues, large, complex projects often encounter day-to-day issues that require more local project management support. Translational Research Support Office staff and program officers will focus on broader, global issues related to a project, while institutionally based project managers will focus on narrower, local issues.

The guidelines for STRAP and academic/industry collaboration awards will require an institutionally based project management plan and allow awardees to request funding for project management support. The guidelines for multiproject collaborative P50, P01, and U-series translational research awards as well as Phase I and II clinical trial contracts will be modified to encourage onsite project management and allow for funding of institutionally based project managers.

It is not anticipated that each translational research project or award will have a dedicated internal project manager. Rather, individual institutionally based project managers might provide support for several different projects, with each award contributing funds to support the position. One option would be for cancer centers to establish a project management core resource that would serve and be additionally supported through charge-backs from the centers' various STRAP, academic/industry collaboration, P50, P01, and U-series translational awards as well as Phase I and II clinical trial contracts.

The exact roles and responsibilities of an institutionally based project manager will be determined by the principal investigator and specified in the funding application. However, the following provides a general overview of the types of functions that institutionally based project managers may be assigned:

- Prioritize team activities and make recommendations on appropriate courses of action in response to project results.
- Coordinate with the principal investigator and NCI staff on the allocation of resources in the most effective fashion, given current priorities and timelines.
- Facilitate access to institutional and/or regional core services to meet project needs.
- Develop implementation plans, timelines, and budgets.
- Ensure timely contributions by all team members.
- Conduct regular team meetings and ensure that action items are executed.
- Identify potential bottlenecks and work with all team members, the principal investigator, and NCI staff to resolve impediments.
- Prepare non-IND regulatory filings.
- Prepare progress reports as needed.

### ***Project Management Training***

Formal training in project management is crucial to ensure that project managers have the requisite skills. Therefore, Support Office staff and any NCI program officers with project management responsibilities will be provided with formal training. Project management training for institutionally based project managers will be an allowable cost for the award.

Several project management training programs exist, including within business schools, professional associations, and private organizations. The Translational Research Support Office will conduct an analysis of currently available project management training programs to determine if they will provide the skills and training needed for management of academic translational research projects. If existing programs are determined to be inadequate, Support Office staff will work with providers to tailor programs to meet NCI translational research needs.

## Initiative C2: Establish a system to coordinate core services essential for early translational research.

### Rationale

NCI has long recognized the value of consolidated centers that provide critical infrastructure support, including core services, as demonstrated by the establishment of cancer centers beginning in 1961. The Clinical and Translational Science Awards (CTSA) program recently established as part of the NIH Roadmap has similar objectives. The new CTSA program, together with the development over the past several years of several other NCI programs that support core services, provide the potential of creating independent, perhaps redundant, core services infrastructures. This has led to concern among the cancer research community that core services supporting translational research need to be more effectively coordinated, with capacity well matched to need.

Developing a more efficient and coordinated core services network will facilitate and accelerate access to a broad range of services and ensure that services are available in a coordinated and cooperative manner across funding programs. It may also minimize redundancies, ensure efficiency and economy of scale by operating services at optimal capacity, and increase standardization, quality assurance, and cross-core reliability.

To realize the goals of this initiative, the TRWG proposes the implementation plan described below.

### Implementation Plan

#### *Analysis of Existing Core Services*

The Translational Research Support Office, with assistance from other NCI and contractor staff as necessary, will analyze NCI-funded intramural and extramural core services with the goal of identifying possible functional redundancies. This analysis will require an investigation of funded core awards (i.e., facilities, equipment, infrastructure, staff time, supplies) to distinguish between totally independent cores for the same service at a single institution versus cores that utilize the same core facility and equipment and simply provide incremental funding for staff time, supplies, specific services, etc.

**Identification of Existing Core Services.** During the TRWG portfolio analysis, a preliminary list of 1,364 core awards was generated that includes Cancer Centers (P30s), Specialized Programs of Research Excellence, and P01s by institution. As no database currently exists that maintains the information for all extramural cores, this list was assembled from data provided directly by the Cancer Centers program, the identification of cores on the Computer Retrieval of Information on Scientific Projects (CRISP) database, and by searching the SPORE Web site or individual abstracts on the CRISP database. All P30 cores are included on this list, but the cores listed for SPORE and P01 awards have not been verified and might not be complete. In addition, cores funded through U-series programs, R24 awards, etc., are not included. This preliminary list of P30, P50, and P01 core service awards includes 93 U.S. institutions with the majority (55%) funded through Cancer Center grants, followed by SPORE (27%) and P01 (18%) grants.

In order to develop a comprehensive list of all translational research core services, this initial list will be expanded to include all SPORE and P01 cores, cores located at the intramural Center for Cancer Research, and any cores associated with U-series awards, CTSA awards, etc. Grant applications and progress reports for all SPORE and translational<sup>22</sup> P01 awards not included in the current list and all translational U-series awards will be analyzed to identify funded cores and determine whether the core funds support self-contained services or are used to procure services from an already existing core facility. This information will be used to assemble a comprehensive list of all NCI-funded translational research core services.

**Analysis for Redundancies.** The comprehensive list of funded cores will be reviewed to identify potential redundancies at individual institutions. Based on the list of cores prepared as part of the TRWG portfolio analysis, it appears that “redundancies by title” (i.e., more than one core of a single type at an institution) exist primarily for biostatistics/bioinformatics, clinical trials, and tissue cores. However, because “redundancy by title” does not necessarily equate to

<sup>22</sup> P01 awards categorized as translational for this analysis will be those identified in the original TRWG portfolio analysis.

actual redundancy, a functional assessment is required to determine the nature of the overlap. For example, although biospecimen cores may have certain aspects that are unique to the organ site or study, other aspects such as administration, IT support, equipment, etc., might be appropriately consolidated.

The functional assessment will involve analyzing grant applications and the most recent progress reports for those cores at an institution that appear to be redundant according to title. Based on the existing list of 1,364 cores, there are 733 (54%) that are redundant by title. The goal of the analysis is to determine if these cores are functionally redundant or whether they utilize a common core infrastructure. If possible, this analysis will also include core services funded in whole or in part by the host institution.

### ***Consolidation of Core Services***

If the redundancy analysis identifies institutions where there is true duplication of one or more significant core service infrastructures, a plan for consolidation will be developed, including an analysis of any financial impact from the proposed consolidation. For institutions with cancer centers, consolidation will be achieved by strengthening the role of cancer centers as the primary providers of core services. For institutions without cancer centers, individual awardees will be expected primarily to use existing institutional services or those of neighboring institutions. Consolidation will be promoted by adjusting review criteria to reward collaboration and resource sharing in core services. As grants come up for renewal, consolidation will be implemented according to the plan developed for that institution.

Guidelines for Cancer Center and P50, U-series, and RFA-directed P01 awards will be revised as necessary to incorporate the following principles for core services resource sharing.

1. Cancer centers will provide the core services infrastructure for key translational research resources at institutions with cancer centers.
2. Individual P50, U-series, P01, and other relevant awards will request funds either to access cancer center or other institutional core services or for materials/salary support for project staff to use those services.
3. New translational research Requests for Applications and Program Announcements will specify use of cancer center or other institutional core services.
4. If applicants consider required core services nonexistent or unavailable at their cancer center or institution, they must present a list of the relevant core services that do exist and a specific rationale for creation of the proposed new cores.
5. If a service is not available at an investigator's home institution, a preferred option will be to provide funds to use the services of a neighboring institution.
6. No award will mandate the creation of a separate core service if an appropriate core service is locally available at cancer centers, the home institution, or the NCI intramural program.

Guidelines will be changed to formally reward sharing of core services and facilities. While cancer center and SPORÉ guidelines already specify that core resources and facilities should be shared, additional incentives in the review process are needed to encourage efficiency. Cancer center guidelines will be modified to provide formal recognition during the grant renewal process for core facilities that provide services to investigators or projects funded by other programs or institutions.

### ***Comprehensive, Publicly Accessible Core Services Database***

A database will be created containing regularly updated information on all NCI-funded core services. The database will initially focus on key NCI-funded translational research core services, but could be expanded to include core services funded by CTSAAs, other NIH Institutes, academic institutions, and industry. Two components of the database will be necessary: 1) a restricted portion that will be used by NCI reviewers and program officers, and 2) a public portion that

will be open to the research community. Such a database will serve as a useful tool for NCI program staff when they are determining whether or not to fund a new core service at an institution.

Database development will be the responsibility of the NCI Center for Bioinformatics, working in coordination with Translational Research Support Office staff, NCI program staff, and extramural investigators and will be implemented in accordance with the caBIG™ design principles and standards. This database will serve as a foundation for the expanded resource database developed in support of the project management system (see Operational Effectiveness Initiative C1).

**Potential Data Fields.** NCICB and Translational Research Support Office staff will work with NCI program officers and representatives from both the intramural and extramural research communities to define the important data fields to collect. Potential fields include:

- Type of service
- Specific capabilities
- Available equipment
- Number of users
- Number of projects supported
- Number of studies, analyses, etc., performed
- Number of samples processed
- Percent of capacity currently in use
- Core service costs
- Average turnaround time
- Other funding sources for the facility.

The database is ultimately intended to raise standards and encourage best practices. Therefore, incorporation of a user rating feature (e.g., a rating scale and comments section) will be considered.

**Reporting System and Data Submission.** Reporting and updating information in the database will become a routine obligation of all NCI awards that support an independent core services facility, regardless of funding program. Data will be collected and managed on a core-by-core basis and the database will retain a cumulative record of activity. At institutions where cancer centers exist, information on all core services will be held and maintained centrally and reported by the cancer center.

**Design Principles.** Core service principal investigators will submit a standardized electronic file containing specific data on their core services that will serve as the building blocks for an online database. This online database will then be available to NCI staff and investigators through a unified, Web-based interface or portal that shields the user from the mechanics of the underlying system. The system will be designed such that investigators can update their core services data on an as-needed basis. Controlled access will be granted through appropriate specialized interfaces to all other users for authorized purposes.

**Database Functionality.** The database will provide the following standard functions.

1. Searches. The database will be equipped with software tools that allow searches on any field or combination of fields, using keywords or combinations of keywords. Searching will be facilitated with predefined menus of keyword options (e.g., type of service, geographic location of participating centers).



2. Reporting. Both interactive and batch-mode reporting will be supported, and predefined report templates will be available for common search requests.
3. Access Controls. Access privileges will be defined to address the diverse needs of database users. Two user categories are envisioned:
  - Extramural investigators from both academia and industry will have access to fundamental information such as location of cores, services offered, capacity, cost of service, contact information, etc.
  - NCI program staff will have access to all data in the system, including raw data that might be useful for review (e.g., number of users of the core, other funding for the service), as well data accessible to extramural investigators

### **Regional Centers of Excellence**

**Overall Approach.** As core services are streamlined and consolidated, regional centers will be established for highly technical, service-based, equipment- or expertise-intensive core services that cannot be as efficiently operated if located at every cancer center or other research institution. The research world is already evolving towards the concept of regional or national centers of excellence. The Human Genome Sequencing Centers are an example of national cores, which are selected by an advisory committee.

The Advisory Committee will convene a Working Group of NCI program staff and extramural investigators to identify a list of core services that are candidates for regionalization. Core services that would potentially benefit from creation of regional centers or networks include:

- GMP/GLP manufacturing
- Mass spectrometry
- State-of-the-art proteomics
- High-throughput genomics/SNP analysis
- Image archiving and/or analysis.

**Identifying and Selecting Regional Centers.** Once the core services appropriate for regionalization have been identified, NCI will determine if appropriate regional centers already exist for the identified services or whether new or expanded centers are required. If new or expanded centers are required, NCI will issue an RFA soliciting proposals for establishment of such centers. The RFA will stipulate the scope and quality of service to be provided, the projected usage, etc. Successful applicants will receive funding for the core infrastructure and a baseline level of service activity. The cores will be designed to expand in response to incremental funding from users. Regional centers likely will be based at cancer centers, though this should not be a limiting requirement in the RFA.

The transition to regional centers need not be a drastic change from the status quo and should not require the creation of new facilities. Rather, once centers are established, grants requiring the service will be funded for using the service. In general, individual institutions will not be funded for providing a core service available from a regional center.

**Oversight and Management.** Regional core service centers must have a management plan to ensure adequate access by investigators from other institutions and appropriate standardization and quality control. In order to ensure quality, efficiency, and accessibility, Translational Research Support Office staff will be involved with oversight of the regional centers.

**Standardization and Quality Assurance.** Regional core service centers will establish standardized processes, quality control, etc., to ensure comparability of data and high-quality outputs. Translational Research Support Office staff will work with extramural researchers to determine which services need to be standardized or certified to ensure comparability



between institutions. Oversight and certification processes will be established by the Support Office in coordination with the regional center principal investigators to ensure that core services and facilities maintain state-of-the-art equipment, procedures, etc.

### **Initiative C3: Enhance quality and accessibility of annotated biospecimen repositories and associated analytic methods.**

#### **Rationale**

Continuing advances in genomic and proteomic technologies are driving an increased demand by the translational research community for standardized, high-quality, clinically annotated human biospecimens. However, biospecimen resources of sufficient quality to meet the technical requirements of these new analytic tools fall far short of the demand. This shortage of annotated biospecimens—collected, processed, transported, stored, and analyzed using standard operating procedures—is a key barrier to translational research. Three other translational research barriers associated with biospecimens have also been identified. The first barrier is the absence of standardized analytic methods that can obtain consistent, standardized data from biospecimens regardless of the collection technique. The second barrier is the low-level representation in current repositories of specimens from minority populations. The third barrier is the low-level representation of precancerous specimens which are essential for effective translational research focused on prevention. An enhanced system of biospecimen repositories and analytic methods would improve standardization, quality assurance, and reliability, while minimizing access barriers and strengthening the comprehensive nature of this key translational research resource.

To realize the goals of this initiative, the TRWG proposes the implementation plan described below.

#### **Implementation Plan**

Enhancing the quality and accessibility of annotated biospecimens for use in translational research will require a two-pronged approach. The first is to expand the number of fully annotated biospecimens collected, processed, transported, and stored using standardized operating procedures. However, since such procedures will only be appropriate for use in major academic medical centers, this will limit the total number of specimens available for research. Therefore, a parallel approach will be to increase the overall number of biospecimens, especially those from minority populations, by encouraging smaller centers and nonacademic hospitals—especially those that are part of the New Community Cancer Centers Program (NCCCP)—to collect and fully annotate biospecimens under carefully controlled, but not uniformly standardized, procedures. These specimens can then be used for studies examining research questions that do not necessitate a high degree of standardization and with standardized analytic tools that give consistent results with tissues obtained under variable conditions.

#### ***Reinforce Ongoing Standardization Efforts***

The NCI Office of Biorepositories and Biospecimen Research (OBBR) was established in 2005 to address the key barriers in biospecimen collection, standardization, and storage. OBBR is currently working to develop and implement standards that will enable a national cancer biospecimen resource infrastructure and promote specimen and data sharing to facilitate multi-institutional, high-throughput genomic and proteomic studies. To this end, OBBR has proposed First Generation Biorepository Guidelines (FGGs) to harmonize policies and procedures for NCI-supported biospecimen resources, including clinical and epidemiological annotation and patient privacy aspects.<sup>23</sup> The TRWG strongly endorses these OBBR activities and proposes the following additional approaches to further enhance their mission.

#### ***Modification of Guidelines***

Guidelines for cancer centers, SPOREs, cooperative groups, and other large NCI-specific programs that involve biospecimen collection will be revised as necessary to incorporate use of the FGGs as they are finalized. Prospectively, recipients of these awards will be required to adhere to standardized collection, storage, retrieval, and dissemination procedures to promote consistency and comparability of derived data between institutions. Standardization will not pertain solely to tumor tissue, but also to normal and premalignant tissues, as well as ancillary specimens. Review criteria for

<sup>23</sup> First Generation Guidelines for NCI-Supported Biorepositories, April 2006. Available at: [http://biospecimens.cancer.gov/biorepositories/guidelines\\_full\\_formatted.asp](http://biospecimens.cancer.gov/biorepositories/guidelines_full_formatted.asp).

cancer centers, SPOREs, and other NCI-specific programs will be modified to formally reward standardized collection of biospecimens.

Such modifications will dictate a cultural shift from an investigator-centric to a collaborative approach to biospecimens. Cooperation and buy-in will be required from Institutional Review Boards (IRBs) and informatics groups. Selected NCI programs (e.g., the Cancer Genome Atlas Biospecimen Core Resource, the Clinical Proteomic Technology Assessment for Cancer Initiative, the NCCCP) have already incorporated the FGGs into recent RFAs and RFPs and can be used as models for guideline revision.

### ***Funding for Biospecimen Collection***

Until the real expense of standardized biospecimen collection and storage is funded as a separate cost, such standardized collection will never become widespread. In the past, pathology departments collected tissues without being paid to do so, but many institutions will no longer allow this practice. Furthermore, even when an institution is reimbursed for specimen collection, the funds are not always allocated to the pathologists responsible for the tissues, resulting in an unwillingness to cooperate.

Funding for biospecimen collection related to clinical trials should be provided up front as a portion of the trial cost when tissue procurement is a specific component of the protocol. Guidelines will be modified to formally recognize the importance of funding standardized specimen collection and storage. This funding will be separable from the lump sum of the grant so that the pathology group receives the support directly. One possibility is to consider a “tethered” funding model that gives credit to multiple principal investigators and allows funds to be divided as needed. Funding will be contingent on biospecimen collection and storage being conducted in accordance with the FGGs.

### ***Informed Consent***

In order to facilitate collection of a wide variety of samples, enable continued collection of data for sample annotation (e.g., epidemiologic and outcomes data) beyond the date of the sample collection, and authorize biospecimen testing not anticipated at time of collection, a standard, national informed consent template is needed. The template must be compliant with the Health Information Portability and Accountability Act and the Office of Human Research Protections regulations. Additionally, because IRBs tend to modify most consent forms to accommodate local issues, it will be advantageous to develop a common template that can be plugged into the consent forms used by any institution.

Several informed consent templates for the future use of tissues have been developed and are currently used in cooperative groups and cancer centers. A new informed consent template has also been proposed under the FGGs. The Biorepository Coordinating Committee (BCC) is currently working to harmonize these forms to establish a standardized template. Guidelines for cancer centers, SPOREs, cooperative groups, etc., will be revised to require use of the standardized template, once developed. The Translational Research Support Office staff will assist OBBR and the BCC with these efforts. Obtaining widespread acceptance may require organizing expert workshops including bioethicists, patient advocates, patients, government representatives, academic and nonacademic health professionals, industry representatives, and other leaders in the cancer research community.

### ***National Biospecimen Repository Network***

There have been efforts in the past to develop an integrated network of biospecimen repositories served by a common informatics infrastructure and a common access portal. For example, OBBR developed and piloted a National Biospecimen Network Blueprint (NBN) concept<sup>24</sup> which outlines an approach for creating a public-private partnership to establish a national resource of standardized, privacy-protected, high-quality biospecimens for genomic- and proteomic-based research. Use of the standardized procedures required for the NBN concept was piloted in a series of Prostate Cancer SPOREs. However, the pilot proved difficult to implement due to the challenges of multi-institutional standardization and biospecimen sharing. The NBN concept may now be pursued in the context of the NCCCP.

24 <http://biospecimens.cancer.gov/nbn/blueprint.asp>.

Additional efforts to implement the NBN concept are warranted. The Translational Research Support Office will work with OBBR to develop new approaches for implementing such a national virtual network potentially including specimens collected under both standardized and institution-specific procedures and with an increased focus on the inclusion of specimens from minority populations and specimens from precancerous tissues. The goal is for the network to link numerous repositories containing properly annotated biospecimens, including lifestyle and epidemiologic information where possible. If such a network is realized, program guidelines will be modified to require that biospecimens collected in conjunction with NCI-funded clinical trials be properly annotated and made available as part of the network.

**Comprehensive Database.** A database of all relevant repositories will be critical to the success of a biospecimen network. Previous analyses of the NCI biospecimen resource portfolio indicated that NCI supports hundreds of biospecimen-related activities. Building on the existing Specimen Resource Locator,<sup>25</sup> OBBR is already exploring the possibility of creating a Web-based catalogue to provide the extramural community with information on existing biospecimen collections. This catalogue could be a starting point for the database.

**Specimen Access.** Once the database is created, individuals seeking access to the specimens will submit an application that clearly explains the number of specimens needed, the amount required, and the purpose of the study. Applications will be reviewed and access granted based on merit. OBBR will be responsible for developing and managing a transparent, fair, and scientifically based process for prioritizing access to the biospecimens.

**Industry Collaboration.** Because a national biospecimen repository network will be expensive to build and maintain, a government-industry consortium model will be explored. The Translational Research Support Office and OBBR will explore with the Foundation for NIH the potential of establishing a consortium of industry partners who would support the network through charitable donations. The Support Office will draw on the resources of NIH's Program on Public-Private Partnerships within the Office of the Director in support of establishing such a consortium.

The industry partners in the consortium would have the ability to apply for access to the specimens. They would not receive prioritized access, but would have the same ability as any academic researcher to apply and compete based on importance of the research project proposed. Companies that are not members of the consortium could also apply for access to the specimens, but would be charged more for those specimens than would consortium members.

In order to successfully develop such a consortium, a convincing case must be presented to potential partners establishing the advantages they would receive from participation. To support such a case, all specimens will need to have a minimum annotation data set that is attractive to industry and a fair prioritization process must be developed to regulate access to the limited tissue resources.

There are some public/private partnerships already in existence that might serve as models for such a consortium. For example, the International Genomics Consortium (IGC) has a project called the Expression Project for Oncology (expO) that aims to build on the technologies and outcomes of the Human Genome Project to accelerate improved clinical management of cancer patients. This consortium facilitates partnerships between academic institutions and pharmaceutical companies and has led to the development of a standardized method of tumor tissue collection that is being used for expression profiling.<sup>26</sup>

### **Standardized Analytic Methods**

While the standardization of biospecimen collection and processing is one approach to obtaining high-quality genomic and proteomic data from human biospecimens, it does not address all facets of the problem. For example, new standard procedures will not affect tissues that were collected in the past and some aspects of tissue collection are likely to remain beyond the reach of standardization (e.g., temperature at time of collection, time period of tissue devascularization). Furthermore, improved collection and processing techniques will continue to be developed. Therefore, specimens collected over time may not necessarily be uniform.

<sup>25</sup> <http://pluto3.nci.nih.gov/tissue/default.htm>.

<sup>26</sup> International Genomics Consortium: <http://www.intgen.org/expo.cfm>.

Moreover, because uniform collection of tissues under standard conditions is extremely expensive, such methods will probably be implemented only for specific studies or tissues. Many institutions, particularly nonacademic hospitals—which are an extremely important potential source of tissue—are unlikely to implement these methods as standard operating procedures. Therefore, in addition to standard collection and processing methods, standard analytic methods must be developed for use with tissues obtained under routine, and thus variable, conditions.

Development of standard analytic techniques is an emerging area that warrants additional attention and funding. Such efforts are focused on the development of methodologies that can yield consistent, comparable, quantitative, and reproducible analytic results no matter how or when the tissue was collected. The NCI Innovative Molecular Analysis Technologies program in the Office of Technology and Industrial Relations (OTIR), as well as other NCI programs, is beginning to support these efforts. The Translational Research Support Office will work with OTIR, OBBR, the BCC, and relevant program staff to determine how these current efforts can be enhanced and incorporated into future endeavors.

## **Initiative C4: Develop enhanced approaches for negotiation of intellectual property agreements and agent access.**

### **Rationale**

Translational research requires effective collaboration among industry, academia, NCI, and foundations. Developing approaches, procedures, and tools that promote rapid negotiation of intellectual property agreements and facilitate researchers gaining access to important agents will improve the translational research process by minimizing barriers that often delay or prevent potentially productive collaborations.

Three general situations can be identified within NCI-funded translational research where intellectual property issues are frequently problematic:

- Industry providing materials to academic institutions for research purposes
- Exchange of materials between academic institutions
- Licensing of NCI-funded intellectual property by academic institutions to industry.

The approaches described below are targeted at promoting rapid negotiation of intellectual property agreements in these situations.

In addition, having available NCI-supported agent repositories would reduce search and negotiation costs for researchers needing specific agents for their research. Through these repositories, researchers would be able to readily access agents using a prenegotiated materials transfer agreement. If research results were promising, the investigator could then negotiate further with the patent owner of the agent. Such repositories could also serve as a centralized source for compounds that do not have patent protection.

To realize the goals of this initiative, the TRWG proposes the implementation plan described below.

### **Implementation Plan**

#### ***Model Agreements and Best Practices***

Some of the difficulties in resolving intellectual property issues result from beginning negotiations without any clear guidelines. The availability of model agreements and best practices should facilitate negotiations, thereby speeding the process of sharing intellectual property.

The Translational Research Support Office will work with the NCI Technology Transfer Branch (TTB) to coordinate development of model agreements and best practices. The first step will be to conduct an analysis of existing agreements and practices. The analysis will include but not necessarily be limited to the following:

- Standardized language for clinical trial and material transfer agreements developed by the Cancer Therapy Evaluation Program
- Model agreements and licensing best practices developed by the NIH National Human Genome Research Institute
- Model agreements developed by foundations and advocacy groups
- Model licensing language developed by the Association of University Technology Managers
- Intellectual property agreements developed by the planning grant participants of the Academic Public-Private Partnership Program
- Master Material Transfer Agreements developed by NCI and universities.

Based on the analysis of existing models, the Support Office, in consultation with TTB and relevant NCI program staff, will develop model agreements and best practices for use in the following situations:

- NCI-funded academic researchers obtaining materials from industry
- NCI-funded academic researchers obtaining materials and/or licensing intellectual property from another academic researcher
- Industry licensing intellectual property from NCI-funded academic researchers.

Depending on the results of the analysis, one model and set of best practices applicable to each situation may be developed. Alternatively, several models and sets of best practices may be developed for each situation. Examples of conditions that may require specially tailored agreements and best practices include the following:

- Early-stage development versus later-stage development
- Combination studies versus single-agent studies
- Significant potential applications versus unknown potential applications
- Co-exclusivity versus a single, exclusive license.

NCI will convene a series of meetings with key stakeholders, including industry sponsors, foundation and advocacy group representatives, and academic technology transfer representatives, to review the assembled set of model agreements and best practices. The goal of this series of meetings will be to develop, with input from a wide audience of stakeholders, a set of harmonized agreements and practices. Active participation by industry, academia, foundations and advocacy groups, and NCI to address their individual needs will enhance the likelihood that the final set of model agreements and best practices will be widely adopted by both the private- and public-sector research communities. These meetings will be coordinated with similar meetings concerning clinical trial contracts organized as part of the Clinical Trials Working Group Report implementation.

The model agreements and best practices will be made available on a public Web site maintained by TTB for any researcher to access and use. Use of these agreements and best practices by translational researchers funded by NCI will be promoted by articles in cancer center publications and reference to the public Web site in NCI grant and program announcements. Following development of the model agreements and best practices, NCI, in collaboration with industry and university technology transfer representatives, will conduct an annual review to determine whether changes are needed and whether additional model agreements and best practices should be established.

### **Alternative Approaches**

More efficient negotiation of individual agreements is not the only approach that has been developed for addressing intellectual property issues. Other approaches that have been developed and applied in various fields include patent pools and industry-government consortia.

**Patent Pools.** Patent pools have been used in several fields within the United States during the last 150 years, including sewing machine manufacturing, aircraft manufacturing, radio and television transmissions, and digital audiovisual technology.<sup>27</sup> A patent pool is composed of two or more patent owners who agree to license their patents to other members of the patent pool or an outside party. The licensing can be conducted by either the members of the patent pool or by a specific mechanism, such as a joint venture, developed to oversee the patent pool. When the patent pool is administered by a joint venture, potential licensees only have to negotiate with one entity for patents within the pool rather than with several different patent owners, thereby reducing negotiation costs and time.

<sup>27</sup> This history and description of patent pools is taken from Clark J, Piccolo J, Stanton B, Tyson K. Patent pools: a solution to the problem of access in biotechnology patents? United States Patent and Trademark Office, 2000. Available at: <http://www.uspto.gov/web/offices/pac/dapp/opla/patentpool.pdf>.



Although used in several fields, patent pools have not been developed for the biotechnology or pharmaceutical industries. A white paper produced by the U.S. Patent and Trademark Office argued for the following benefits for biotechnology patent pools:<sup>28</sup>

- Elimination of difficulties due to blocking patents or stacking licenses as licensees will obtain access to all patents within the patent pool
- Reduction of legal costs as disputes can be settled through the patent pool
- Pooling of the risks of research and development
- Facilitation of exchange of information that is not protected by patents.

Such a patent pool could potentially be pursued for agents developed by industry that the industry has no plans to exploit. Access to these agents by academic researchers could be governed by a common set of intellectual property terms negotiated through the pool.

**Government-Industry Consortia.** The most famous example of a government-industry consortium is SEMATECH (SEmiconductor MANufacturing TECHnology). SEMATECH was formed in 1987 by 14 U.S.-based semiconductor manufacturers and the U.S. Government with the goal of solving widespread manufacturing problems through commonly supported research and development.<sup>29</sup> Federal funding for this consortium ended in 1996, but the industrial partners have maintained the consortium. Subsequently, international members and an academic partner have been included. SEMATECH holds intellectual property rights to technology developed under the consortium. Member companies are allowed to use technologies developed within SEMATECH without any additional licensing, and, after a specified time period, the technologies are made available to nonmembers through licensing agreements.<sup>30</sup> Such a consortium might be appropriate for developing a large, comprehensive, annotated cancer biospecimen repository (see Operational Effectiveness Initiative C3), a comprehensive agent repository (see below), and/or comprehensive molecular analysis technologies for cancer biospecimens.

In conjunction with TTB, the Translational Research Support Office will evaluate these alternative models to determine whether they can be adapted to NCI-funded translational research projects. If either of these approaches seems feasible, Support Office staff will begin discussions with potential industry partners, in conjunction with TTB, to determine interest in forming such relationships.

### **NCI Agent Repositories**

Because of the potential benefits associated with decreased search and negotiation costs, the Translational Research Support Office will evaluate the feasibility of developing or enhancing the size, quality, and accessibility of the following types of agent repositories.

**Compounds without Patent Protection.** This repository would include compounds that have lost or cannot receive patent protection. A survey of compounds that have lost patent protection as well as a survey of natural products or other agents that cannot be patented will be conducted and their availability for inclusion in the repository assessed.

**NCI-Developed Compounds.** This repository would include compounds developed and/or characterized by NCI researchers. A survey of NCI intramural researchers will be conducted to develop a list of compounds appropriate for such an inventory. The requirements necessary to protect the research interests of the intramural researchers will also be evaluated.

28 Clark J, Piccolo J, Stanton B, Tyson K. Patent pools: a solution to the problem of access in biotechnology patents? United States Patent and Trademark Office, 2000. Available at: <http://www.uspto.gov/web/offices/pac/dapp/opla/patentpool.pdf>.

29 See “SEMATECH History” at <http://www.sematech.org/corporate/history.htm>.

30 U.S. Congressional Budget Office, 1987. The Benefits and Risks of Federal Funding for Sematech. Available at: <http://www.cbo.gov/showdoc.cfm?index=6205&sequence=0>.

**Compounds from NCI-Funded Extramural Researchers.** This repository would include compounds resulting from research conducted under NCI awards. A survey of NCI translational research grantees will be conducted to identify compounds appropriate for this repository and determine under what terms such compounds might be made available to other researchers.

**Industrial Compounds.** This repository would include compounds provided by pharmaceutical and biotechnology companies. A survey of pharmaceutical and biotechnology companies will be conducted to determine their interest in participating in this repository. If interest is sufficient, an inventory of compounds that industry is willing to contribute will be assembled.

If developing or improving such repositories is feasible, the Support Office will develop policies and procedures to ensure that appropriate annotated information is available on each sample in an electronic, searchable format and that the repositories are maintained and updated on a regular periodic basis. The Support Office will also work with NCI staff and management to identify facilities and funding for the repositories and work with the TTB to develop standard language covering intellectual property issues.

## **Initiative C5: Enhance interactions and collaborations with foundations and advocacy groups to advance early translational research.**

### **Rationale**

Partnerships that bring together foundations and advocacy groups with NCI and academic medical centers are becoming increasingly important in biomedical research. Such partnerships have allowed foundations and advocacy groups to contribute valuable enthusiasm, patient-centered expertise, and, at times, funding for many translational research initiatives and training programs. For example, with encouragement from the NIH Director's Panel Report in 1997, several foundations, such as the Doris Duke Charitable Trust, the Burroughs Wellcome Foundation, and the Howard Hughes Medical Institute, provided project funding for clinical researchers and developed translational research training programs at academic medical centers.<sup>31</sup> It is vital to the translational research enterprise that NCI foster and strengthen these relationships.

The enhanced interactions and collaborations proposed below are designed to capitalize on the complementary skills and resources of foundations and advocacy groups to advance early translational research. They also provide an opportunity to benefit from the strengths of foundations and advocacy groups in facilitating integration of academia, industry, NCI, and philanthropic organizations.

To realize the goals of this initiative, the TRWG proposes the implementation plan described below.

### **Implementation Plan**

#### **Overall Approach**

To strengthen the relationship of NCI with foundations and advocacy groups in the area of translational research, NCI should establish a leadership position responsible for developing and sustaining such relationships and addressing potential collaborative efforts in translational research among foundations, including the Foundation for NIH, advocacy groups, and all NCI Divisions, Centers, and Offices. This position will be responsible for leading, developing, and maintaining the efforts described below and coordinating activities with the Office of Liaison Activities (OLA) and the Director's Consumer Liaison Group (DCLG) to ensure maximal impact and authorities for these endeavors. This position will also interface, as appropriate, with NIH's Program on Public-Private Partnerships within the Office of the Director for assistance in developing these efforts.

In addition, the DCLG will take a leadership role in coordinating the participation of advocacy groups and individual advocates in implementation not only of this initiative but all of the TRWG initiatives. This will include gathering input on funding priorities and program operations, recommending representatives for the various committees and working groups, disseminating information on implementation to the larger patient community, and promoting a better understanding of the productive roles advocates can play in the research process.

#### **Structured Interactions**

OLA will organize regular periodic meetings involving program staff responsible for translational research from all NCI Divisions, Centers, and Offices and representatives from appropriate foundations and advocacy groups for the purpose of addressing the full spectrum of translational research activities. The goal is to increase overall awareness and understanding of the full breadth and depth of translational research infrastructures and activities being planned, prioritized, and conducted by both NCI and foundations and advocacy groups. This includes outreach and communication programs as well as scientific infrastructure and research programs, including SPOREs, the Early Detection Research Network, Phase I/II clinical trial contracts, Development of Clinical Imaging Drug Enhancers, RAID, RAPID, cancer centers, etc. One additional mechanism for enhancing interactions will be to conduct "Translational Needs and

31 Nathan DG. Careers in translational clinical research—historical perspectives, future challenges. *JAMA*, 2002;287:2424-87. Available at: <http://jama.ama-assn.org/cgi/content/full/287/18/2424#REF-JCO20035-18>.

Opportunities” meetings convened as part of the new translational research prioritization process (see Coordinated Management Initiative A4) in association with foundation or advocacy group meetings.

### ***Participation in NCI Prioritization Process***

Advocacy groups and foundations have built strengths in scientific review and planning, including conducting scientific reviews to inform their funding decisions. Moreover, about one-third of the proposals submitted to foundations and advocacy groups are translational. Consequently, representatives from these communities can provide valuable input as NCI prioritizes translational research programs and projects across the translational research enterprise.

At least one representative from a foundation or advocacy group active in translational research funding will be named to each year’s Prioritization Working Group (see Coordinated Management Initiative A4). The advocacy representative will be named in coordination with OLA staff and drawn from the broad cancer advocacy and foundation community. The selection process will ensure that the participant has appropriate expertise and that the advocacy community is well represented in NCI’s processes for prioritizing translational research opportunities.

### ***Avoidance of Duplicative Review***

Representatives from foundations and advocacy groups indicate that many of the translational research proposals submitted to these organizations are either simultaneously submitted to NCI or have been previously rejected by NCI. Consequently, foundations, advocacy groups, and NCI perform duplicative reviews in many instances.

NCI cannot coordinate review with any outside agency or foundation. However, there is one advocacy group that solicits summary statements from applicants who are just outside the NCI payline and then makes its funding decisions based on those summary statements without conducting a separate scientific review. NCI staff assist in this process by making applicants aware of this additional funding opportunity, but the applicant must independently pursue the foundation or advocacy group application process. The feasibility of extending this process to additional foundations or advocacy groups will be explored during the regular meetings between NCI program staff and the advocacy organizations. If interest in this process is high, OLA will work with the Translational Research Support Office to develop an approach for communicating with NCI grant applicants, foundations, and advocacy groups about this option.

### ***Funding Partnership Development***

In collaboration with the Translational Research Support Office and drawing on the resources of NIH’s Program on Public-Private Partnerships within the Office of the Director, OLA will investigate the feasibility of creating, through the Foundation for NIH, joint funding opportunities. These could include the following:

- Foundation/advocacy group funding of a component of a STRAP award (see Tailored Funding Programs Initiative B3)
- Foundation/advocacy group funding of a fellowship for work in association with a specific translational research project embedded within a STRAP, P01, SPORE, or other award
- Joint NCI and foundation/advocacy group funding of fellowships and other training awards
- Foundation/advocacy group funding of a research project or program via the Foundation for NIH, modeled on previous successful examples such as the AVON Partners for Progress program.

### ***Enhanced Outreach Concerning Tissue Donation and Image Collection***

Enhanced public, patient, and physician outreach emphasizing the critical role of tissue donation and image collection to cancer research progress is particularly important as there are generally no direct benefits to patients and no incentives for community oncologists who refer patients. This is a vastly underappreciated aspect of cancer research.

Staff from the Translational Research Support Office will work with the Office of Education and Special Initiatives (OESI), the Office of Communications (OC), the Office of Biorepositories and Biospecimen Research, and OLA to

develop a proactive program that involves foundations and advocacy groups in increasing overall public, patient, and community oncologist awareness and understanding of the value of tissue sample donation and image collection during participation in clinical trials as well as during clinical follow-up. OESI, OC, and OLA staff will take the lead in developing this program. As a similar initiative is being pursued as part of the Clinical Trials Working Group Report implementation, this program would be optimally executed in tandem with public and patient outreach for clinical trial participation. As increased public outreach efforts should result in both increased collection of tissue samples and images as well as increased awareness among researchers of the availability of these resources, issues related to the ownership and sharing of these resources may become increasingly prominent and will need to be addressed.

The feasibility and potential effectiveness of several approaches for outreach will be explored, including the following.

1. Assemble case studies that demonstrate the importance of tissue donation in advancing cancer research and treatment and distribute through cancer centers, cooperative groups, community cancer centers, and advocacy groups.
2. Develop cooperative communication programs with sister Federal agencies, such as the Centers for Disease Control and Prevention and the Office of the Surgeon General.
3. Develop informational material with NCI's Cancer Information Service that can be distributed to patients, cancer centers, cooperative groups, community cancer centers, and advocacy groups.
4. Compile best communication practices from cancer centers regarding tissue donation and image collection and distribute to cancer centers, cooperative groups, community cancer centers, and advocacy groups.
5. Fund community research projects through the Clinical and Translational Science Awards program to determine why individuals do or do not donate tissues or images for research purposes.

Initial meetings will be conducted with individual foundation and advocacy groups to identify opportunities for effective public and patient outreach. If the exploratory meeting with an individual organization indicates there is potential for collaboration, specific action plans will be developed for implementing the activities and programs identified. NCI will also contact broad-based advocacy groups, such as the American Cancer Society, the National Coalition for Cancer Survivorship, and the Lance Armstrong Foundation to consider developing a general public awareness campaign on the value of tissue sample donation and image collection. This campaign will utilize many of the same communication tactics, but be aimed at a larger and more diverse audience.

## Initiative C6: Enhance training and career incentives for early translational research.

### Rationale

Integration of a wide range of disciplines from both laboratory and clinical research in a well-coordinated team effort is essential to early translation. The future vitality of the translational research enterprise will therefore depend on a new generation of researchers who have mastered relevant scientific and clinical disciplines, understand both the laboratory and clinical perspective, and are skilled in goal-oriented management of cross-disciplinary teams.

In its recent report on obstacles to the development of new drugs, the Government Accountability Office noted several concepts for improving the productivity of drug development that were highlighted by experts consulted for the report. Among these suggestions were the following points relevant to workforce development:

*Academia could place a greater emphasis on developing research scientists with knowledge of translational medicine by providing financial incentives such as scholarships for students to pursue this discipline. Private and public partnerships could also create these incentives to develop such scientists. One of the panelists suggested that academia, industry, and the FDA (Food and Drug Administration) formally develop a paper that describes the skills most needed by this new type of translational scientist and develop funding and training mechanisms that would specifically support these individuals.<sup>32</sup>*

Current approaches to funding and administration of biomedical research and training in academia often promote the maintenance of independent silos. These relatively rigid organizational elements not only stand in the way of team science and cross-disciplinary research and training today but they also retard adaptation to changes in translational science for the future. Changes in academic organizational strategies and structures complemented with more effective use of NCI funding mechanisms for training and increased availability of NCI award programs focused on translational research will be essential to develop a committed translational research workforce to meet the recognized needs of today and the emerging needs of tomorrow.

To realize the goals of this initiative, the TRWG proposes the implementation plan described below.

### Implementation Plan

#### Translational Research Training Program Announcement

The Cancer Training Branch of the Office of Centers, Training and Resources (OCTR) will develop a Program Announcement addressing training for early translational research. The PA will draw attention to opportunities for the use of existing institutional funding mechanisms, such as the K12, R25T, and T32 awards, as complementary elements in the development of integrated training programs for translational researchers and teams.

#### Early Translational Research Training Working Group

NCI will establish a Translational Research Training Working Group under the auspices of the Advisory Committee and with the logistical support of the Translational Research Support Office. The Working Group will include 8-10 members encompassing a range of key stakeholders, including:

- Two members of the Advisory Committee
- The Associate Director for Training, OCTR

32 NEW DRUG DEVELOPMENT: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts, GAO-07-49. Washington, DC: Government Accountability Office, November 2006, p. 36



- Extramural translational researchers with experience running formal translational and clinical research training programs
- Industry representative(s).

The Working Group will be asked to report within 1 year on the findings and recommendations derived from its investigation, consultation, and consensus-building in the areas described below.

**Training of Clinician-Scientists for Translational Research.** To meet the challenge of ensuring a continual flow of well-qualified researchers who can lead and participate in the complex, multidisciplinary research activities that are the foundation of translational research, it is necessary to define the required mix of skills more clearly and ensure that clinician-scientist training programs provide those skills in a manner that facilitates career development.

To address this issue, the Working Group will undertake the following tasks:

1. Define a common set of skills that qualify clinician-scientists for leadership of and participation in translational research teams; these are likely to include foundational skills in basic science, statistics and study design, regulatory affairs, and management of large, complex, multidisciplinary project teams.
2. Review existing clinician-scientist training programs and awards to assess the extent to which they provide these skills and to identify gaps and best practices.
3. Design a model curriculum with associated training standards, incentives, and best practices that can be used for creation of new training programs and/or adaptation of existing ones.
4. Identify specific clinical specialties that are inadequately represented in translational research.
5. Review existing industry fellowship programs to assess the scope of current activity and identify best practices.
6. Disseminate the information gathered to the scientific community through appropriate presentations or publications.

The Working Group will consult widely with the leaders of existing clinician-scientist training programs, NCI staff, leaders of professional organizations such as the Association of American Medical Colleges (AAMC), FDA staff, and translational research leaders from industry.

**Training of Ph.D. Scientists for Translational Research.** To provide Ph.D. scientists with the requisite training to lead and participate most effectively in translational research, Ph.D. programs in laboratory bioscience, public health, and behavioral science should be enhanced with opportunities to gain a foundation of clinical knowledge, including clinical trials.

To address this issue, the Working Group will undertake the following tasks.

1. Define a common set of skills that qualify Ph.D. scientists for leadership of and participation in translational research teams; these are likely to include foundational skills in clinical medicine and clinical trials, statistics and study design, regulatory affairs, and management of large, complex, multidisciplinary project teams.
2. Review existing Ph.D. training programs in laboratory bioscience, public health, and behavioral science to assess the degree to which they provide the opportunity for learning about clinical topics, regulatory affairs, and team management.
3. Identify approaches for incorporating clinical topics into laboratory bioscience, public health, and behavioral science Ph.D. programs, including taking medical school courses.



4. Identify specific scientific, non-M.D., specialties (including biostatistics) that are in short supply for early translational research.
5. Disseminate the information gathered to the scientific community through appropriate presentations or publications.

The Working Group will consult widely with the leaders of existing Ph.D. programs in laboratory bioscience, public health, and behavioral science; NCI staff; and leaders of relevant professional organizations.

**Training of Ph.D. Nurses for Translational Research.** Translational research would benefit from the participation of nursing researchers who can link discovery research on biological mechanisms with nursing research in the patient care environment. This participation would facilitate translational research initiatives addressing new interventions for supportive care and quality of life, as well as the incorporation of supportive care and quality-of-life dimensions into translational research on therapeutic interventions. The Working Group will consult with the National Institute of Nursing Research to determine how the two Institutes can best collaborate to facilitate appropriate translational research training activities.

**Cross-Disciplinary Sharing of Best Practices and Implications of the Clinical and Translational Science Awards (CTSA) Program for Translational Research Training.** The Working Group will consult with representatives of other biomedical research disciplines and other NIH Institutes to identify issues and best practices in translational research training that are common across disciplines. In addition, the Working Group will consult with the CTSA program leadership on the potential implications of CTSA for training in cancer-related translational research.

### ***Regulatory Affairs Training***

The TRWG identified an acute need for greater understanding of the FDA regulatory process on the part of those who lead translational research. In collaboration with FDA and industry, NCI will seek to expand the number of short courses, intensive workshops, sabbatical fellowships in industry, and other training activities that can fit into the calendars of active clinician-scientists and provide the knowledge and skills needed to interact effectively with the FDA in drug and device development.

### ***Enhancement of Career Support and Incentives***

A key element in developing a robust translational research workforce is to provide adequate support and incentives to attract young researchers to a career in translational science. Three approaches for addressing this challenge will be pursued. The first is optimizing funding programs to encourage and reward translational research. The second addresses expanding the use of the legislative salary cap to include training awards. The third is to engage academic institutions in an active dialogue concerning appropriate modifications to institutional practices that will facilitate academic careers in translational science.

**Funding Programs and Award Guidelines.** The TRWG has proposed several initiatives that will strengthen translational research funding programs (see Tailored Funding Programs Initiatives B1, B3, and B4). The guideline changes proposed in these initiatives will reward and encourage projects that take concepts through development to early human testing. The enhanced emphasis in these programs on translational research as opposed to discovery will provide greater funding opportunities for researchers primarily interested in moving concepts forward to early human testing rather than solely working at the interface of discovery and translation. These programs can also provide appropriate recognition for investigators participating in large collaborative studies by utilizing the NIH-wide multiple principal investigator and “tethered awards” concepts in funding these programs. In addition, guidelines for cancer centers will be modified to reward the conduct of focused translational research projects as well as high-quality, investigator-initiated, industry-sponsored studies.

**Legislative Salary Cap for Training Awards.** NCI leadership will work with overall NIH leadership to modify K08, K23, and K24 training awards to allow salary support up to the legislative cap. This is in accord with Recommendation 7 of the AAMC’s Task Force II on Clinical Research (CRTF II) 2006 report entitled, “Promoting Translational and Clinical Science: The Critical Role of Medical Schools and Teaching Hospitals.”<sup>33</sup>

**Academic Reward Practices.** NCI and NIH leadership will work proactively with the AAMC, the Institute of Medicine, and other organizations to persuade medical school and academic deans of the need to adjust their institutions’ incentive structures to reward collaborative, multidisciplinary translational research. The NCI will also examine the intramural program’s incentive structures to be sure that collaborative translational research is properly recognized and rewarded. The Clinical Trials Working Group Report included an initiative to pursue realignment of academic recognition policies, including promotion and tenure guidelines, to reward collaborative clinical research. This effort will be combined with this new TRWG proposed effort to realign those same policies to reward collaborative translational research that moves discoveries toward early human testing. Such changes would reward academics not only for individual discovery scholarship but also for advancing discoveries to patient benefit. This initiative parallels Recommendation 6 of the AAMC CRTF II Report.<sup>34</sup>

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33 Report of the AAMC’s Task Force II on Clinical Research. Washington, DC: Association of American Medical Colleges, 2006

34 Report of the AAMC’s Task Force II on Clinical Research. Washington, DC: Association of American Medical Colleges, 2006.

## Timeline and Budget

### Timeline

Implementation of the TRWG initiatives according to the plans outlined in this report are projected to 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. All initiatives are targeted to begin implementation by the end of year three. A summary timeline is presented in Figure 4 and a summary budget in Figure 5 (page 80). A schedule of key activities and milestones associated with each initiative is presented in Table 1 (page 83).

Major items for each year include the following:

#### Year 1

##### *Coordinated Management Initiatives*

- Establish Translational Research Support Office.
- Expand Clinical Trials Advisory Committee oversight to include translational research.
- Establish Translational Research Operations Committee.
- Set initial translational research budget target.
- Establish translational research award codes.
- Establish Prioritization Working Group.
- Initiate first annual prioritization process.
- Establish Industry Relations Working Group.

##### *Tailored Funding Program Initiatives*

- Modify multiproject, collaborative award guidelines (P50, U-series, etc.).
- Develop STRAP award structures.
- Establish integrated review procedures for translational research awards and development resource programs.
- Establish Industry Relations Working Group.

##### *Operational Effectiveness Initiatives*

- Hire project management staff.
- Begin to develop inventory of early translational research resources.
- Develop project management training plan.
- Analyze core services redundancies.
- Begin interactions with Office of Biorepositories and Biospecimen Research concerning biospecimen repositories.
- Analyze current intellectual property agreements/practices.
- Initiate regular foundation and advocacy group meetings.
- Establish Training Working Group.

**Figure 4. 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: Integrated Development 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					

**Figure 5. 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: Integrated Development 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
<b>TOTAL</b>	<b>\$4.05M</b>	<b>\$3.99M</b>	<b>\$13.65M</b>	<b>\$28.5M</b>	<b>\$44.1M</b>

**Year 2*****Coordinated Management Initiatives***

- Begin coding of new translational research awards.
- Complete retrospective coding of translational research awards.
- Select initial set of translational research priorities.

***Tailored Funding Program Initiatives***

- Implement revised guidelines for multiproject collaborative awards.
- Issue initial STRAP award solicitation.
- Begin integrated reviews of translational research awards and development of resource programs.

***Operational Effectiveness Initiatives***

- Complete inventory of translational research resources.
- Initiate project management training program.
- Develop core services database.
- Identify core services for regionalization.
- Convene consensus meetings on intellectual property agreements/best practices.
- Begin interaction with academic and medical school deans regarding academic incentives.
- Begin to implement Training Working Group recommendations.

**Year 3*****Coordinated Management Initiatives***

- Analyze newly coded translational research portfolio.
- Select second set of translational research priorities.

***Tailored Funding Program Initiatives***

- Fund initial STRAP awards.
- Issue initial academic/industry collaboration award solicitation.

***Operational Effectiveness Initiatives***

- Begin translational research resource database development.
- Conduct 2-year evaluation of project management system.
- Implement core services consolidation, if appropriate.
- Develop harmonized intellectual property agreements/practices.
- Develop agent repositories/databases, if appropriate.

## Years 4-5

### *Coordinated Management Initiatives*

- Begin managing translational research portfolio to budget target.
- Continue to select annual translational research priorities.

### *Tailored Funding Program Initiatives*

- Fund second and third round of STRAP awards.
- Fund first and second round of academic/industry collaboration awards.

### *Operational Effectiveness Initiatives*

- Complete translational research resource database development.
- Conduct 4-year evaluation of project management system.
- Establish core services Regional Centers.

## Budget

The estimated costs for implementing the TRWG initiatives according to the plans outlined in this report are presented in Tables 2 and 3. Table 2 presents the costs by category—Extramural, Analysis/Development Projects, NCI Operational Activities, and Meeting Support. Table 3 presents the costs by year. The estimated incremental cost for Year 1 (FY 08) and Year 2 (FY09) is \$4M annually. The estimated cost increases in Year 3 (FY10) to \$13.5M, in Year 4 (FY11) to \$28.5M, and in Year 5 (FY12) to \$44M are entirely due to implementation of new extramural funding programs. Thus, these cost increases are not truly incremental, but represent shifting of a small fraction of ongoing NCI translational research extramural funding into the new STRAP and academic/industry collaboration awards.

Of the annual \$4M in nonextramural funding throughout the 5-year period, 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. If the TRWG initiatives are fully implemented, there may be additional incremental expenses that cannot be estimated at this time. Examples include expansion of the project management system if it is successful and demand grows (see Operational Effectiveness Initiative C1) and creation of agent repositories and associated databases if these are deemed worthwhile and feasible (see Operational Effectiveness Initiative C4).

**Table 1. Implementation Timeline**

		Key Milestones and Activities			
Initiative	Year 1 (Oct. 2007–Sept. 2008)	Year 2 (Oct. 2008–Sept. 2009)	Year 3 (Oct. 2009–Sept. 2010)	Years 4–5 (Oct. 2010–Sept. 2012)	
Coordinated Management A1 Integrated NCI Management	<ul style="list-style-type: none"> <li>Establish TRSO (Oct. 2007)</li> <li>Expand CTAC oversight (Jan. 2008)</li> <li>Establish TROC (Jan. 2008)</li> <li>Establish Special Populations Working Group</li> </ul>	<ul style="list-style-type: none"> <li>Implement recommendations of Special Populations Working Group</li> </ul>	<ul style="list-style-type: none"> <li>Analyze newly coded portfolio (Oct. 2009–Mar. 2010)</li> <li>Evaluate value of consortia concept</li> </ul>	<ul style="list-style-type: none"> <li>Begin managing portfolio to budget target (Oct. 2010)</li> </ul>	
A2: Budget Designation	<ul style="list-style-type: none"> <li>Set initial budget target (Sept. 2008)</li> </ul>	<ul style="list-style-type: none"> <li>Review and confirm or change budget target</li> </ul>	<ul style="list-style-type: none"> <li>Review and confirm or change budget target</li> </ul>	<ul style="list-style-type: none"> <li>Review and confirm or change budget target</li> </ul>	
A3: Translational Research Coding	<ul style="list-style-type: none"> <li>Establish codes (Oct. 2007–Mar. 2008)</li> <li>Analyze feasibility of investigator-assigned codes</li> </ul>	<ul style="list-style-type: none"> <li>Begin coding of new awards (Oct. 2008)</li> <li>Complete retrospective coding</li> <li>Continue analysis of feasibility of investigator-assigned codes</li> </ul>	<ul style="list-style-type: none"> <li>Continue coding of new awards</li> </ul>	<ul style="list-style-type: none"> <li>Continue coding of new awards</li> </ul>	
A4: Prioritization Process	<ul style="list-style-type: none"> <li>Establish Prioritization Working Group (Jan. 2008)</li> <li>Develop prioritization process (Oct. 2007–Jan. 2008)</li> <li>Solicit ideas (Jan. 2008)</li> <li>Perform literature review (Jan. –Mar. 2008)</li> <li>Develop concept package (Apr. –Jun. 2008)</li> <li>Evaluate concepts (Jul. 2008)</li> <li>Perform portfolio analysis of most promising concepts (Aug.–Sept. 2008)</li> </ul>	<ul style="list-style-type: none"> <li>Publish/present prioritized opportunities for comment (Oct. 2008)</li> <li>Select initial priorities (Jan. 2009)</li> <li>Initiate FY10 prioritization process (Jan. 2009)</li> </ul>	<ul style="list-style-type: none"> <li>Complete FY10 prioritization process</li> <li>Select annual priorities (Jan. 2010)</li> <li>Initiate FY11 prioritization process (Jan. 2010)</li> </ul>	<ul style="list-style-type: none"> <li>Continue annual prioritization process</li> <li>Select annual priorities (Jan. 2011 and Jan. 2012)</li> </ul>	



**Table 1. Implementation Timeline (continued)**

Initiative	Key Milestones and Activities				
	Year 1 (Oct. 2007–Sept. 2008)	Year 2 (Oct. 2008–Sept. 2009)	Year 3 (Oct. 2009–Sept. 2010)	Years 4–5 (Oct. 2010–Sept. 2012)	
Tailored Funding Programs					
B1: Modify Translational Research Award Guidelines	<ul style="list-style-type: none"> <li>Revise guidelines</li> <li>Examine review panels</li> </ul>	<ul style="list-style-type: none"> <li>Implement revised guidelines</li> <li>Continue guideline revision if necessary</li> </ul>	<ul style="list-style-type: none"> <li>Continue to implement revised guidelines</li> <li>Perform rolling review evaluation</li> </ul>	<ul style="list-style-type: none"> <li>Continue to implement revised guidelines</li> <li>Implement rolling review if appropriate</li> </ul>	
B2: Improve Investigator-Initiated Translational Research Awards		<ul style="list-style-type: none"> <li>Examine study sections</li> <li>Begin NIH-wide dialogue</li> </ul>	<ul style="list-style-type: none"> <li>Continue NIH-wide dialogue</li> </ul>	<ul style="list-style-type: none"> <li>Continue NIH-wide dialogue</li> </ul>	
B3: Special Translational Research Acceleration Project (STRAP) Awards	<ul style="list-style-type: none"> <li>Develop STRAP award structures (Jan.–Sept. 2008)</li> </ul>	<ul style="list-style-type: none"> <li>Continue to develop STRAP award structures (Oct.–Dec. 2008)</li> <li>Prepare initial STRAP solicitation (Jan.–Mar. 2009)</li> <li>Issue STRAP solicitation (Apr. 2009)</li> <li>Review STRAP applications (Jul.–Sept. 2009)</li> </ul>	<ul style="list-style-type: none"> <li>Issue first STRAP awards (Jan. 2010)</li> </ul>	<ul style="list-style-type: none"> <li>Issue second and third round of STRAP awards (Jan. 2011 and 2012)</li> </ul>	
B4: Academia/ Industry Collaboration Awards	<ul style="list-style-type: none"> <li>Establish Industry Relations Working Group</li> </ul>		<ul style="list-style-type: none"> <li>Prepare academic/industry collaboration solicitation (Oct. –Dec. 2009)</li> <li>Issue solicitation (Jan. 2010)</li> <li>Review applications (Apr.–Jun. 2010)</li> </ul>	<ul style="list-style-type: none"> <li>Issue first awards (Oct. 2010)</li> <li>Issue second round of awards (Oct. 2011)</li> </ul>	
B5: Integrated Development Services	<ul style="list-style-type: none"> <li>Establish integrated review procedures</li> </ul>	<ul style="list-style-type: none"> <li>Begin integrated reviews</li> <li>Evaluate potential for assay/molecular analysis device development program</li> </ul>	<ul style="list-style-type: none"> <li>Continue integrated reviews</li> </ul>	<ul style="list-style-type: none"> <li>Continue integrated reviews</li> </ul>	

**Table 1. Implementation Timeline (continued)**

Initiative	Key Milestones and Activities				
	Year 1 (Oct. 2007–Sept. 2008)	Year 2 (Oct. 2008–Sept. 2009)	Year 3 (Oct. 2009–Sept. 2010)	Years 4–5 (Oct. 2010–Sept. 2012)	
<b>Operational Effectiveness</b>					
<b>C1: Project Management</b>	<ul style="list-style-type: none"> <li>Hire project management TRSO staff member (Oct. 2007)</li> <li>Begin to develop inventory of resources</li> <li>Revise guidelines</li> <li>Develop training plan</li> <li>Begin liaison with P50/U-series program staff (Apr. 2008)</li> <li>Hire Divisional project management staff</li> </ul>	<ul style="list-style-type: none"> <li>Continue to establish inventory of resources</li> <li>Implement revised guidelines</li> <li>Initiate training program</li> </ul>	<ul style="list-style-type: none"> <li>Begin resource DB development*</li> <li>Continue to implement revised guidelines</li> <li>Continue training program</li> <li>Conduct 2-year evaluation</li> </ul>	<ul style="list-style-type: none"> <li>Continue resource DB development</li> <li>Continue to implement revised guidelines</li> <li>Continue training program</li> <li>Conduct 4-year evaluation</li> </ul>	
<b>C2: Core Services Coordination</b>	<ul style="list-style-type: none"> <li>Analyze core services redundancies</li> <li>Revise guidelines</li> <li>Begin to develop core services database</li> </ul>	<ul style="list-style-type: none"> <li>Continue to develop core services database</li> <li>Identify services for regionalization</li> <li>Develop consolidation plans, as appropriate</li> </ul>	<ul style="list-style-type: none"> <li>Implement consolidation</li> <li>Implement regionalization, as appropriate</li> </ul>	<ul style="list-style-type: none"> <li>Continue to implement consolidation</li> <li>Continue to implement regionalization</li> </ul>	
<b>C3: Enhance Biorepositories</b>	<ul style="list-style-type: none"> <li>Revise guidelines</li> <li>Begin interactions with OBRR/BCC</li> </ul>	<ul style="list-style-type: none"> <li>Continue interactions with OBRR/BCC</li> </ul>	<ul style="list-style-type: none"> <li>Continue interactions with OBRR/BCC</li> </ul>	<ul style="list-style-type: none"> <li>Continue interactions with OBRR/BCC</li> </ul>	
<b>C4: Improve Intellectual Property Negotiations</b>	<ul style="list-style-type: none"> <li>Analyze current agreements/practices</li> </ul>	<ul style="list-style-type: none"> <li>Convene consensus meetings</li> <li>Analyze alternate IP models</li> <li>Analyze repository options</li> </ul>	<ul style="list-style-type: none"> <li>Develop harmonized agreements/practices</li> <li>Develop agent repositories/databases, if appropriate</li> </ul>	<ul style="list-style-type: none"> <li>Continue to develop agent repositories/databases, if appropriate</li> </ul>	
<b>C5: Enhance Foundation/Advisory Group Collaborations</b>	<ul style="list-style-type: none"> <li>Initiate regular foundation and advocacy group meetings                             <ul style="list-style-type: none"> <li>Avoid duplicative review</li> <li>Explore funding partnerships</li> <li>Begin outreach for tissue donation</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Continue and expand interactions</li> <li>Implement identified initiatives</li> </ul>	<ul style="list-style-type: none"> <li>Continue and expand interactions</li> <li>Implement identified initiatives</li> </ul>	<ul style="list-style-type: none"> <li>Continue and expand interactions</li> <li>Implement identified initiatives</li> </ul>	
<b>C6: Enhance Training Programs and Career Incentives</b>	<ul style="list-style-type: none"> <li>Develop training PA (Oct. 2007 –Mar. 2008)</li> <li>Establish Working Group (Jan. 2008)</li> <li>Conduct Working Group deliberations (Jan.–Sept. 2008)</li> <li>Analyze regulatory training options (Apr.–Sept. 2008)</li> <li>Work with NIH leadership concerning legislative cap in training awards</li> </ul>	<ul style="list-style-type: none"> <li>Complete Working Group deliberations (Dec. 2008)</li> <li>Begin to implement WG recommendations</li> <li>Begin interaction with academic deans/AAMC/IOM regarding academic incentives</li> </ul>	<ul style="list-style-type: none"> <li>Continue to implement Working Group recommendations</li> <li>Continue interaction with academic deans/AAMC/IOM regarding academic incentives</li> </ul>	<ul style="list-style-type: none"> <li>Continue to implement Working Group recommendations</li> <li>Continue interaction with academic deans/AAMC/IOM regarding academic incentives</li> </ul>	
<b>Evaluation</b>					
<b>Implementation of TRWG initiatives</b>	<ul style="list-style-type: none"> <li>Develop evaluation system</li> <li>Conduct baseline evaluation</li> </ul>		<ul style="list-style-type: none"> <li>Conduct 2-year evaluation</li> </ul>	<ul style="list-style-type: none"> <li>Conduct 4-year evaluation</li> </ul>	

\* Further development of core services database (Initiative C2).

Table 2. Estimated Implementation Budget by Category

Initiative	Expenses					Total
	Extramural	Analysis/Development Projects	NCI Operational Activities	Meeting Support		
A1: Coordinated NCI Management						
Integrated NCI Management	N/A	Portfolio Analysis Yr 3-5 ..... \$50K/yr	Translational Research Support Office* Yr 1-5 ..... \$700K/yr	Working Group Meetings Yr 1-5 ..... \$100/yr	Yr 1 ..... \$800K Yr 2 ..... \$800K Yr 3 ..... \$850K Yr 4 ..... \$850K Yr 5 ..... \$850K	
A2: Budget Designation	N/A	N/A	See Note 1	N/A	See Note 1	
A3: Translational Research Coding	N/A	N/A	RAEB Staff Yr 2-5 ..... \$150K/yr	N/A	Yr 1 ..... \$0 Yr 2 ..... \$150K Yr 3 ..... \$150K Yr 4 ..... \$150K Yr 5 ..... \$150K	
A4: Prioritization Process	N/A	Prioritization Working Group Support (Literature review, portfolio analysis, etc.) Yr 1 ..... \$400K Yr 2-5 ..... \$200K/yr	Translational Research Support Office Yr 1-5 ..... \$350K/yr	Prioritization Working Group Meetings Yr 1-5 ..... \$200K/yr	Yr 1 ..... \$950K Yr 2 ..... \$750K Yr 3 ..... \$750K Yr 4 ..... \$750K Yr 5 ..... \$750K	

Note 1: Included in Translational Research Support Office expenses for Initiative A1 (see above).

\* Expanded management and professional staff for the Translational Research Support Office of the Coordinating Center for Clinical Trials, including clerical, office expenses, travel, etc. The prorated Translational Research Support Office staff and operating expenses for managing the prioritization and project management systems are not included in the total shown; these expenses are included in the expenses for Initiative A4 and Initiative C1, respectively.

**Table 2. Estimated Implementation Budget by Category (continued)**

Initiative	Expenses					Total
	Extramural	Analysis/Development Projects	NCI Operational Activities	Meeting Support		
Tailored Funding Programs						
B1: Modify Translational Research Award Guidelines	N/A	N/A	See Note 1	N/A	See Note 1	See Note 1
B2: Improve Investigator-Initiated Translational Research Awards	N/A	N/A	See Note 1	N/A	See Note 1	See Note 1
B3: Special Translational Research Acceleration Project (STRAP) Awards	Yr 3..... \$10M Yr 4..... \$20M Yr 5..... \$30M	N/A	See Note 2	N/A	Yr 1 ..... \$ 0 Yr 2 ..... \$ 0 Yr 3 ..... \$10M Yr 4 ..... \$20M Yr 5 ..... \$30M	
B4: Academia/ Industry Collaboration Awards	Yr 4..... \$5M Yr 5..... \$10M	N/A	See Note 1	N/A	Yr 1 ..... \$ 0 Yr 2 ..... \$ 0 Yr 3 ..... \$ 0 Yr 4 ..... \$ 5M Yr 5 ..... \$10M	
B5: Integrated Development Services	N/A	N/A	See Note 1	N/A	See Note 1	See Note 1

NOTE 1: Included in Translational Research Support Office expenses for Initiative A1 (see page 86).

Note 2: Included in prioritization process expenses (Initiative A4, see page 86).

**Table 2. Estimated Implementation Budget by Category (continued)**

Expenses					
Initiative	Extramural	Analysis/Development Projects	NCI Operational Activities	Meeting Support	Total
C1: Project Management		Training Analysis Yr 1..... \$50K	Translational Research Support Office Yr 1-5.....\$350K/yr		Yr 1..... \$1.35M
		Resource Inventory Yr 1-2.....\$200K/yr			Yr 2..... \$1.30M
		Resource Database Development* Yr 3-5.....\$200K/yr	Divisional Project Managers Yr 1-3.....\$750K/yr	N/A	Yr 3..... \$1.55M
		Evaluation Yr 3..... \$250K			Yr 4..... \$1.75M
		Yr 5..... \$250K			Yr 5..... \$2.00M
C2: Core Services Coordination		Core Services Analysis Yr 1..... \$200K		Regionalization Working Group Meeting Yr 2..... \$120K	Yr 1..... \$200K
	N/A	Core Services Initial Database Development Yr 2..... \$250K	See Note 1		Yr 2..... \$370K
					Yr 3..... \$ 0K
					Yr 4..... \$ 0K
					Yr 5..... \$ 0K
C3: Enhance Biorepositories	N/A	N/A	See Note 1	N/A	See Note 1
C4: Improve Intellectual Property Negotiations		IP Agreement Analysis Yr 1..... \$100K		Consensus Meetings Yr 2..... \$120K	Yr 1..... \$100K
		Alternate IP Models Analysis Yr 2..... \$200K			Yr 2..... \$520K
	N/A	Analysis of Repository Options Yr 2..... \$200K	See Note 1		Yr 3..... \$ 0K
					Yr 4..... \$ 0K
					Yr 5..... \$ 0K

Note 1: Included in Translational Research Support Office expenses for Initiative A1 (see page 86).

\* Further development of core services database (Initiative C2).

**Table 2. Estimated Implementation Budget by Category (continued)**

Initiative	Expenses					Total
	Extramural	Analysis/Development Projects	NCI Operational Activities	Meeting Support		
Operational Effectiveness						
C5: Enhance Foundation/Advisory Group Collaborations	N/A	N/A	See Note 1	N/A	See Note 1	
C6: Enhance Training Programs and Career Incentives	N/A	Working Group Support Yr 1 ..... \$150K Yr 2 ..... \$ 50K	See Note 1	Working Group Meetings Yr 1 ..... \$150K Yr 2 ..... \$ 50K	Yr 1 ..... \$300K Yr 2 ..... \$100K Yr 3 ..... \$ 0K Yr 4 ..... \$ 0K Yr 5 ..... \$ 0K	
Evaluation						
Implementation of TRWG Initiatives	N/A	Yr 1 ..... \$350K Yr 3 ..... \$350K Yr 5 ..... \$350K	N/A	N/A	N/A	N/A

Note 1: Included in Translational Research Support Office expenses for Initiative A1 (see page 86).

**Table 3. Estimated Implementation Budget by Year**

Initiative	Expenses					
	Year 1—FY08	Year 2—FY09	Year 3—FY10	Year 4—FY11	Year 5—FY12	
Coordinated Management						
A1 Integrated NCI Management	\$800K	\$800K	\$850K	\$850K	\$850K	
A2: Budget Designation	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1
A3: Translational Research Coding	N/A	\$150K	\$150K	\$150K	\$150K	
A4: Prioritization Process	\$950K	\$750K	\$750K	\$750K	\$750K	
<b>Tailored Funding Programs</b>						
B1: Modify Translational Research Award Guidelines	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1
B2: Improve Investigator-Initiated Translational Research Awards	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1
B3: Special Translational Research Acceleration Project (STRAP) Awards	N/A	N/A	\$10M	\$20M	\$30M	
B4: Academia/Industry Collaboration Awards	N/A	N/A	N/A	\$5M	\$10M	
B5: Integrated Development Services	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1
<b>Operational Effectiveness</b>						
C1: Project Management	\$1.35M	\$1.30M	\$1.55M	\$1.75M	\$2.0M	
C2: Core Services Coordination	\$200K	\$370K	N/A	N/A	N/A	
C3: Enhance Biorepositories	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1
C4: Improve Intellectual Property Negotiations	\$100K	\$520K	N/A	N/A	N/A	
C5: Enhance Foundation/Advisory Group Collaborations	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1	See Note 1
C6: Enhance Training Programs and Career Incentives	\$300K	\$100K	N/A	N/A	N/A	
<b>Evaluation</b>						
Implementation of TRWG Initiatives	\$350K	N/A	\$350K	N/A	\$350K	
<b>TOTALS</b>	<b>\$4.05M</b>	<b>\$3.99M</b>	<b>\$13.65M</b>	<b>\$28.5M</b>	<b>\$44.1M</b>	
<b>5-YEAR TOTAL</b>						<b>\$94.29M</b>

Note 1: Included in Translational Research Support Office expenses for Initiative A1 (see page 86).



## Evaluation and Outcome Measures

### Introduction

Formal evaluation is an integral part of effective program or enterprise management. It provides a rational basis for assessing the relationship between the strategies and tactics implemented in a program and their efficacy in achieving the desired goals and for identifying appropriate corrective action if needed.

The initiatives proposed by the TRWG recognize the importance of evaluation in the context of activities, such as early translational research, that are strongly goal oriented. The introduction of milestone-based project management for complex projects such as those supported by the proposed STRAP awards brings evaluation down to the project level and deploys it as a tool to increase productivity. A comparable evaluative discipline must be applied to measuring the effect of the TRWG initiatives on the translational research enterprise as a whole in order to ensure effective use of the scarce resources entrusted to it.

Evaluation at the program or enterprise level should address both process and outcomes. Process assessment is important in order to have confidence that the effort is proceeding appropriately during its initial phase, as well as to create a basis for charting a revised course of action if needed. Outcomes assessment is essential to confirm that the effort is achieving its goals.

Evaluation of translational research programs presents several challenges. First, important dimensions of performance cannot be fully captured using purely objective and quantitative measures. The measures must include a judicious blend of qualitative and quantitative, objective and subjective measures. Second, although translational research is strongly goal oriented, its results nevertheless remain somewhat unpredictable, and can depend to a significant degree on factors beyond the control of the participants. And third, translational research is a complex system in which multiple internal and external factors interact in many different ways—some observable, and some not—to affect outcomes. Thus, attribution of observed outcomes to particular policies, organizational structures, or management decisions can be difficult.

### Use of Measures

An evidence-based approach is essential. The determination of success or failure and decisions on any needed course corrections will not be automatic or mechanical, but a matter of judgment by experts in the field. However, this expert judgment must be informed by systematic, structured empirical data so that there will be a shared basis for discussion and decision-making. The measures used do not serve as the sum total of the evaluation, but as essential “raw material” for a larger process of expert judgment in which the broad oncology research community must participate.

The needed measures fall into three categories:

- Program management process measures that evaluate implementation of the initiatives recommended by the TRWG
- System process measures that evaluate the effect of the changes in operational processes on coordination, prioritization, management, funding, and conduct of translational research
- System outcome measures that assess the intended result—an increased number of new treatments, diagnostic methods, etc., that are “handed off” to middle and late-stage trials for definitive evaluation.

To evaluate the impact of the proposed initiatives, it is essential to conduct a baseline evaluation of selected measures prior to implementation. Only then can the effect of change be recognized. It is also essential to set realistic timelines for achievement of the objectives so that evaluation is not attempted either too early or too late in the process. For example, certain process measures may be relevant only after other processes on which they depend have been completed. Similarly, it may be a matter of years before it is reasonable to expect certain outcomes to be apparent. Nevertheless, many process measures can be fruitfully assessed at intervals to document the progress of the initiatives.

As well-defined measures do not currently exist for many elements of the NCI translational research enterprise, establishing specific measures will be an ongoing and iterative process. NCI will engage experienced evaluation specialists to assist in development of these measures as well as the survey instruments, statistical adjustments, and other tools required to conduct the evaluations and render the evaluation measures practical and valid. These specialists will also work with NCI to determine the appropriate timing for examining the various measures based on implementation timelines and the impacts envisioned. A baseline evaluation of relevant elements of the current system will be conducted as soon as possible to provide a reliable basis for ascertaining the value of the initiatives. The results of this baseline evaluation will be analyzed to determine whether the chosen measures are valid or should be eliminated or revised.

## Categories of Measures

### Program Management Process Measures

These measures will be tracked by NCI on a continuing basis as part of its management of initiative implementation and will be assessed in light of the proposed implementation plan and timeline. Questions to be addressed include:

- Were the tasks initiated on time?
- Did they follow the implementation plan as outlined?
- If obstacles were encountered, were alternate plans implemented quickly and effectively?
- Were the tasks accomplished on time or were timelines revised in a timely and realistic fashion?

### System Process Measures

The proposed initiatives have three key process objectives:

- Improved coordination and more active, goal-oriented, and transparent management of the translational research enterprise
- More effective tailoring of funding programs to the specific characteristics and needs of translational research
- Enhanced operational efficiency and effectiveness of translational research projects and the many supporting activities that are essential to the enterprise.

In addition, these improvements are expected to encourage greater interest and involvement in translational research by investigators. Thus, a fourth process objective can be added:

- Increased translational research activity.

To accomplish these objectives, the proposed initiatives envision implementing new structures, processes, and behaviors on the part of participants in the enterprise. The system process measures must therefore provide empirical evidence of whether the new structures and processes are effective, whether the targeted behaviors are changing in the intended ways, whether the level of activity is increasing, and whether the impacted components and the system as a whole are in fact becoming more coordinated, more collaborative, more transparent, more goal oriented, more efficient, and more productive, as well as better managed and better prioritized. Measures should also be included to verify that the new objectives are not achieved at the expense of other valued characteristics of the translational research enterprise as it exists today.

Some of the system characteristics can be assessed via objective measures, while others must be assessed subjectively, through a systematic and transparent process of soliciting expert opinion. It is important to remember that no single measure will provide a conclusive indicator of success, nor a basis for attribution of cause and effect. Rather, each

measure must be combined with the others and included in a larger, comprehensive evaluation by a broad range of critical stakeholders.

### **System Outcome Measures**

The most important and meaningful outcome measures for evaluating the success of the TRWG initiatives will be those that assess the extent to which there is an increased number of new cancer treatments, diagnostic methods, and other interventions advanced to middle- and late-stage trials.

In practice, however, development often occurs on very long timescale—as long as a decade or more. In evaluating programs that are characterized by such long timescales, it is common to include proxy outcome measures as well. Such proxy measures capture certain critical aspects of system activity, and as such could also be viewed as process measures. However, if the proxy measures are sufficiently tightly linked to the ultimate desired outcome, they can constitute a useful interim guide to progress.

Proposed system outcome measures will therefore include the following:

- Number of new therapies, diagnostic/screening tests, lifestyle alternations, preventive agents, etc., that successfully complete NCI-supported early (Phase I or II) human testing and are judged suitable for late-stage testing
- Number of new therapies, diagnostic/screening tests, etc., handed off to industry for further development from any point in the developmental pathway
- Number of new therapies, diagnostic/screening tests, lifestyle alternations, preventive agents, etc., under NCI-supported development according to one of the TRWG developmental pathways (proxy measure).

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## Appendices

**Appendix A: Foundational Documents**

**Appendix B: TRWG Translational Research Definition and Scope of Activity**

**Appendix C: TRWG Developmental Pathways to Clinical Goals**

**Appendix D: Translational Research Portfolio for the NCI Translational Research Working Group**

**Appendix E: Process Analysis for the NCI Translational Research Working Group**

**Appendix F: TRWG Meeting Dates**

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## Appendix A: Foundational Documents

Food and Drug Administration. Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products, March 2004.

<http://www.cancer.gov/pdf/trwg/Critical-Path-whitepaper.pdf>

National Cancer Advisory Board. Advancing Translational Cancer Research: A Vision of the Cancer Center and SPORE Programs of the Future, Report of the P30/P50 Ad Hoc Working Group, February 2003.

<http://deainfo.nci.nih.gov/advisory/ncab/p30-p50/P30-P50final12feb03.pdf>

National Cancer Advisory Board. Cancer at a Crossroads: A Report to Congress for the Nation, Report of the Subcommittee to Evaluate the National Cancer Program, September 1994.

<http://www.cancer.gov/pdf/trwg/Cancer-at-a-Crossroads.pdf>

National Cancer Advisory Board. Restructuring the National Cancer Clinical Trials Enterprise, Report of the Clinical Trials Working Group, June 2005.

[http://integratedtrials.nci.nih.gov/ict/CTWG\\_report\\_June2005.pdf](http://integratedtrials.nci.nih.gov/ict/CTWG_report_June2005.pdf)

National Cancer Institute. Report of the Kidney/Bladder Cancers Progress Review Group, August 2002.

<http://planning.cancer.gov/pdfprgreports/2002kidneyreport.pdf>

National Cancer Institute. Report of the Leukemia, Lymphoma, and Myeloma Progress Review Group, May 2001.

<http://planning.cancer.gov/pdfprgreports/2001llm.pdf>

National Cancer Institute. Report of the Lung Cancer Progress Review Group, August 2001.

<http://planning.cancer.gov/pdfprgreports/2001lung.pdf>

National Cancer Institute. Report of the Sarcoma Progress Review Group: A Roadmap for Sarcoma Research, January 2004.

<http://planning.cancer.gov/pdfprgreports/2004sarcoma.pdf>

National Cancer Institute. Report of the Stomach/Esophageal Cancers Progress Review Group, December 2002.

[http://planning.cancer.gov/stomach/stomach\\_esophageal.pdf](http://planning.cancer.gov/stomach/stomach_esophageal.pdf)

National Institutes of Health. NIH Roadmap for Medical Research, Re-engineering the Clinical Research Enterprise, October 2006.

<http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp>

The President's Cancer Panel. Translating Research into Cancer Care: Delivering on the Promise, 2004-2005 Annual Report, National Institutes of Health, National Cancer Institute, June 2005.

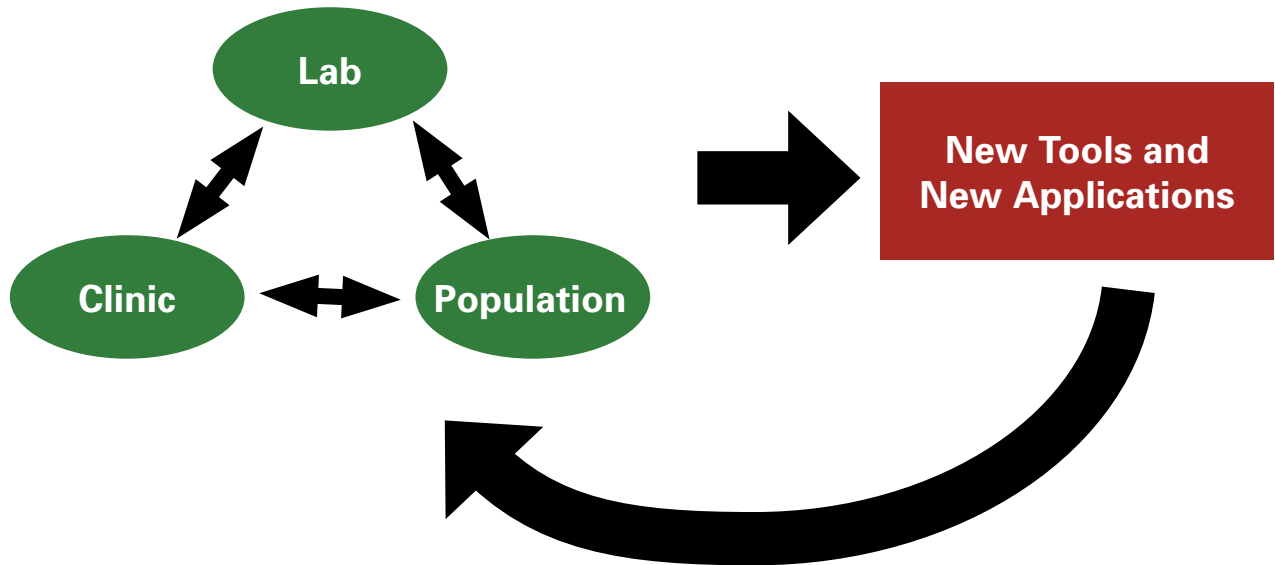
<http://deainfo.nci.nih.gov/ADVISORY/pcp/pcp04-05rpt/ReportTrans.pdf>



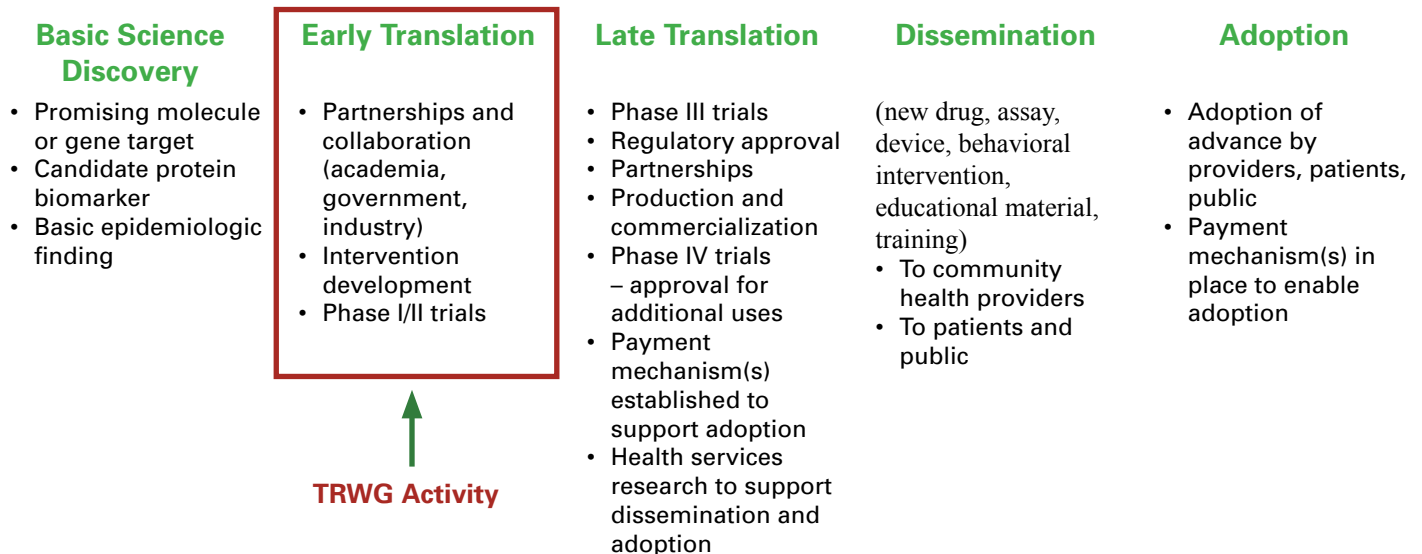
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## Appendix B: TRWG Translational Research Definition and Scope of Activity

*“Translational research transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce cancer incidence, morbidity, and mortality.”*



### The Translational Continuum\*



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

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## Appendix C: TRWG Developmental Pathways to Clinical Goals

### Introduction to the TRWG Developmental Pathways

The TRWG has constructed six “developmental pathways” that characterize the transformation of scientific discoveries into new clinical modalities for oncology. These modalities fall into two fundamental and complementary categories:

Risk assessment modalities, intended to characterize the cancer-related health status of an individual:

- Biospecimen-based risk assessment devices (protocols, reagents, instruments, etc.)
- Image-based risk assessment (agents or techniques).

Interventive modalities, intended to change the cancer-related health status of an individual, via prevention or treatment:

- Agents (drugs or biologics)
- Immune response modifiers (vaccines, cytokines, etc.)
- Interventive devices
- Lifestyle alterations.

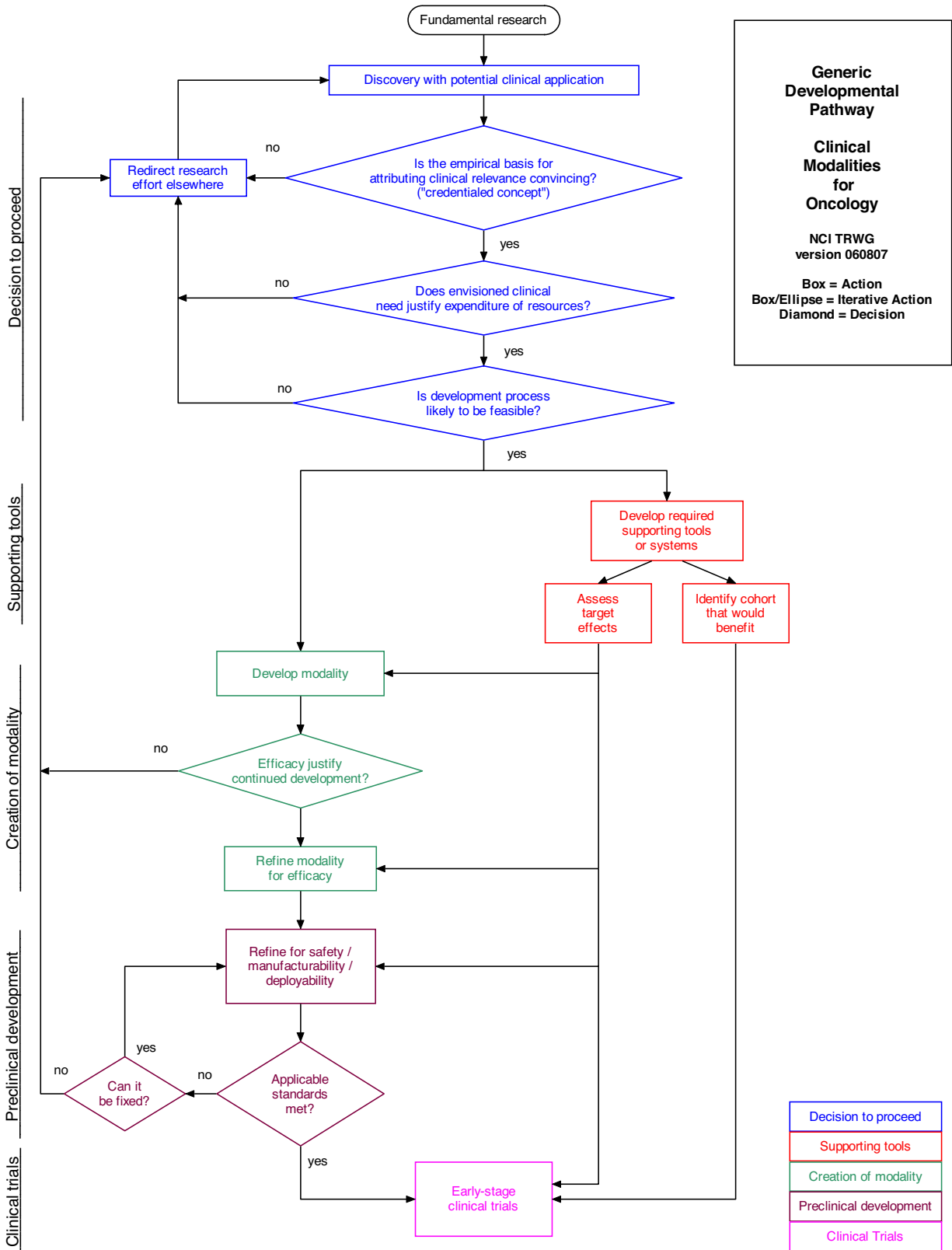
The developmental pathway diagrams outline the processes through which fundamental scientific discoveries are transformed into these clinical modalities. The diagrams specify key activities and decision points along the development path, clarify dependencies among different steps as well as key events that occur in parallel, and show important feedback loops and iterative processes that are embedded within the development process.

The primary purpose of these pathways is to facilitate TRWG discussions by clarifying certain essential characteristics of the early translation process. TRWG members have used them to help understand the challenges faced by translational researchers and to identify ways to help the translational research process function more effectively. For example, the pathway diagrams stimulated fruitful discussion among TRWG members and participants in the first TRWG public roundtable about relationships among different elements of the translational research effort, resources needed, and barriers that stand in the way of more rapid progress.

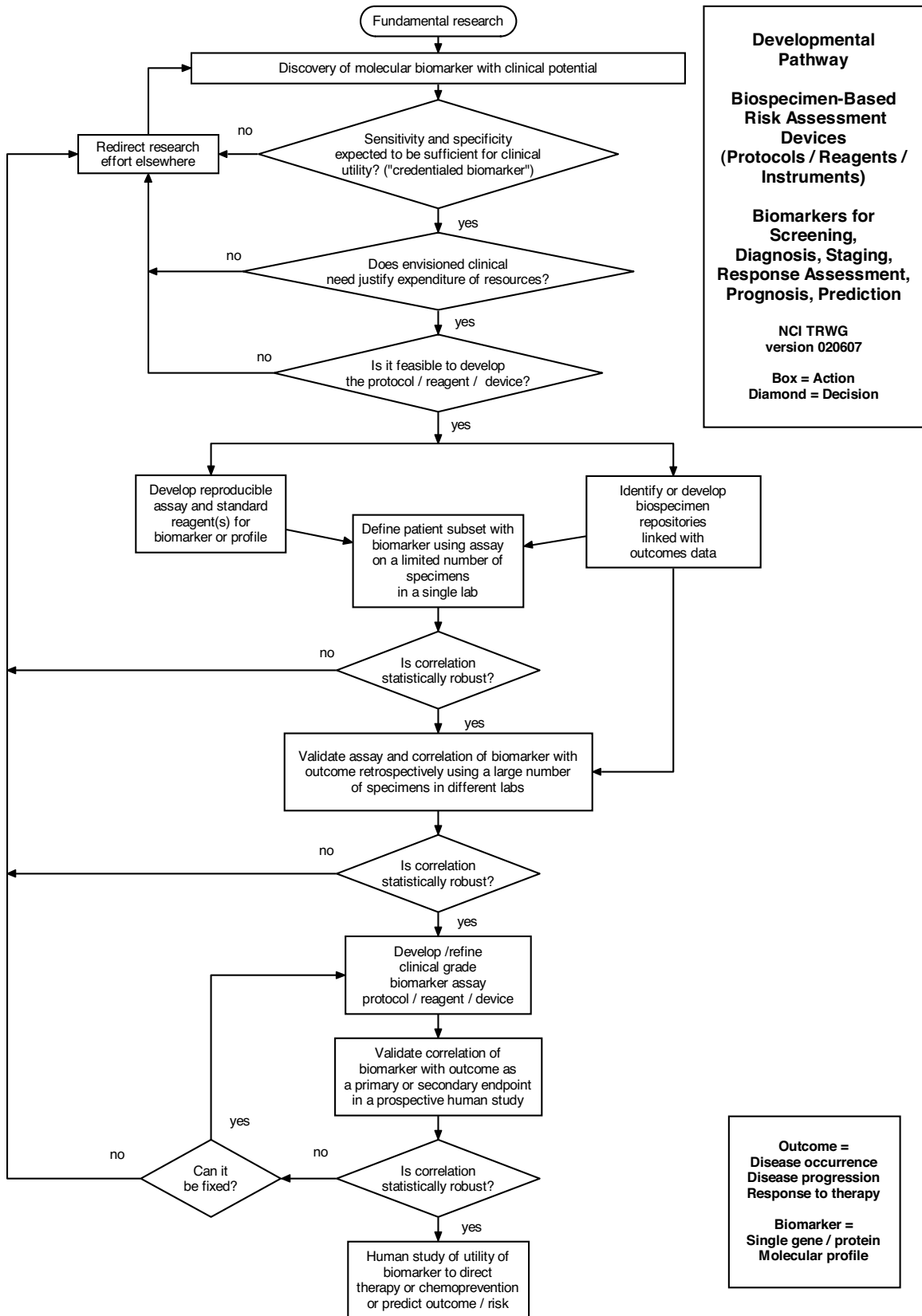
In creating these pathways, the TRWG was aware that such idealized representations cannot capture the full complexity of the real world. For each activity, decision point, parallel path, or feedback loop, it is understood that there are many more variations that can occur—and indeed have occurred—in practice and that not all steps may occur in each instance. In addition, these diagrams do not capture the full range of possible interactions between the pathways, nor do they address the ways in which insights gained from late-stage clinical trials can influence the development process. Finally, there has been no attempt to address the influence of market conditions, projected financial return, or reimbursement considerations on development pathway decisions made in the commercial sector.

To facilitate understanding of the pathways, a generic pathway template was also created which captures the common elements of the pathways in simplified form. The generic pathway applies equally to both the risk assessment and the interventive modalities. Note that, for interventions, some of the supporting tools required in the development process (red box in the right-hand sequence of the generic pathway) are themselves risk assessment modalities.

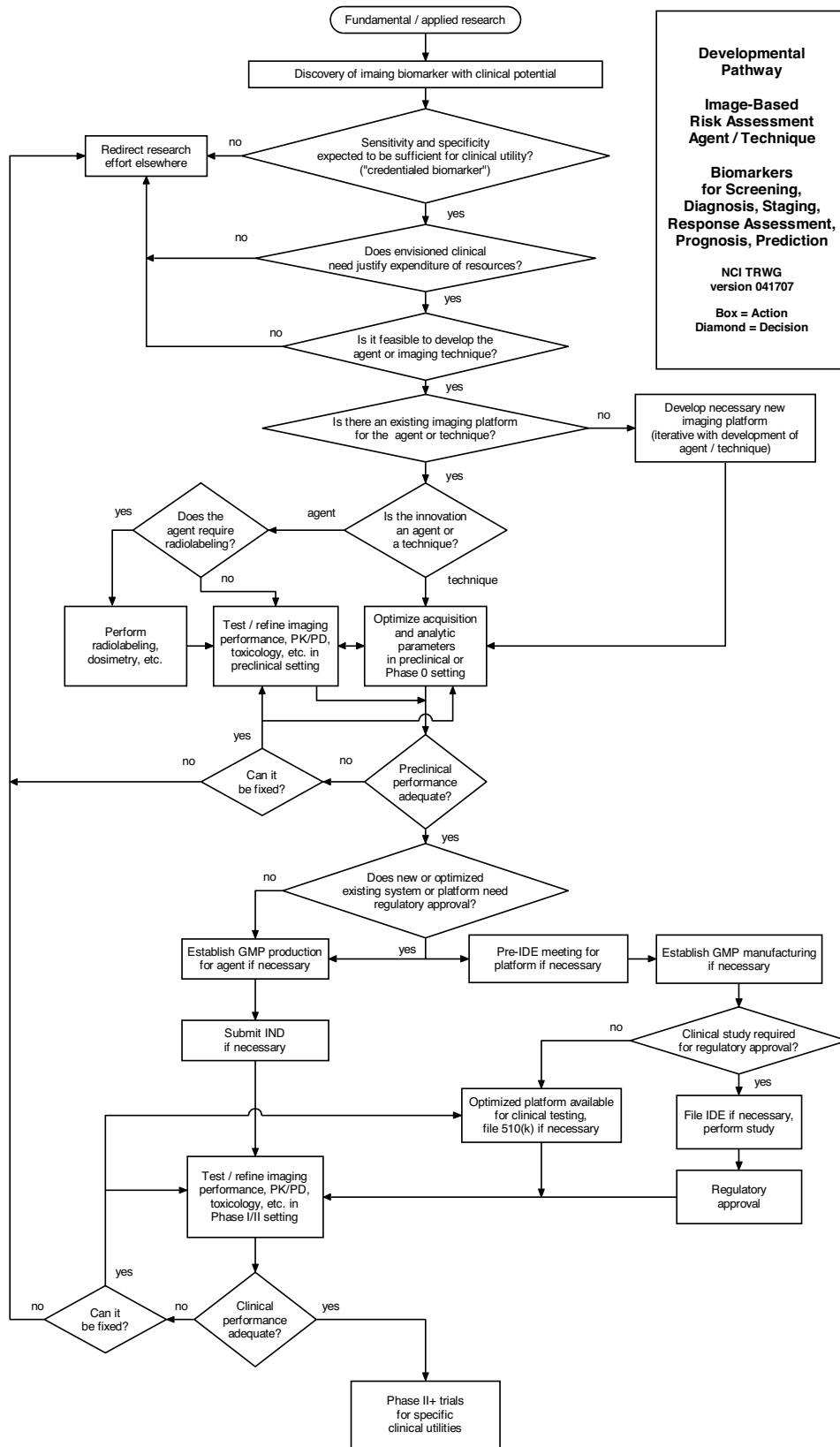
**Generic Developmental Pathway: Clinical Modalities for Oncology**



**Biospecimen-Based Risk Assessment Devices (Protocols, Reagents, Instruments, etc.)**

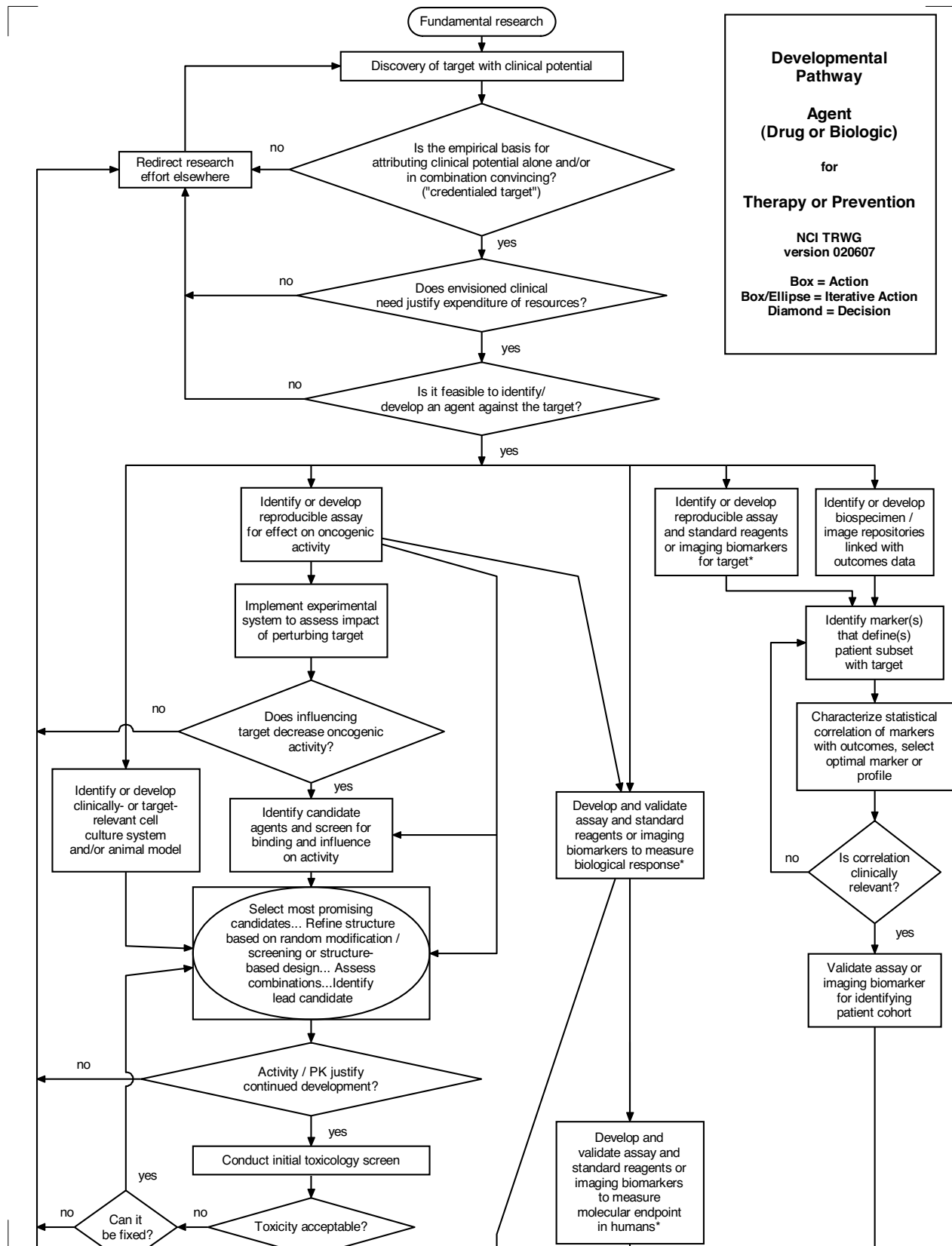


### Image-Based Risk Assessment (Agents or Techniques)

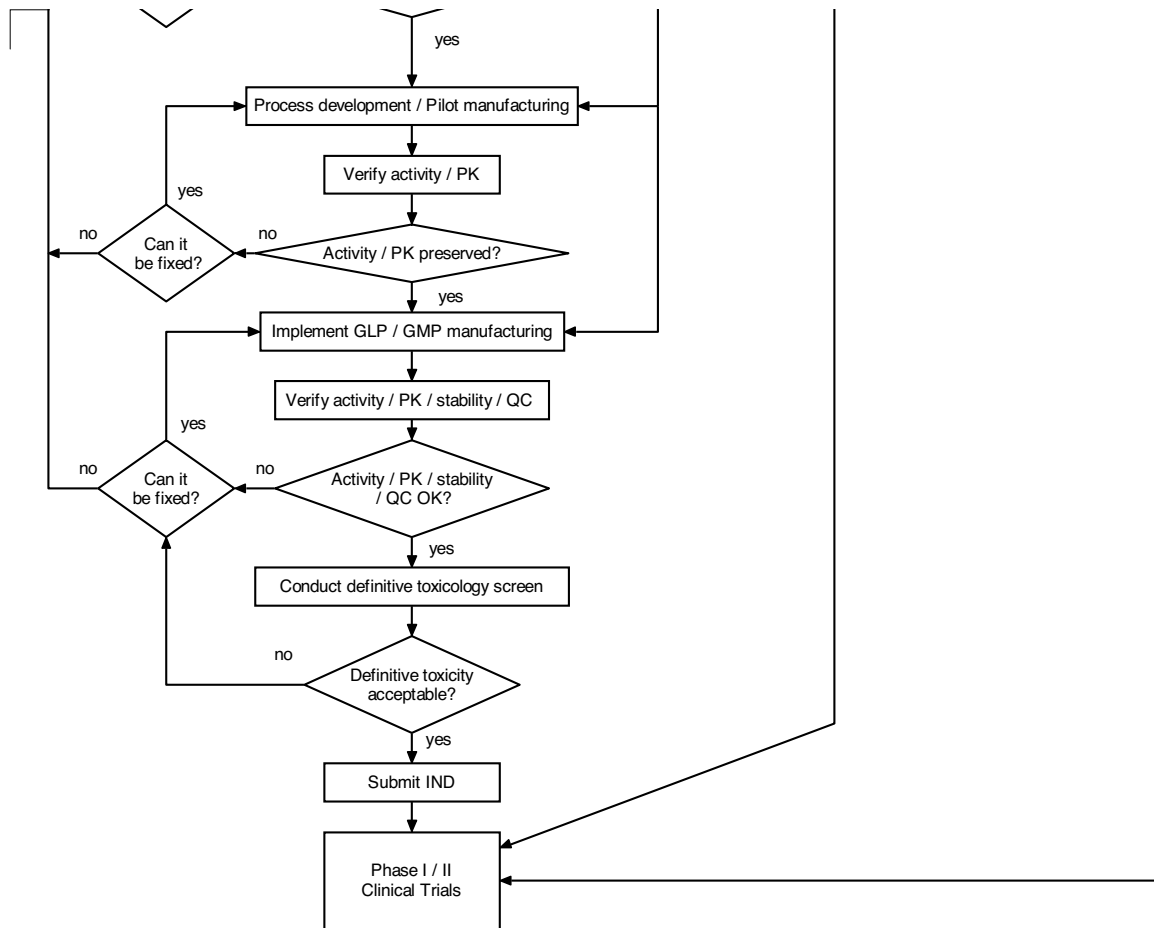




Agents (Drugs or Biologics) page 1 of 2

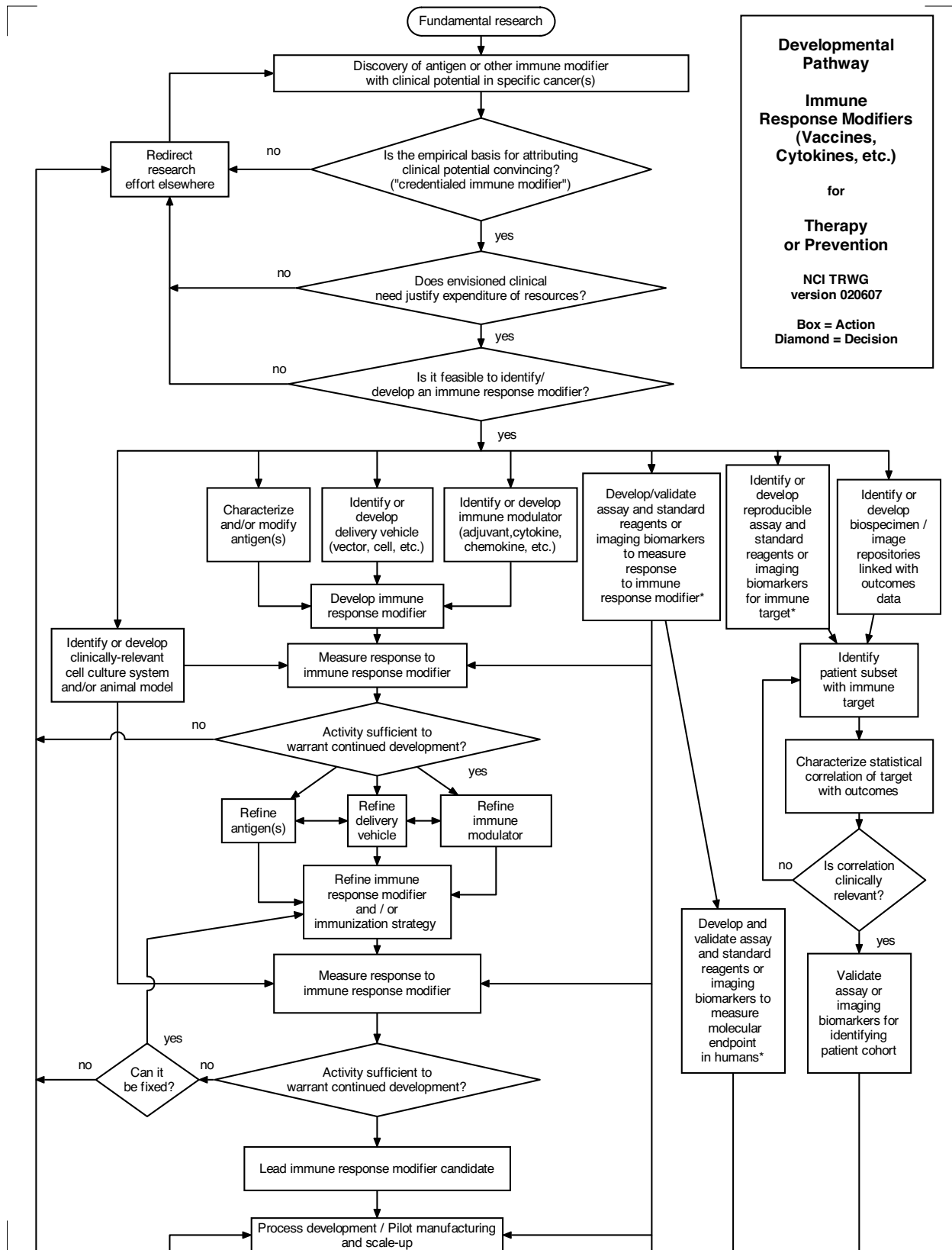


Agents (Drugs or Biologics) page 2 of 2

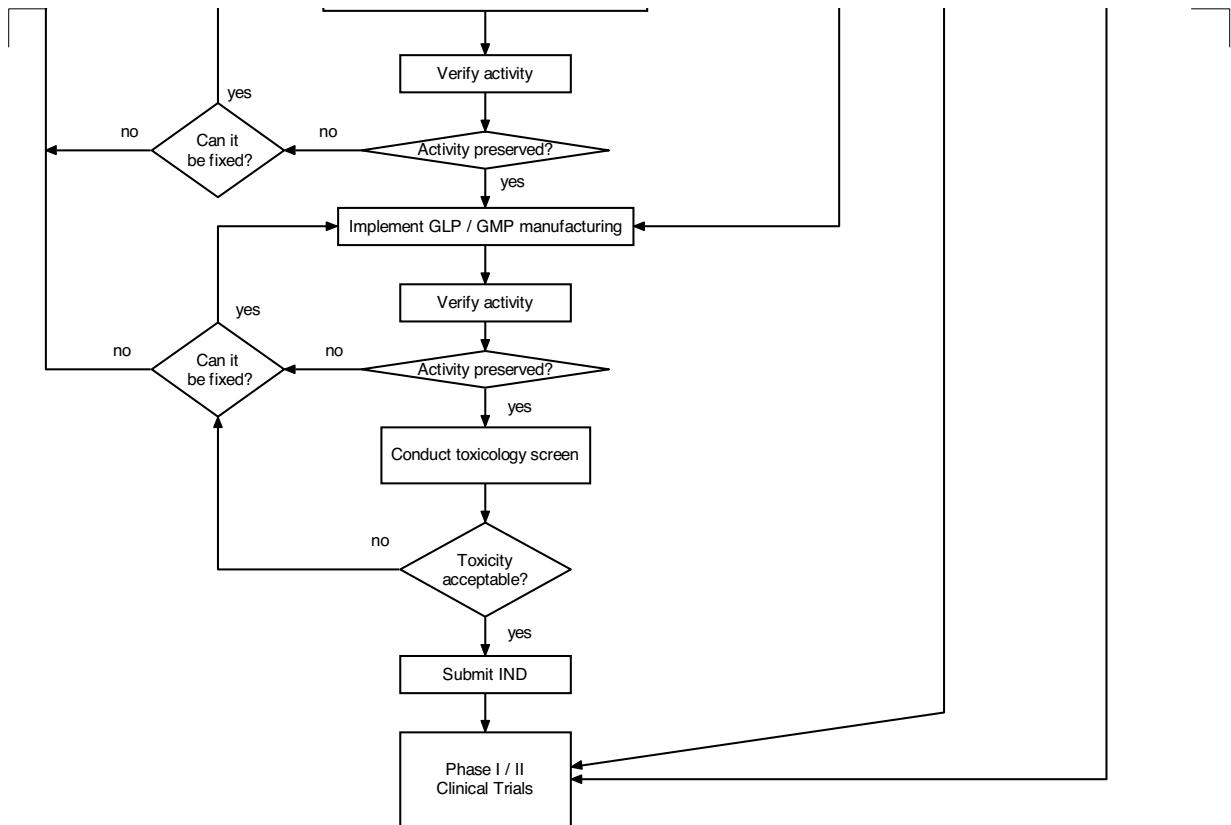


\*see Biospecimen RAD and Imaging Pathways

**Immune Response Modifiers (Vaccines, Cytokines, etc.) page 1 of 2**



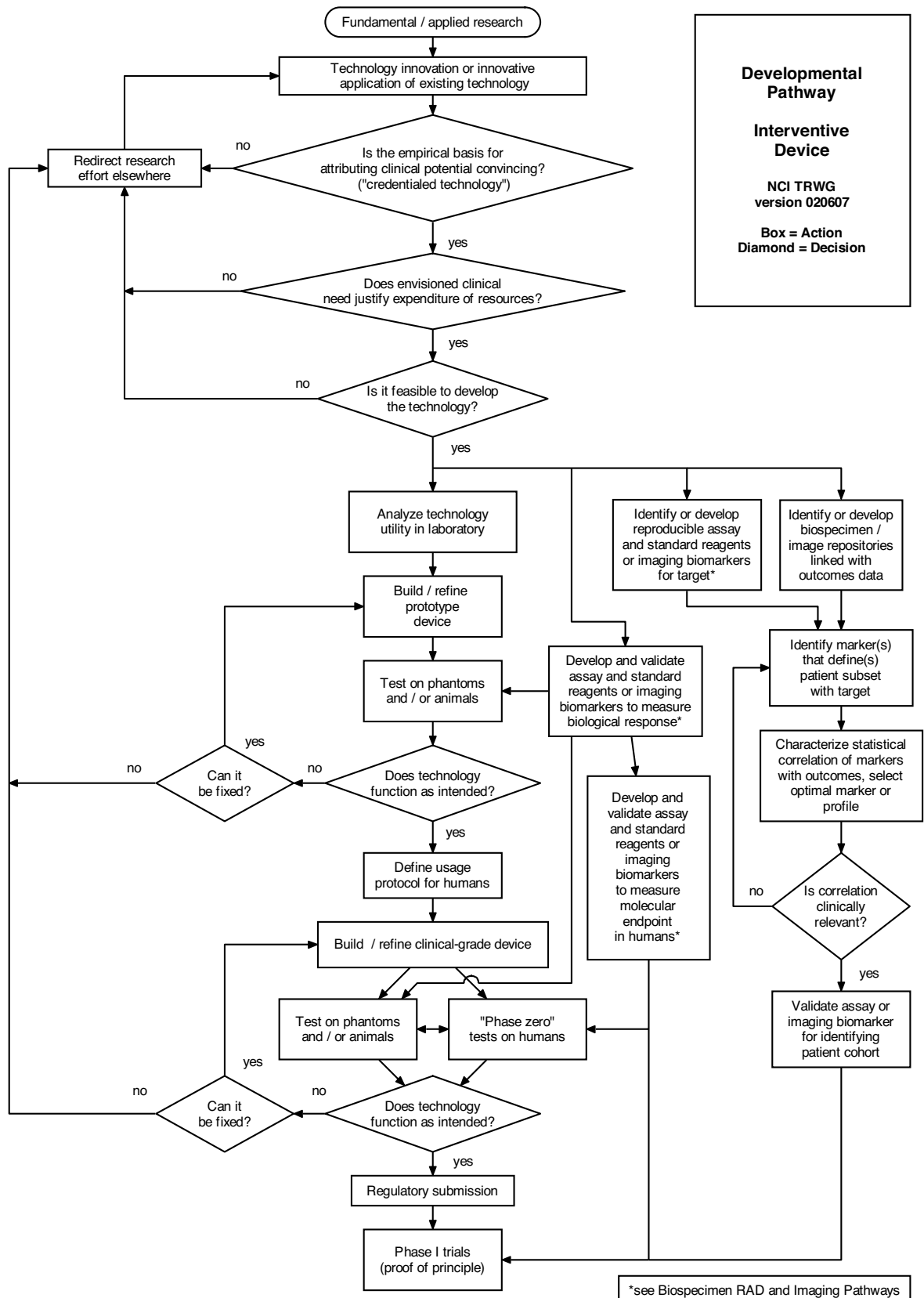
Immune Response Modifiers (Vaccines, Cytokines, etc.) page 2 of 2



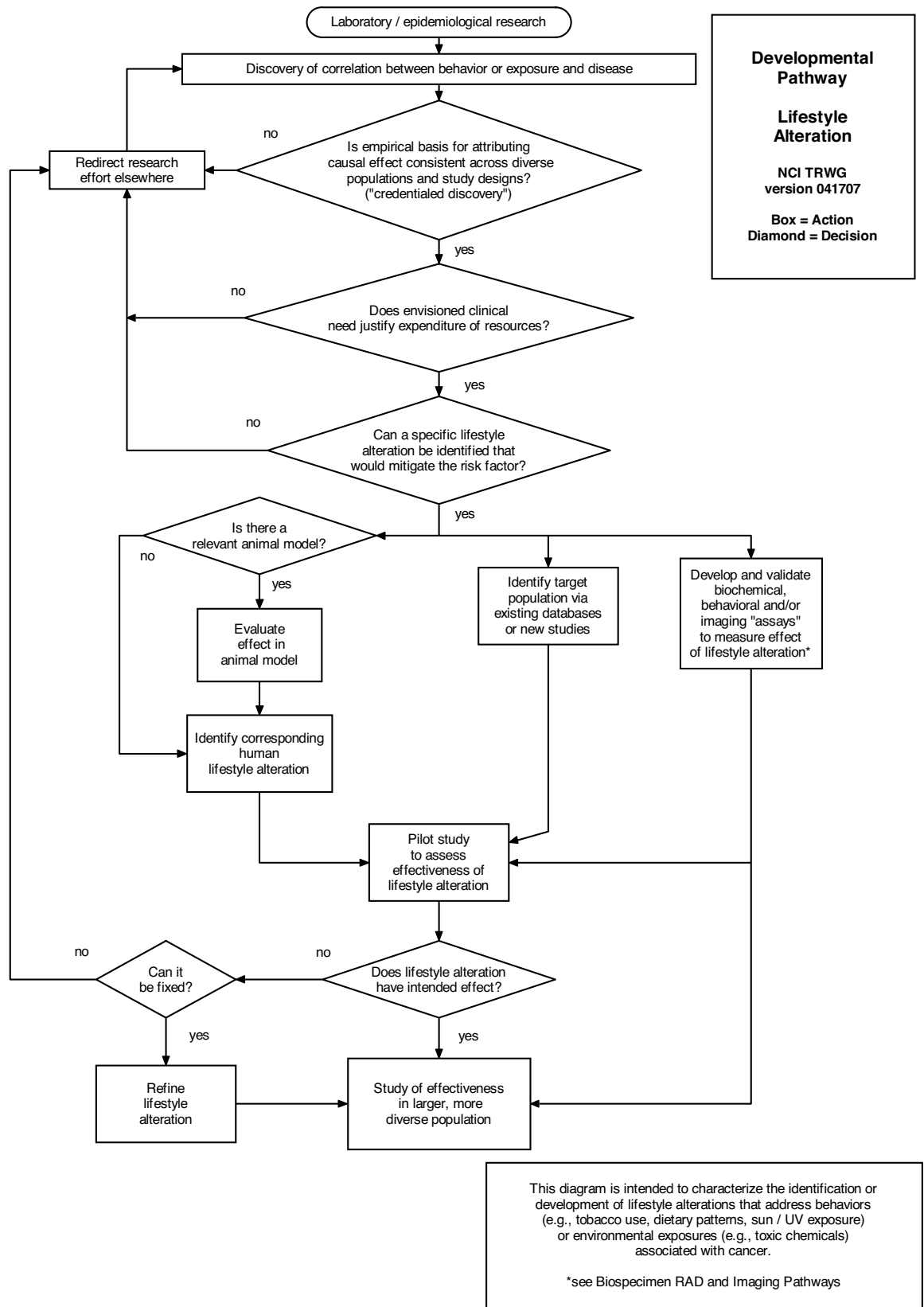
Note: This pathway is designed to accommodate immune response modifiers of two types: "simple" (such as a cytokine used directly as a therapeutic agent) and "composite" (such as a vaccine that incorporates an antigen, a vector and an immune modulator). For simple agents, the extra boxes that are incorporated in the diagram to capture parallel development of the components of a composite product may be ignored.

\*see Biospecimen RAD and Imaging Pathways

Interventive Devices



Lifestyle Alterations



## Appendix D: Translational Research Portfolio for the NCI Translational Research Working Group

### Introduction and Summary

The National Cancer Institute (NCI) supports research that spans basic through clinical investigations. Specific research awards may predominantly address basic research, translational research, clinical research, or a combination. The NCI's fiscal year 2004 research portfolio was analyzed to understand the Institute's overall effort in translational research, inform the deliberations of the NCI Translational Research Working Group (TRWG), and serve as a pilot for future efforts at analyzing translational research. This document presents the methods used for identifying NCI's translational research awards and programs and the summarized results of the analysis.

### Key Findings

1. The portfolio analysis identified awards valued at \$1.3 billion (relative to a total NCI research budget of \$4.4 billion in FY 2004<sup>1</sup>) that fit the inclusion criteria for “translational research” (see subsequent discussion for specific criteria). As the criteria were applied expansively—including as “translational” all awards that had any translational component—the portfolio likely overestimates the value of NCI-sponsored translational research. A more detailed assessment of a sample of 65 R01 awards for the degree of their translational research relevance (see page 114, Validity of Translational Research Funding Estimate) suggests that this estimate of overall funding for translational research may be high by 20-40%.
2. Awards identified as “translational” are distributed throughout the Institute. All NCI award-sponsoring Offices, Centers, and Divisions fund translational research, to varying degrees (Figures 1A, 1B, and 1C).
3. Awards identified as “translational” are distributed across many different funding mechanisms to varying degrees (Figures 2A, 2B, and 2C and Tables 1 and 2). Approximately the same dollar value of “translational” funds is awarded through program and cooperative award mechanisms and through individual research awards.
4. The majority of “translational” funds are awarded to institutions with NCI-designated cancer centers (Figures 3A and 3B). The percentage of NCI funding identified as “translational” at both institutions with NCI-designated cancer centers and those without them is similar (Figure 3C).

### Methodology

#### Criteria for Including Awards as “Translational Research”

The scope of activity of the TRWG can be defined as “early translation” based on the continuum developed by the President's Cancer Panel.<sup>2</sup> With this and the interest in capturing the broadest possible landscape in mind, criteria were defined to identify awards to be included in the analysis. An award abstract that met at least one of the inclusion criteria for a single specific aim was considered “translational,” even if a significant portion of the proposed work did not meet the criteria. Generally, awards were identified as “translational research” based on the award abstract proposing to conduct research that would result in moving a discovery along the pathway to a defined clinical goal or product according to the bench-to-bedside model, including using clinical research results to guide basic laboratory studies. If an award abstract did not meet any of the inclusion criteria, the award was not considered translational.

The following criteria were used to identify awards to be included in the portfolio:

- 1 “Fact Book,” National Cancer Institute, 2004, page B-2. Available at: <http://fmb.cancer.gov/financial/04Factbk.pdf>. The total NCI budget in FY 2004 was \$4.7 billion, from which the \$329 million for “Program Management and Support” was excluded.
- 2 <http://deainfo.nci.nih.gov/advisory/pcp/pcp04-05rpt/ReportTrans.pdf>.



- Studies of agents, including chemical, biological, immunologic, imaging, etc., at any stage from evaluating the agent in relevant model systems through Phase II clinical trials
- Studies of markers and assays to measure the efficacy of an agent or interventional device, at any stage from development of an assay to testing for clinical utility in preclinical and clinical studies
- Studies of interventional devices anywhere along the continuum from building a complete prototype device to testing a device in Phase II clinical trials in humans
- Studies of biomarkers and assays for detection, diagnosis, prognosis, and prediction anywhere along the path from epidemiologic findings to a trial of the clinical utility of the marker in humans
- Studies of imaging devices anywhere along the continuum from building a complete prototype device to testing the clinical utility of the device in humans
- Endogenous (e.g., genetic and molecular) and exogenous (e.g., viral, dietary, environmental) epidemiologic studies involving a sample population of at least 150 cases
- Awards that include the creation or expansion of repositories of cohort data and/or specimen banks
- Lifestyle, dietary, or behavioral studies that develop and validate or test an intervention for cancer control and/or prevention purposes (e.g., tobacco use cessation, changes to diet/exercise, increased participation in cancer screening)
- “Bedside-to-bench” studies in which results from preclinical and clinical studies of agents and devices are used to enhance the capacities of the agents or devices, including the evaluation of basic mechanisms newly inspired by the preclinical or clinical studies
- Awards for core facilities and shared resources involved in translational research
- Awards that propose to conduct Phase I and/or Phase II clinical trials
- Phase III clinical trial awards that include a correlative research component.

The following are examples of types of awards that were not considered “translational”—awards that fell only into these categories were excluded from the translational research portfolio:

- Discovery or mechanistic studies
- Studies designed entirely to develop a model, whether biologic, population, statistical, or other type
- Small-scale, hypothesis-generating epidemiology studies
- Development of tools to enable basic or clinical research (e.g., computer software, nonclinical assays, enhancements to proteomics/arrays)
- Late-phase clinical trials, with no indication of correlative components
- Surveillance, survivorship, and outcomes research
- Studies to develop components of new devices/assays but not to develop a complete prototype device or assay
- Development of educational materials for care providers or general cancer educational materials—materials not directly intended to change a behavior to control or prevent cancer
- Studies that reference long-term translational goals subsequent to the current grant funding period
- Awards for which the abstract is ambiguous or unavailable.

## Data Collection

The analysis was based on all awards active in Fiscal Year 2004 as contained in the Cancer Research Portfolio database system.<sup>3</sup>

Analyzing research projects requires either using data from an established coding system or evaluating research project abstracts to classify the projects. Translational research is not captured in any of the codes applied to grants, such as Special Interest Category (SIC) or NIH Clinical Aspect (NIHCA) codes; therefore, individual project abstracts were evaluated to identify the translational grants. Projects were filtered to limit the analysis to the subset of the portfolio most likely to include translational research projects. A set of funding mechanisms and initiative programs was entirely included in the analysis due to the focused translational nature of the programs (e.g., Specialized Programs of Research Excellence [SPOREs], Small Business Innovation Research [SBIR]/Small Business Technology Transfer [STTRs], Rapid Access to Intervention Development [RAID]). For other funding mechanisms, the NIHCA<sup>4</sup> code was used to filter the projects to analyze only those with 25%-100% clinical aspect. Other funding mechanisms were entirely excluded due to either the unavailability of abstracts (e.g., contract awards such as the N01 mechanism) or their emphasis on nonresearch goals (e.g., training and education awards such as T32 and R25).

The following award categories were included without review of abstracts or specific application of the inclusion criteria due to (1) the lack of detail in project abstracts and the perception that these are translational, and (2) the inclusion of Phase I and II clinical trials as translational research:

- All Clinical and Comprehensive P30 Cancer Centers (but no Basic Cancer Centers)
- All K12 mechanism clinical oncology research career development awards
- All projects of the RAID and Drug Development Group (DDG) programs, sponsored by the NCI's Developmental Therapeutics Program
- All projects of the Rapid Access to Preventive Intervention Development (RAPID) program, sponsored by the NCI's Division of Cancer Prevention.

In the following award categories, abstracts were reviewed for translational components according to the inclusion and exclusion criteria:

- All awards funded through the following initiatives: Specialized Programs of Research Excellence, Early Detection Research Network (EDRN), Mouse Models of Human Cancers Consortium (MMHCC), Network for Translational Research: Optical Imaging (NTROI), *In Vivo* Cancer Molecular Imaging Centers (ICMICs), and Integrative Cancer Biology (ICB)
- All Phase 1 and Phase 2 SBIR and STTR awards (mechanisms R41, R42, R43, and R44)
- All intramural research awards (Center for Cancer Research [CCR] and "Parent" Division of Cancer Epidemiology and Genetics [DCEG])
- R24 and U24 Core facility awards.

<sup>3</sup> The Cancer Research Portfolio (CRP) is a public Web site with information on cancer research and funding opportunities gathered from the NIH-wide Information for Management, Planning, Analysis, and Coordination (IMPAC II). The CRP is managed through the NCI Office of Science Planning and Assessment.

<sup>4</sup> NIHCA codes are quartile-based measures, assigned by NCI's Research Analysis and Evaluation Branch (RAEB), of the relevance of projects to the NIH definition of clinical research. NIH defines human clinical research as follows: (1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies. (2) Epidemiologic and behavioral studies. (3) Outcomes research and health services research.

In the following award categories, only awards with 25%-100% NIHCA codes were reviewed for translational components according to the inclusion and exclusion criteria:

- K01, K05, K07, K08, K22, K23, and K24 career development awards
- P01, P20, R01, R03, R21, R33, R37, U01, U19, U54, and U56 awards.

Awards coded as translational were stratified using the sponsoring Division, the common scientific outline (CSO) codes, and the institutions where the research grants are held to identify patterns of translational research projects. For example, research institutions were aggregated into three categories based on the available institutional data. All translational intramural awards were collected in one category, and the translational extramural awards were divided into two categories—those where the research grants were held at clinical and comprehensive NCI-designated cancer centers and those where the grants were held at other institutions (including basic cancer centers).

### **Assessment of Inclusion Criteria—P01/R01 Analysis**

To gain insight into the validity of the classification system for P01 and R01 awards, two analyses were undertaken. First, NCI program directors identified awards in two groups: translational and not translational. They identified a total of seven P01 awards as translational and 11 P01 awards as not translational. For each of these awards, the classification assigned by the program directors was compared with the classification of these same awards in the original portfolio analysis based on review of the abstracts. In this exercise, six of the seven P01 awards identified as translational by the program directors had also been coded as translational during the original portfolio analysis. Moreover, 9 of the 11 P01 awards identified as not translational by the program directors had also been coded as not translational during the original portfolio analysis.

Second, a set of 36 R01 awards active in FY 2004 were identified by TRWG members as translational awards. The classification of these awards based on abstract review during the original portfolio analysis was as follows:

- Thirty awards had been classified as translational.
- Two awards had been classified as not translational.
- Four awards were not included in the abstract review because they had a 0% NIHCA code.

These results indicate that the inclusion criteria were reasonably accurate in identifying awards that would be considered translational by NCI program directors and TRWG members.

### **Validity of Translational Research Funding Estimate**

To gain insight into the accuracy of the translational research funding estimate (see Table 1), 100 randomly selected awards from the list of R01 awards classified as translational in the original portfolio analysis were evaluated for the extent to which they were truly translational based on specific aims. Of the 100 awards, 65 were determined to have abstracts that clearly identified specific aims. Each of these 65 award abstracts was reviewed a second time to assess the extent of translational research relevance and assigned a translational score according to the percent of the specific aims that were considered translational. Of the 65 awards reviewed, 40 received translational scores of 76%-100%, eight received scores of 51%-75%, 13 received scores of 26%-50%, and two received scores of 1%-25%. The remaining two projects previously identified as translational based on the original abstract review were considered to have no translational components in this second review. Applying these translational scores to calculate a weighted average of translational character for this set of awards suggests that the overall estimate of funds attributable to translational activity may be overstated by approximately 20-40%.

## Findings: Translational Research Awards by Award Category

Table 1 (page 117) summarizes by mechanism the awards coded as “translational.” The mechanisms are also grouped by award category. The second column identifies the number of active awards identified as “translational” according to the criteria discussed earlier. The third column identifies the total number of active awards in that mechanism in FY 2004. The fourth column is the result of dividing column 2 by column 3, to show the percentage of awards in that mechanism identified as translational. The fifth column shows an estimate of the total funding in FY 2004 for the awards coded as translational.

“Awards for core facilities and shared resources involved in translational research” was one of the inclusion criteria employed. That criterion identified a set of award mechanisms that fund research infrastructure, including the Cancer Centers (P30 mechanism) and R24 and U24 awards. As these infrastructure awards may be used for purposes spanning basic, translational, and clinical research, they were separated from those mechanisms intended to fund translational research projects. These infrastructure awards are summarized in Table 2 (page 118). It was also noted that many of the collaborative research mechanisms (e.g., P01, and P50) also fund core facilities as one facet of the overall award. Therefore, these core facilities were evaluated for the degree to which they supported translational research, and the results are included in Table 2.

## Future Considerations for Translational Research Analysis: Recommended Improvements in Award Coding System to Facilitate More Accurate Analysis of Translational Research Portfolio

When the portfolio analysis exercise was prepared, it revealed that there was no existing coding system that captured translational research; the TRWG therefore developed an ad hoc system to support its deliberations. The ad hoc system was labor-intensive to apply and resulted in a set of findings that some TRWG members found to be counterintuitive (especially the overall size of the enterprise and the substantial amount of translational research conducted under individual investigator awards). Managing translational research more effectively in the future requires a more logistically straightforward and precisely defined method for coding awards as translational research. To that end, the following recommendations are made.

1. ***New coding methods need to be developed to identify, classify, and categorize “translational research.”*** As shown in Figure 4, awards identified as “translational” are distributed across NCI’s CSO codes. Figures 5A and 5B show that awards identified as “translational” are distributed across NIHCA codes as well. Moreover, analysis of the R01 awards designated as translational by TRWG members suggests that the 0% NIHCA code also contains some translational projects. Figure 5B suggests that NIHCA codes are a partially effective filter, however, as the likelihood of being identified as “translational” increased from the NIHCA 25% quartile to the 75% quartile.<sup>5</sup> The difficulty in using standard coding mechanisms in classifying research as “translational” or “not translational” suggests that new mechanisms need to be developed to identify, classify, and categorize “translational research.” It will be important to code several specific aspects of translational research (e.g., study population by organ, stage of cancer development, intended clinical goal(s)—risk assessment device, intervention agent, intervention device, immunologic intervention, lifestyle modification, and mechanistic pathway under investigation) in a consistent manner.
2. ***Precise definitions of translational research and subcomponents of translational research and specific examples of both translational and nontranslational awards will be required as part of developing any new coding process.*** Operationalizing the TRWG’s inclusion criteria for translational research proved difficult even when individual award abstracts were reviewed. However, the exercises performed to assess the inclusion criteria suggest that review of abstracts, though laborious, resulted in judgments consistent with those of scientists closely associated with the individual projects.

5 Figure 5C, however, shows that only 1% of NCI awards active in FY 2004 were classified as being in the 75% NIHCA quartile.

3. ***A database needs to be created that completely and accurately collects the current status of core facilities and infrastructure, captures their total dollar value or number, and allocates their usage to basic, translational, and clinical research.*** Core facilities and infrastructure are funded through many mechanisms. The dollar amounts for P30, R24, and U24 awards can be captured, but these awards are not 100% infrastructure. It is also possible to determine the number of P30, P50, and P01 cores but not the dollars associated with them. Moreover, any cores associated with R01, U-series mechanisms, etc., are not captured at any level. For the reasons discussed earlier, it also proved difficult to classify core facilities and infrastructure as either “translational” or “not translational.”
4. ***A database needs to be created that completely and accurately tracks and codes the individual components and projects of multiproject mechanisms (e.g., P01, EDRN, SPORE, and P30 awards).***

**Table 1. Awards Identified as Translational by Project Funding Mechanisms**

Award Category	Awards Coded as Translational	Total Active Awards*	% of Active Awards Coded as Translational	Estimated Funds in FY04 for Translational Awards (\$M)
<b>Program and Cooperative Awards</b>				
P01	107	207	51.7	215.0
P20	8	34	23.5	3.0
SPORE (P50)	58	58	100.0	131.7
ICMIC (P50)	7	7	100.0	15.8
EDRN (U01/U24)	28	28	100.0	21.8
MMHCC (U01)	10	23	43.5	8.1
Other U01	122	209	58.4	98.6
U19	5	18	27.8	3.7
NTROI (U54)	3	3	100.0	3.8
Other U54	10	19	52.6	13.0
U56	4	40	10.0	1.6
DDG projects	18	18	100.0	11.1
RAID projects	45	45	100.0	16.3
RAPID projects	19	19	100.0	3.1
<b>Career Development</b>				
K01	14	116	12.1	1.9
K05	1	19	5.3	0.1
K07	37	93	39.8	4.8
K08	21	139	15.1	2.5
K12	21	21	100.0	8.8
K22	13	42	31.0	1.4
K23	55	64	85.9	6.8
K24	25	34	73.5	2.2
<b>Individual Research</b>				
R01	1,161	4,450	26.1	447.0
R03	150	320	46.9	8.1
R21	288	599	48.1	43.8
R33	62	121	51.2	24.2
R37	11	74	14.9	6.6
<b>Small Business</b>				
R41 (STTR Phase 1)	28	42	66.7	4.7
R42 (STTR Phase 2)	12	19	63.2	3.8
R43 (SBIR Phase 1)	87	246	35.4	13.3
R44 (SBIR Phase 2)	102	176	58.0	39.4
<b>Intramural</b>				
Z01	257	630	40.8	164.4
<b>Total</b>	<b>2,789</b>	<b>7,933</b>	<b>35.2</b>	<b>1,330.4</b>

\* Total awards identified as being active in fiscal year 2004 from the Cancer Research Portfolio (intramural awards and initiative programs like ICMIC), the Developmental Therapeutics Program (DDG and RAID), the Division of Cancer Prevention (RAPID), and the Research Analysis and Evaluation Branch (all other mechanisms).

**Table 2. Awards Identified as Translational by Infrastructure Funding Mechanisms**

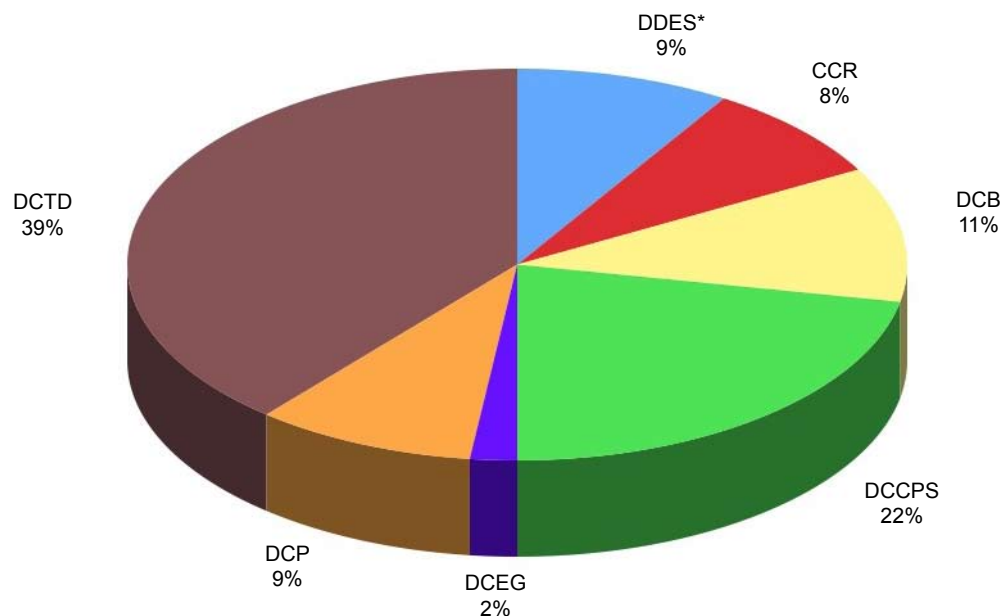
Award Category	Awards Coded as Translational	Total Active Awards*	% of Active Awards Coded as Translational	Estimated Funds in FY04 for Translational Awards (\$M)
<b>Infrastructure*</b>				
P30 Cancer Centers	54	61	88.5	212.5
R24	8	43	18.6	1.5
U24 (excluding EDRN)	8	14	57.1	6.0
Total	70	118	61.0	220.0
<b>Extramural Core Facilities</b>				
Core Facilities supported through SPORE, P30, and P01 awards†	1,165	1,364	85.4	N/A

\* It should be recognized that some individual awards of “project funding” mechanisms are in fact used to fund infrastructure (e.g., 14 Z01 and two U54 awards were identified that were solely for infrastructural purposes) and some Cancer Center funds are used to support projects.

† The Extramural Core Facilities section shows numbers for the core facilities identified at SPOREs, comprehensive and clinical P30s, and translational P01s (Awards Coded as Translational) and at all SPOREs; basic, comprehensive, and clinical P30s; and translational and nontranslational P01s (Total Awards Reviewed). The number of core facilities is not directly related to the estimated FY2004 funding of the Infrastructure award category, which does not include funds for SPOREs and P01s.

### Appendix Figures: Cross-Tabulations of NCI Translational Research Portfolio

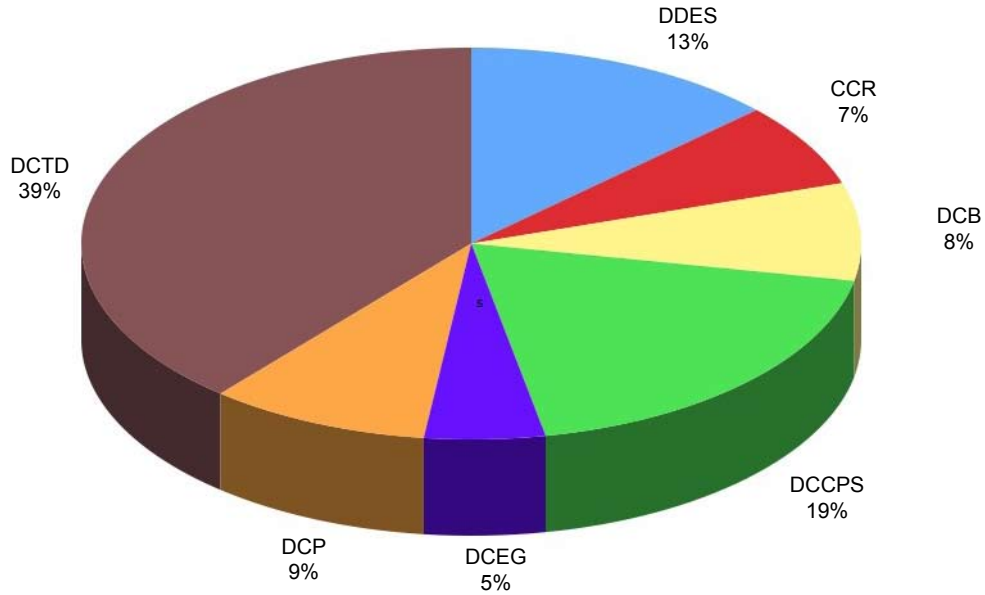
**Figure 1A. Percentage of the total 2,789 project funding awards identified as translational in FY 2004 supported by each NCI Division, Center, and Office.**



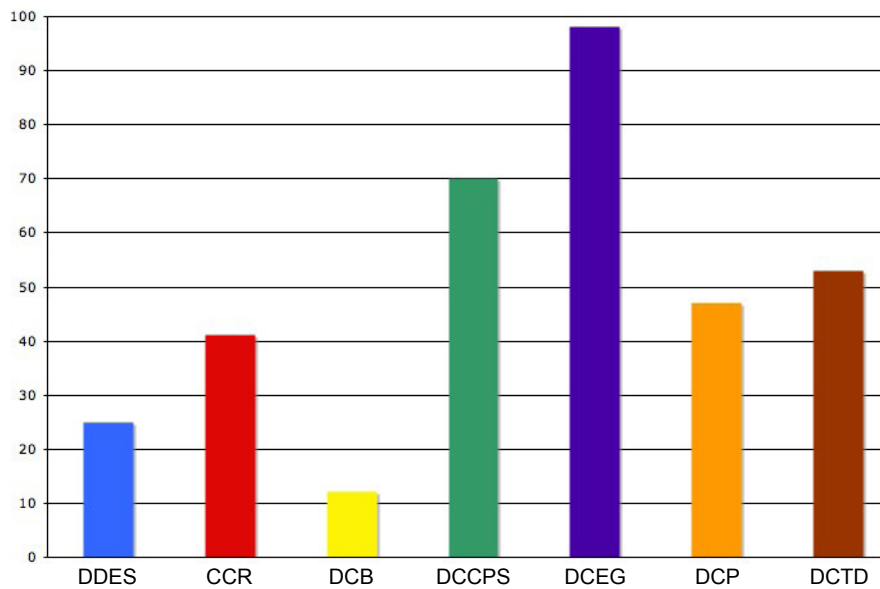
\* Office of the Deputy Director for Extramural Science (DDES) includes the Office of Centers, Training and Resources (Cancer Centers and SPOREs), the Office of Cancer Complementary and Alternative Medicine, and the Office of Grant Program Coordination.



**Figure 1B. Percentage of the total \$1.33 billion in funding identified as translational in FY 2004 supported by each NCI Division, Center, and Office.**



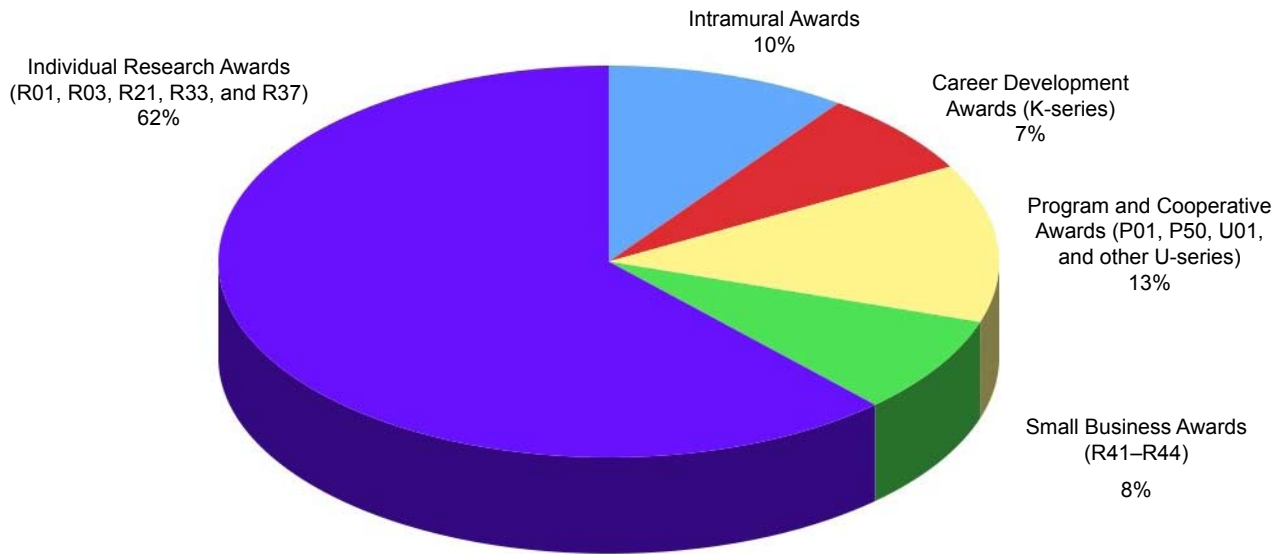
**Figure 1C. Percentage of total FY 2004 funding in each NCI Division, Center, and Office identified as translational.\***



\* Most awards with NIHCA codes of 0% were excluded from the review; however, the percentages shown in the figure are based on the total number of active awards in FY 2004 for each Division, Center, or Office. Therefore, the percentages represent minimal percentage values. The extent that projects with NIHCA quartile of 0% are translational was beyond the scope of this analysis.

**Figure 2A. Percentage of the 2,705 awards identified as translational in FY 2004 that are funded through the major funding mechanisms.\***

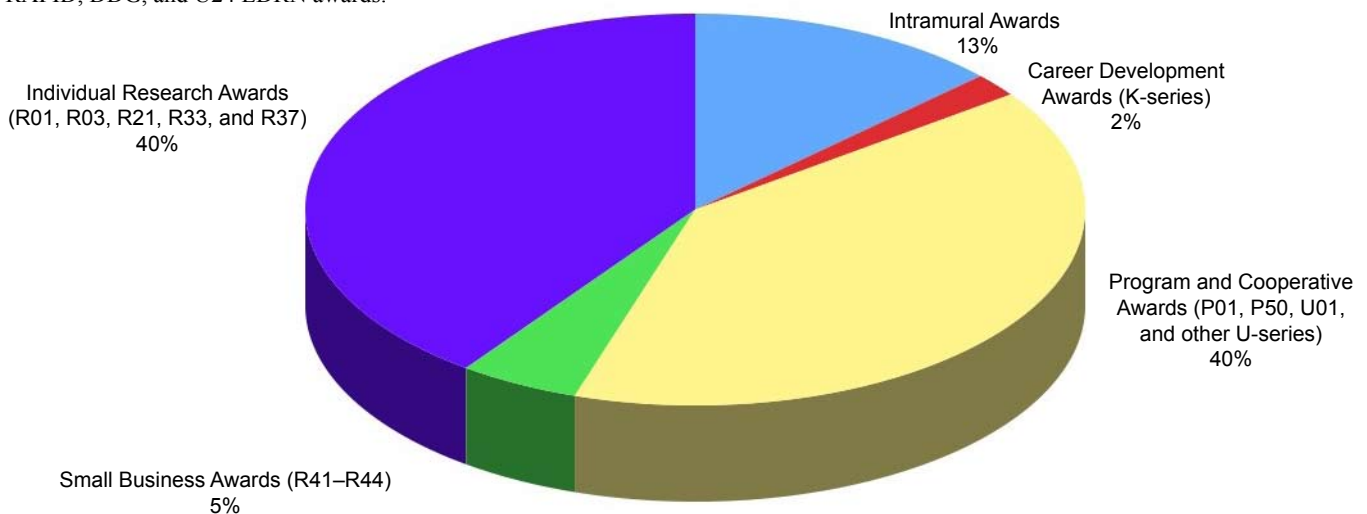
Included: Career Development Awards (K-awards), Program and Cooperative Awards (P01, P20, P50, U01, U19, U54, and U56), Small Business Awards (R41–R44), Individual Research Awards (R01, R03, R21, R33, and R37), and Intramural Awards. Not included: RAID, RAPID, DDG, and U24 EDRN awards.



\* The number of awards is different from the total number of awards identified as translational (2,789) due to exclusion of 82 RAID, RAPID, and DDG projects active in FY 2004 that were primarily funded through contracts and not through the major funding mechanism categories and two EDRN U24 infrastructure-based awards that also did not match the major funding mechanism categories.

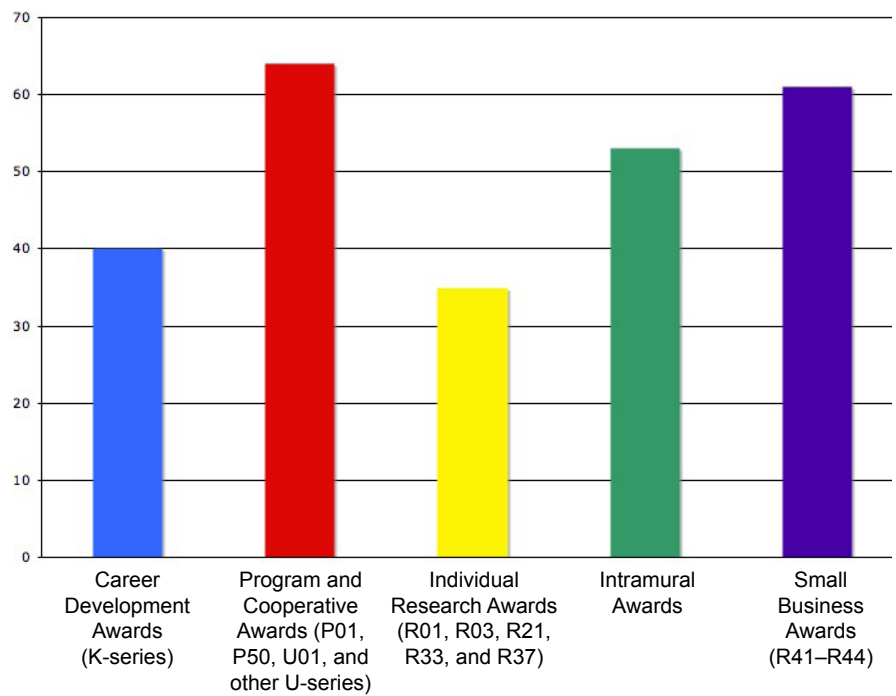
**Figure 2B. Percentage of the \$1.30 billion in funding identified as translational in FY 2004 supported through the major funding mechanisms.**

Included: Career Development Awards (K-awards), Program and Cooperative Awards (P01, P20, P50, U01, U19, U54, and U56), Small Business Awards (R41–R44), Individual Research Awards (R01, R03, R21, R33, and R37), and Intramural Awards. Not included: RAID, RAPID, DDG, and U24 EDRN awards.



**Figure 2C. Percentage of total FY 2004 funding within each award mechanism that was identified as translational.\***

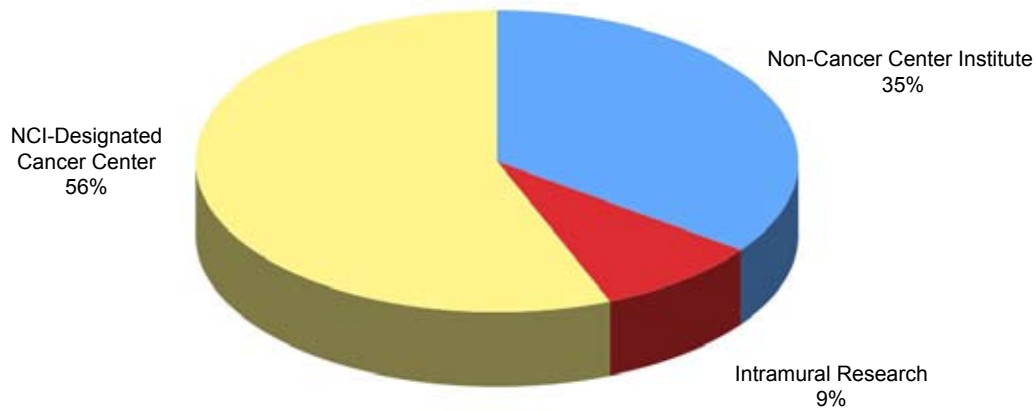
Included: Career Development Awards (K-awards), Program and Cooperative Awards (P01, P20, P50, U01, U19, U54, and U56), Small Business Awards (R41-R44), Individual Research Awards (R01, R03, R21, R33, and R37), and Intramural Awards. Not included: RAID, RAPID, DDG, and U24 EDRN awards.



\* A majority of individual research awards were not reviewed because they had the NIHCA quartile of 0%, while a majority of awards in the other mechanism categories were reviewed. The percentages in this figure may be considered minimal percentages, as in Figure 2A (see footnote 6 on page 25).

**Figure 3A. Percentage of the 2,707 project funding awards identified as translational in FY 2004 made to major categories of institution.\***

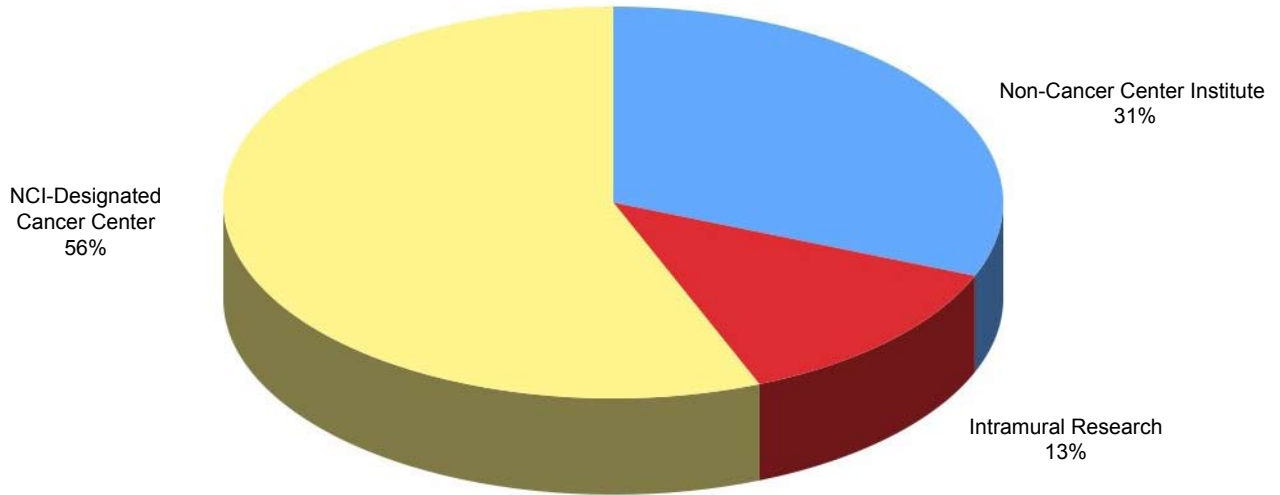
Included: Research awards to institutions designated as comprehensive or clinical cancer centers, research awards to institutions not designated as comprehensive or clinical NCI cancer centers, and NCI intramural awards. Not included: RAID, RAPID, and DDG awards..



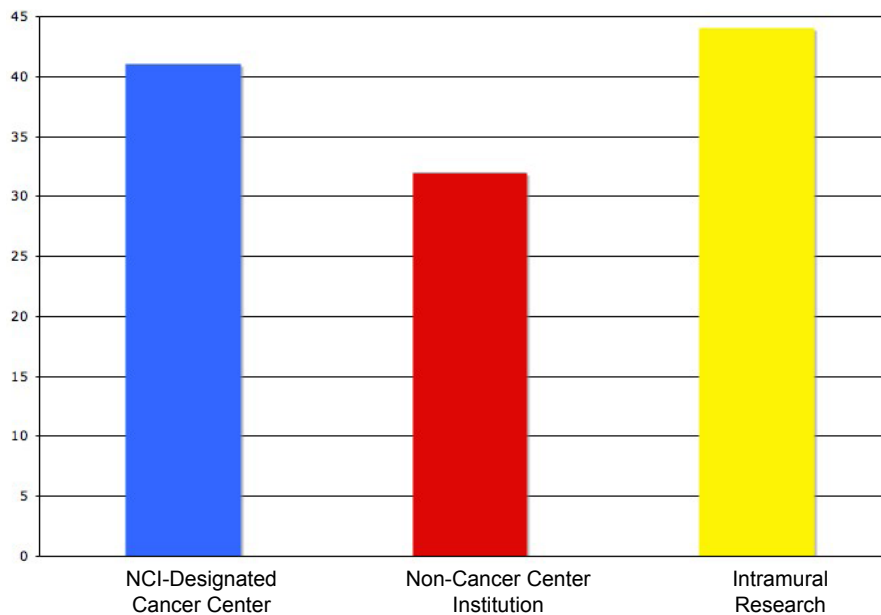
\* The number of awards is different from the total number of awards identified as translational (2,789) due to exclusion of the 82 RAID, RAPID, and DDG projects.

**Figure 3B. Percentage of the \$1.30 billion in funding identified as translational in FY2004 awarded to major categories of institution.**

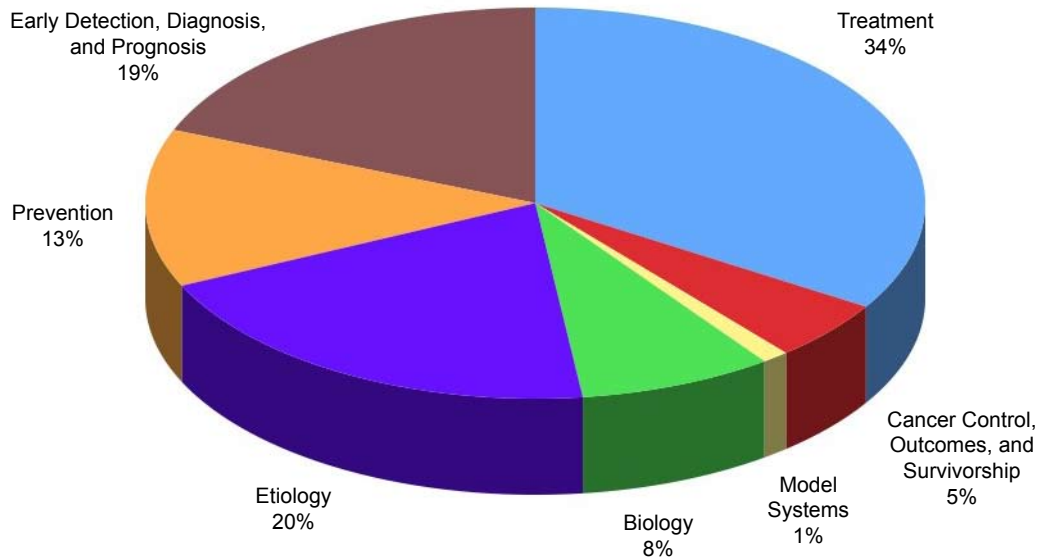
Included: Research awards to institutions designated as comprehensive or clinical cancer centers, research awards to institutions not designated as comprehensive or clinical NCI cancer centers, and NCI intramural awards. Not included: RAID, RAPID, and DDG awards..



**Figure 3C. Percentage of total FY 2004 funding at major categories of institutions that was identified as translational.**



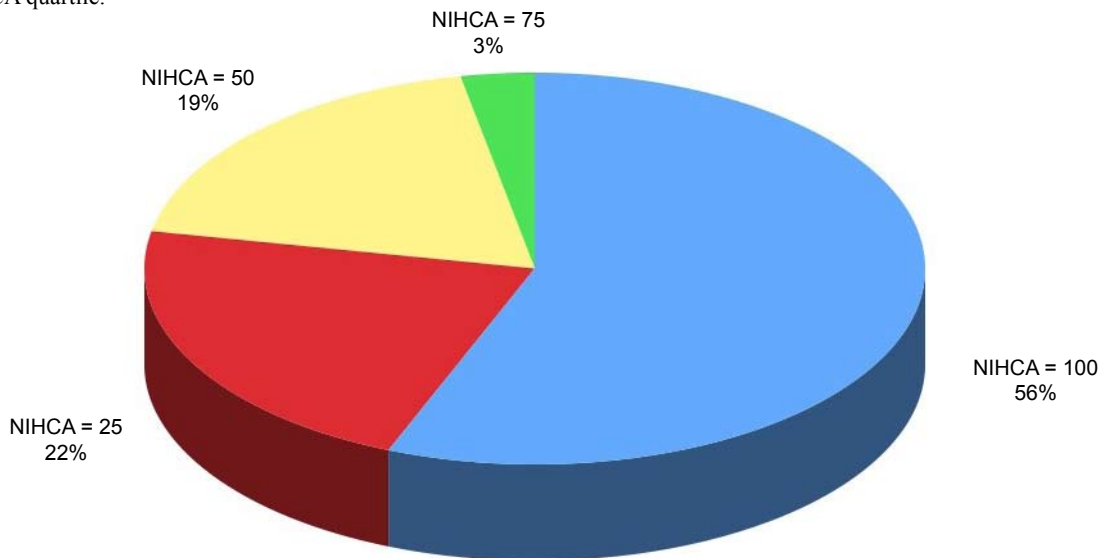
**Figure 4. Percentage of the total 2,789 project funding awards identified as translational in FY2004 cross-tabulated by the seven major CSO categories.\***



\* Awards assigned to two or more CSO categories are counted toward all assigned categories.

**Figure 5A. NIHCA quartile of the 2,296 project funding awards active in FY 2004 that had a 25%-100% NIHCA code and were identified as translational.\***

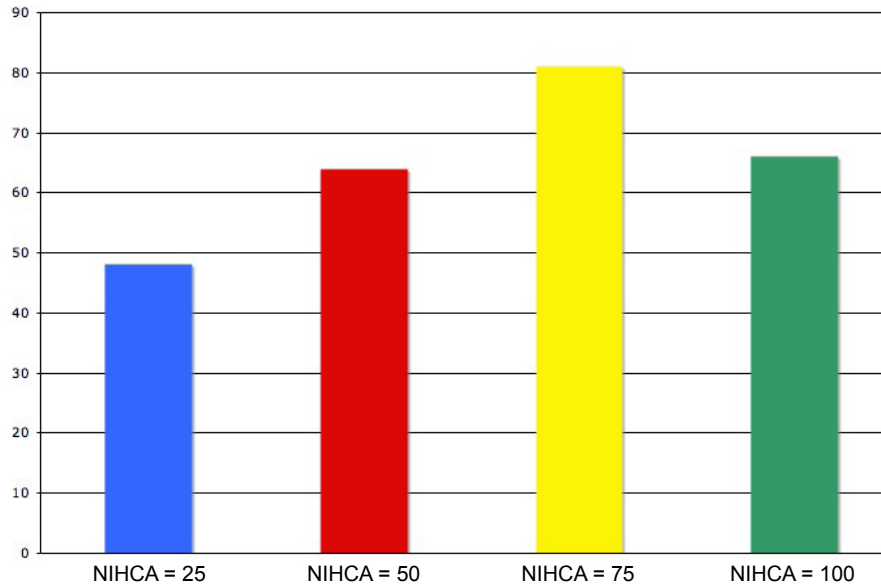
Included: All active extramural awards with NIHCA quartile assignments of 25%-100% identified as translational. Not included: Awards and projects not assigned NIHCA codes, including intramural awards (CCR and DCEG), RAID, RAPID, and DDG projects, and awards with 0% NIHCA quartile.



\* Projects with NIHCA codes of 25%, 50%, and 75% were identified as translational research projects and the set of projects reviewed is not a representative sampling of the 0% NIHCA awards. Examining all such projects was beyond the scope of the portfolio analysis.

**Figure 5B. Percentage of awards in each NIHCA quartile identified as translational.\***

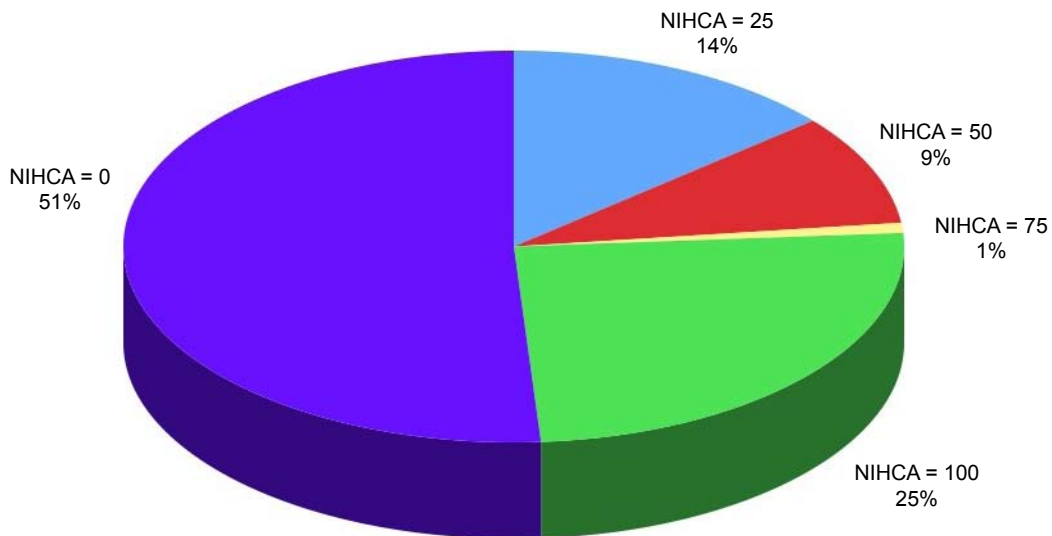
Included: All active extramural awards with NIHCA quartile assignments of 25%-100% identified as translational. Not included: Awards and projects not assigned NIHCA codes, including intramural awards (CCR and DCEG), RAID, RAPID, and DDG projects, and awards with 0% NIHCA quartile.



\* Certain clinical research U-series programs (e.g., Phase I U01 trialists, American College of Radiology Imaging Network [ACRIN], the cooperative groups, and Community Clinical Oncology Programs [CCOPs]) are not intended to be covered by this initiative.

**Figure 5C. Percentage of all active FY 2004 extramural project funding awards by NIHCA quartile.**

Not included: Awards and projects not assigned NIHCA codes, including intramural awards (CCR and DCEG), RAID, RAPID, and DDG projects.



## Appendix E: Process Analysis for the NCI Translational Research Working Group

### Introduction and Summary

In order to inform its deliberations, the National Cancer Institute (NCI) Translational Research Working Group (TRWG) initially developed five developmental pathways to clinical goals encompassing risk assessment devices, agents, immune response modifiers, interventional devices, and lifestyle interventions. At the December 2005 planning meeting, TRWG members decided to examine several case studies of translational “successes” along each of these developmental pathways. The goal was to gain insights into the following questions.

- What paths do successes take? Are there commonalities within/across the cases examined, or is each translation unique?
- Even for successes, are there bottlenecks where discoveries are held up? If so, where?
- What roles do academia, industry, and NCI play in successful translation?
- What insights do the case studies suggest regarding the developmental pathways to clinical goals?

Twenty case studies spanning the five developmental pathways to clinical goals were completed. This document presents the methods used for identifying the NCI-sponsored translational successes, the key findings from the analysis, and representative summaries of the cases examined.

### Methodology

#### Identification of Case Study Candidates

After the December 2005 planning meeting, members of the TRWG nominated candidate case studies representing each of the developmental pathways. The TRWG co-chairs selected case studies from among the nominees, aiming for a diverse set of cases within each developmental pathway.

#### Data Collection

Data collection occurred during January and February 2006. Data collection included identification and review of peer-reviewed publications, trade literature, patent filings, clinical trial abstracts, and funding data (including National Institutes of Health (NIH) and non-NIH funding where available) for each of the translational research successes. Key participants were identified for each translational research success and interviewed where possible. Twenty cases were completed in advance of the TRWG Roundtable in February 2006.

#### Risk Assessment Devices

- Bladder Cancer Early Detection: Microsatellite Instability Assay of Urinary Sediment
- Bladder Cancer Early Detection: Fluorescence In-Situ Hybridization Assay of Urine
- Prostate Cancer Early Detection: Protein Expression in Serum
- FDG-PET for Early Detection



- **Agents**
  - Avastin
  - DNA Methyltransferase Inhibitor (e.g., Vidaza)/Histone Deacetylase Inhibitor Combinations
  - Bortezomib/Velcade
  - Anti-HER2/neu Liposomes
  - Celecoxib
  - TNFerade
- **Immune Response Modifiers**
  - HER2/neu Breast Cancer Vaccine
  - RNA-Transfected Dendritic Cells
  - Combination of MDX-010/anti-CTLA-4 Antibody with Melanoma (and Prostate Cancer) Vaccines
  - Cell-Based Vaccines for Pancreatic Cancer
  - Globo H Breast Cancer Vaccines
- **Interventive Devices**
  - Radiofrequency Ablation
  - Three-Dimensional Conformal Radiation Therapy for Prostate Cancer
  - FDG-PET Device Development
- **Lifestyle Alterations**
  - Exercise, Diet, and Breast Cancer
  - Smoking Cessation and Lung Cancer

### Key Findings

Because only a small sample size was considered, no robust general conclusions can be drawn from the case studies. Nevertheless, several interesting patterns emerged.

1. The cases drew upon a wide variety of NCI and NIH funding mechanisms. Cases included translational activities funded through a single large-scale, team-based program (e.g., Specialized Programs of Research Excellence (SPORE), Early Detection Research Network (EDRN)), others funded through a series of individual-investigator awards (e.g., R01, K-series, Small Business Innovation Research Program (SBIR)/Small Business Technology Transfer Program (STTR)), and still others through the NCI intramural research program. Several cases used a combination of individual-investigator awards and team-based projects, while some were funded through other NIH Institutes (e.g., National Institute of General Medical Science (NIGMS), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID)) as well as NCI. In the cases investigated, it was found that both NCI and industry could be involved at any stage along the translation continuum from early- to late-stage.

2. The majority of the cases encountered bottlenecks or challenges in achieving success. Several cases required the development of new assays or screening techniques to validate the discovery; several encountered bottlenecks in preclinical development (e.g., GMP manufacturing); and others encountered difficulties in early-stage clinical trials because of Food and Drug Administration (FDA) approval or patient recruitment issues.
3. A range of interactions among stakeholders was observed. Cases included “traditional” handoffs from academia to industry, translation that occurred primarily in academia but with industry funding of specific process steps, full public-private partnerships, and even examples where fundamental discoveries made by private industry benefited from NCI-funded translational resources.
4. The case studies suggested certain insights into the developmental pathways.
  - Some cases by definition spanned multiple pathways. FDG-PET, for example, functions as a risk assessment device, but it was developed as a combination of imaging agent (FDG) and an interventional device (PET). In other examples, activity in one pathway led to discoveries relevant to other pathways (e.g., celecoxib development led to the discovery of a new candidate biomarker of biological response).
  - The TRWG developmental pathways are idealized representations of the translational research process. For example, several cases in the interventional device pathway skipped steps or even whole segments of the pathway and several immune response modifier cases involved multiple iterations of refinement before reaching clinical trials.

## Conclusions and Future Considerations for Translational Research Analysis

The process analysis exercise showed that in none of the cases examined was the entire developmental pathway funded by a single, comprehensive program or mechanism or by a systematically coordinated series of programs or mechanisms. Individual investigators or teams assembled funding for each case, with the particular combinations that advanced a concept through the developmental pathway often depending on the ingenuity of the investigators.

The cases suggest that translational research would be facilitated by the availability of more unified and better-coordinated funding mechanisms. They also demonstrate the absence of critical system-level translational research metrics (e.g., the fraction of successes that are advanced through specific programs or mechanisms or the fraction that encounter bottlenecks at specific points in each developmental pathway). Creation of data systems that can provide such information in a logistically straightforward and precisely defined way will be beneficial for improving the management of translational research.

## Case Study Summaries

Summaries of 10 representative case studies, two representing each of the five initial developmental pathways, are presented below. Case studies are not included for the sixth pathway, image-based risk assessment agents/techniques, because this pathway had not been developed at the time the process analysis was conducted. The case studies summarized are listed below.

- **Risk Assessment Devices**
  - Bladder Cancer Early Detection: Microsatellite Instability Assay of Urinary Sediment
  - Bladder Cancer Early Detection: Fluorescence In-Situ Hybridization Assay of Urine
- **Agents**
  - Bortezomib/Velcade
  - Celecoxib

- **Immune Response Modifiers**

- HER2/neu Breast Cancer Vaccine
- Cell-Based Vaccine for Pancreatic Cancer

- **Interventive Devices**

- Radiofrequency Ablation
- Three-Dimensional Conformal Radiation Therapy for Prostate Cancer

- **Lifestyle Alterations**

- Exercise, Diet, and Breast Cancer
- Smoking Cessation and Lung Cancer

## Bladder Cancer Early Detection: Microsatellite Instability Assay of Urinary Sediment

**Summary:** In the early to mid-1990s, several research groups reported studies indicating that microsatellite instability could have potential utility as a marker for early detection of cancer. In 1996, the Sidransky and Schoenberg groups at Johns Hopkins University reported that urine microsatellite instability assays detected bladder cancer in patients with 95% sensitivity whereas urine cytology had only 50% sensitivity. A second study reported in 1997 demonstrated that the urine microsatellite assay could also detect bladder cancer recurrence with approximately 90% sensitivity. Both of these studies were funded by Oncor Inc. and led to filing of patent applications in 1997 which then led to the issuance of four U.S. patents.

The technology and intellectual property were licensed in 2000 to Cangen Biotechnologies, who developed an initial test kit. The Cangen test kit was validated by the EDRN biomarker reference laboratories using retrospective sample sets collected at Johns Hopkins. In 2004 EDRN initiated a multisite prospective Biomarkers Phase III study (which differs from a Phase III clinical trial) with 300 patients and 200 controls to compare microsatellite analysis with cystoscopy and cytology for detection of bladder cancer recurrence. The study was closed to accrual in January 2007 with 270 patients. The results of this trial will be used by Cangen to pursue FDA licensure of its test kit.

### Relationship to TRWG Pathway

Development of the microsatellite assay closely followed the risk assessment device pathway.

### Bottlenecks

1. Bankruptcy by Oncor, the initial licensee of the technology, led to a 2-year delay in development while the intellectual property rights were tied up in legal proceedings. Recovery of the rights required the combined effort of Johns Hopkins and Cangen, which became interested in the technology because a co-discoverer was their Chief Scientific Officer.
2. Development of a practical, validated test kit required migration from the radioactivity-based assay developed at Johns Hopkins, which required subjective reading and interpretation by a trained observer, to a fluorescence-based assay which used automated sequencing, reading, and interpretation. Industry involvement was critical to develop and validate this automated assay.
3. Accrual to the Biomarkers Phase III trial was initially a significant bottleneck, but this was overcome by the addition of more clinical centers.

### Key Observations

1. To move new, broad-based risk-assessment technologies forward, it is important to identify an initial disease target with a strong clinical need in order to attract industry attention.
2. Intellectual property licensing is essential but such licensing may inadvertently encumber the technology and impede its development.
3. Development of practical, validated assay methodologies can be challenging for academic labs.
4. The standard model of industry funding of late-stage rather than early-stage development is not always followed as the early translational work was funded largely by industry while the definitive Biomarkers Phase III trial was funded by NCI.
5. Small device companies often rely on NCI to fund the large clinical studies necessary to support FDA approval of new cancer clinical tests.

### Sources

- Interview with Dr. David Sidransky/Dr. Sudhir Srivastava (January 31, 2006)

### Literature

- Mao L, Lee DJ, Tockman MS, Erozan YS, Askin F, Sidransky D. Microsatellite alterations as clonal markers for the detection of human cancer. *Proc Natl Acad Sci*. 1994;91(21):9871-5.
- Mao L, Schoenberg MP, Scicchitano M, Erozan YS, Merlo A, Schwab D, Sidransky D. Molecular detection of primary bladder cancer by microsatellite analysis. *Science*. 1996;271(5249):659-62.
- Steiner G, Schoenberg MP, Linn JF, Mao L, Sidransky D. Detection of bladder cancer recurrence by microsatellite analysis of urine. *Nat Med*. 1997;3(6):621-4.
- Pepe MS, Etzioni R, Feng Z, Potter JD, Thompson ML, Thornquist M, Winget M, Yasui Y. Phases of biomarker development for early detection of cancer. *JNCI*. 2001;93(14):1054-61.

### Patent Search

- Sidransky. Nucleic acid mutation detection by analysis of sputum (#5,561,041). Filed November 12, 1993; received October 1, 1996.
- Sidransky. Detection of hypermutable nucleic acid sequence in tissue (#5,935,787). Filed May 12, 1997; received August 10, 1999.
- Sidransky. Method for detecting cell proliferative disorders (#6,291,163). Filed August 28, 1997; received September 18, 2001.
- Sidransky. Method for detecting cell proliferative disorders (#6,780,592). Filed September 10, 2001; received August 24, 2004.

## Bladder Cancer Early Detection: Fluorescence In-Situ Hybridization Assay of Urine

Summary: Fluorescence in-situ hybridization (FISH) was originally developed by the Gray group at Lawrence Livermore National Laboratory in the late 1980s using Department of Energy (DOE), NCI, and National Institute of Child Health and Human Development (NICHD) funding. In the early to mid-1990s, several academic researchers began to work on application of FISH technology for early detection of bladder cancer. At the same time, Vysis Inc. was further developing the FISH technology for use in clinical tests and demonstrated to FDA that assays based on FISH were sufficiently robust and reproducible to be used for clinical purposes.

In 1998, Vysis identified the use of FISH for early detection of bladder cancer as a commercial target based upon the combination of clinical need (existing tests had limited sensitivity/specificity) and the assessment that Vysis's FISH technology could improve upon those tests. The company collaborated with the University of Basel and Mayo Clinic to obtain samples and clinical data sets for validating the technology (1999-2000) and to pursue large-scale prospective studies (2000-2001). FDA approval for the UroVysion test was granted in August 2001.

### Relationship to TRWG Pathway

Development of the FISH assay followed the risk assessment device pathway quite closely.

### Bottlenecks

No significant bottlenecks were reported.

### Key Observations

1. The TRWG pathway effectively describes the steps used to translate the FISH technology into a practical test for bladder cancer. All three decision points for entry into translational development were addressed in Vysis's assessment; namely, that the technology was mature and that bladder cancer was an appropriate application to pursue.
2. Successful translation involved industry performing two critical roles. The first was refinement and validation of the FISH technology developed with government funding into a methodology sufficiently robust and reliable to serve as the basis for clinical tests. The second involved building on reports by several academic investigators of the potential utility of FISH for the detection of bladder cancer in order to develop an FDA-approved test.
3. Collaboration with academic investigators was important in order for industry to obtain the clinical specimens necessary to develop and validate the new cancer clinical test.

### Sources

- Interview with Dr. Steve Seelig, Abbot (February 7, 2006)
- Advanced Technology Program fact sheet, "Bar Code Diagnostics for DNA Analysis"

### Literature

- van Dekken H, Pinkel D, Mullikin J, Gray JW. Enzymatic production of single-stranded DNA as a target for fluorescence in situ hybridization. *Chromosoma*. 1988;97(1):1-5.
- Sokolova IA, Halling KC, Jenkins RB, Burkhardt HM, Meyer RG, Seelig SA, King W. The development of a multitarget, multicolor fluorescence in situ hybridization assay for the detection of urothelial carcinoma in urine. *J Mol Diagn*. 2000;2(3):116-23.

- Halling KC. Vysis UroVysion for the detection of urothelial carcinoma. *Expert Rev Mol Diagn.* 2003;3(4):507-19. Erratum in: *Expert Rev Mol Diagn.* 2004;4(2):266.

### **Patent Search**

- Halling et al. Method and probe set for detecting cancer (#6,174,681). Filed March 5, 1999; received January 16, 2001.
- Halling et al. Method and probe set for detecting cancer (#6,376,188). Filed July 21, 2000; received April 23, 2002.



## Bortezomib/Velcade

### Summary

Interest in the role of the proteasome (a complex of enzymes involved in degradation of misfolded proteins) in carcinogenesis grew during the mid-1990s. In 1994 researchers at ProScript Inc. developed a group of proteasome inhibitors that appeared to be effective in promoting apoptosis of cancer cells. As part of their research, the ProScript group also developed an *in vitro* assay for proteasome inhibition, which served as a surrogate marker for the effectiveness of this class of drugs. Beginning in 1995, the NCI Developmental Therapeutics Program (DTP) assisted ProScript with *in vitro* and animal model studies that identified one of these inhibitors (PS-341, later trade-named Velcade) as a likely candidate agent from among the group of compounds ProScript provided for testing. ProScript performed preclinical development of PS-341 internally and DTP assisted with formulation studies.

Phase I clinical trials in prostate cancer were performed by academic investigators beginning in October 1998 with CaPCure (Prostate Cancer Foundation) funding. In 1999, preclinical studies and Phase I trials in multiple myeloma were performed at Dana-Farber Cancer Institute, funded by NCI. The acquisition of ProScript by Millennium Pharmaceuticals in 1999 provided additional resources for development of the drug and Millennium conducted Phase IIB trials in multiple myeloma patients during 2001-2002. The results were presented in late 2002 and led to FDA approval of the drug in 2003. Throughout development, the FDA was quite supportive of bringing this new class of compounds into clinical trials.

### Relationship to TRWG Pathway

Development of Velcade largely followed the TRWG agent development pathway. At the bottom of the pathway, the drug's development branched into multiple Phase I trials for prostate cancer, multiple myeloma, and several other disease sites.

### Bottlenecks

Several bottlenecks in the development of Velcade were identified. These bottlenecks included (a) developing an assay for proteasome inhibition that allowed identification of a safe and effective dosage range (overcome by ProScript scientists), (b) formulation of the drug (overcome by DTP), and (c) interesting academic trialists in bringing the drug into early-stage clinical trials (overcome through entrepreneurship by ProScript scientists).

### Key Observations

1. Development of Velcade involved collaboration among industry, NCI, academic trialists, and foundations. Close coordination among the stakeholders not only facilitated validation of the discovery and preclinical development of the drug but also sped the enrollment of multiple myeloma patients into the Phase II trials that provided the data to support FDA approval.
2. Small-to-midsize companies often do not have sufficient in-house capability to develop a promising therapeutic agent. In this case, DTP provided assay and animal model capabilities that assisted ProScript in identifying a lead agent candidate as well as formulation capabilities. This demonstrates the value of academic-industry-NCI collaboration in translational research.
3. Late-stage development of the drug was facilitated by involvement of a large pharmaceutical company. Without the acquisition of ProScript by Millennium Pharmaceuticals, development may have ceased because ProScript did not have the financial resources to continue with late-stage clinical trials.

## Sources

- “Myeloma Today” (International Myeloma Foundation) profile of Dr. Julian Adams, June 2003
- National Cancer Institute/Developmental Therapeutics Program, “Success Story: Velcade (NSC 681239),” [http://dtp.nci.nih.gov/timeline/noflash/success\\_stories/S6\\_Velcade.htm](http://dtp.nci.nih.gov/timeline/noflash/success_stories/S6_Velcade.htm)
- National Cancer Institute/Developmental Therapeutics Program, “Velcade (PS-341),” <http://dtp.nci.nih.gov/timeline/posters/Velcade.pdf>
- Interview with Dr. Christopher Logothetis, MD Anderson (February 10, 2006)
- Interview with Dr. Kenneth Anderson, Beth Israel Deaconess Medical Center (February 7, 2006)

## Literature

- Adams J, Behnke M, Chen S, Cruickshank AA, Dick LR, Grenier L, Klunder JM, Ma YT, Plamondon L, Stein RL. Potent and selective inhibitors of the proteasome: dipeptidyl boronic acids. *Bioorg Med Chem Lett*. 1998;8(4):333-8.
- Adams J, Palombella VJ, Sausville EA, Johnson J, Destree A, Lazarus DD, Maas J, Pien CS, Prakash S, Elliott PJ. Proteasome inhibitors: a novel class of potent and effective antitumor agents. *Cancer Res*. 1999;59(11):2615-22.
- Teicher BA, Ara G, Herbst R, Palombella VJ, Adams J. Dana-Farber Cancer Institute and Joint Center for Radiation Therapy. *Clin Cancer Res*. 1999;5(9):2638-45.
- Hideshima T, Richardson P, Chauhan D, Palombella VJ, Elliott PJ, Adams J, Anderson KC. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. *Cancer Res*. 2001;61(7):3071-6.
- Richardson P. Clinical update: proteasome inhibitors in hematologic malignancies. *Cancer Treat Rev*. 2003;29(Suppl 1):33-9.
- Twombly R. First proteasome inhibitor approved for multiple myeloma. *JNCI*. 2003;95(12):845.

## Celecoxib

### Summary

The COX-2 inhibitor celecoxib was initially developed as an anti-inflammatory agent by Searle (later Pharmacia and then Pfizer). Epidemiologic data published during the late 1980s showing that aspirin use was associated with declines in colorectal cancer (CRC) suggested that aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) could potentially be used as a preventative or therapeutic agent in cancer. This hypothesis was further supported by studies in animal models of carcinogenesis which examined the potential role of prostaglandins in cancer progression. In the early 1990s, the generation of prostaglandins from arachadonic acid was determined to arise from two distinct cyclooxygenase (COX) enzymes—COX-1, which was associated with a more basal, housekeeping role, and an inducible COX-2, which was responsive to a variety of stimuli associated with inflammation and cancer.

Based on these observations, the DuBois group at Vanderbilt, funded by R01 grants from the National Institute of Diabetes and Digestive and Kidney Diseases and several other sources, demonstrated several important findings. First, overexpression of COX-2 increased the invasiveness and prostaglandin production of colon cancer cells in culture which could be reversed by genetic or pharmacologic COX-2 inhibition. Second, tissue studies showed COX-2 was expressed in human adenocarcinomas. Third, mouse model studies demonstrated that COX-2 inhibitors could reduce tumor formation by colon cancer cell lines constitutively expressing COX-2, but had no effect on cancer cell lines lacking COX-2. These observations were supported by studies from several other epidemiology laboratories which confirmed these data, demonstrated the relevance of COX-2 to early stages of colorectal carcinogenesis, and suggested that NSAIDs and/or COX-2 inhibitors were associated with reductions in colorectal adenoma incidence, colorectal cancer incidence, and CRC-associated mortality. All of these findings suggested that celecoxib and other COX-2 inhibitors could have promise as effective chemopreventive agents with fewer GI side effects (e.g., gastroduodenal ulceration) and thus were particularly appealing agents for clinical trials in colorectal neoplasia prevention.

As preclinical development on celecoxib had been done previously by Searle, it was thought at the time that there was no need for additional toxicology/pharmacology before introducing the agent into cancer chemoprevention clinical trials. NCI-funded phase II prevention trials began in 1998 in patients at very high risk for colorectal cancer due to familial adenomatous polyposis (FAP). Success in this trial led to the initiation of several trials in patients at more moderate risk for CRC due to prior adenomas. Merck initiated a trial of its COX-2 inhibitor—rofecoxib (Vioxx)—in 1999, and the NCI and Pfizer partnered to initiate a three-arm trial of celecoxib (at two doses) versus placebo (the APC trial). Pfizer also initiated a second, multinational trial of similar design with celecoxib versus placebo in 2000 (the PreSAP trial). After rofecoxib was observed in 2004 to cause cardiovascular toxicity, both Pfizer and NCI monitored their large-scale chemopreventive trials closely and in 2005, celecoxib was found to be associated with an elevated risk for serious cardiovascular events in the APC trial as well.

Although celecoxib did not prove sufficiently safe for widespread chemopreventive use in moderate-risk individuals, investigation of the COX-2 pathway's relevance to cancer has led to certain other translational opportunities. For example, subsequent research into the COX-2 pathway has uncovered a downstream pathway step (the final step in prostaglandin PGE2 synthesis) whose disruption may have the same therapeutic benefit without the toxicity of COX-2 inhibition. In addition, the DuBois group has used NCI funding to explore the use of COX-2 levels as a biomarker for diagnosis of colon cancer and EDRN has also funded studies concerning COX-2's potential as a biomarker of risk.

### Relationship to TRWG Pathway

The pre-existing lead agent candidate entered the developmental pathway based on observational/epidemiology studies, preclinical data, and approval of the agent for use in a different disease area. This example also shows linkages between pathways. Work in the agent pathway has suggested concepts for development through the biospecimen-based risk assessment device pathway.

## Bottlenecks

Although toxicology was not viewed as a bottleneck at the time, developing methods that can identify toxicity associated with long-term use is an important potential bottleneck in bringing forward chemopreventive agents for use in low- to moderate-risk populations.

## Key Observations

1. A compound developed by industry for a different disease area was translated for use in cancer through the involvement of academic researchers funded by NCI and other Institutes.
2. Research funded by other NIH Institutes can lead to discoveries relevant to cancer.
3. There may be important differences between agent development for treatment and for prevention even though they can be described using the same TRWG developmental pathway. The celecoxib example highlights the critical role of balancing risks and benefits in prevention, and suggests the important role that new approaches to preclinical toxicologic assessments may play in assessing the risks associated with a preventive compound.
4. Close collaboration between industry and NCI facilitated the conduct of large chemoprevention trials.

## Sources

- Interview with Dr. Raymond DuBois, Vanderbilt University (January 26, 2006)
- Interview with Dr. Ernest Hawk, NCI (February 8, 2006)

## Literature

- Thun MJ, Namboodiri MM, Heath CW Jr. Aspirin use and reduced risk of fatal colon cancer. *N Engl J Med.* 1991;325(23):1593-6.
- Rosenberg L, Palmer JR, Zauber AG, Warshauer ME, Stolley PD, Shapiro S. A hypothesis: nonsteroidal anti-inflammatory drugs reduce the incidence of large-bowel cancer. *JNCI.* 1991;83(5):355-8.
- Eberhart CE, Coffey RJ, Radhika A, Giardiello FM, Ferrenbach S, DuBois RN. Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. *Gastroenterology.* 1994;107(4):1183-8.
- Reddy BS, Rao CV, Seibert K. Evaluation of cyclooxygenase-2 inhibitor for potential chemopreventive properties in colon carcinogenesis. *Cancer Res.* 1996;56(20):4566-9.
- Steinbach G, Lynch PM, Phillips RKS, Wallace MH, Hawk E, Gordon GB, Wakabayashi N, Saunders B, Shen Y, Fujimura T, Su L, Levin B, Godio L, Patterson S, Rodriguez-Bigas MA, Jester SL, King KL, Schumacher M, Abbruzzese J, DuBois RN, Hittelman WN, Zimmerman S, Sherman JW, Kelloff G. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *New Eng J Med.* 2000;342(26):1946-52.
- Solomon SD, McMurray JJV, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M, for the Adenoma Prevention with Celecoxib (APC) Study Investigators: Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med.* 2005; 352:1071-80.
- Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K-M, Tang J, Rosenstein RB, Wittes J, Corle D, Hess TM, Woloj GM, Boisserie F, Anderson WF, Viner JL, Bagheri D, Burn J, Chung DC, Dewar T, Foley TR, Hoffman N, Macrae F, Pruitt RE, Saltzman JR, Salzberg B, Sylwestrowicz T, Gordon GB, Hawk ET for the APC Study Investigators. Celecoxib for the prevention of sporadic colorectal adenomas. *N Engl J Med.* 2006;355:873-84.

- 
- Solomon SD, Pfeffer MA, McMurray JJV, Fowler R, Finn P, Levin B, Eagle C, Hawk E, Lechuga M, Zauber AG, Bertagnolli MM, Arber N, Wittes J for the APC and PreSAP Trial Investigators. Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. *Circulation*. 2006;114:1028-35.

## HER-2/neu Breast Cancer Vaccine

### Summary

Previous work showed that the tumor antigen HER-2/neu is overexpressed in certain types of breast cancer and that some breast cancer patients had existent immune responses against the HER-2/neu protein although the responses fell short of therapeutic levels. These findings suggested the possibility that HER-2/neu vaccines could target HER-2/neu positive breast cancer. The Cheever group at the University of Washington (UW) showed in 1996 that it was feasible to elicit an immune response in mouse models using portions of the HER-2/neu protein as an immunogen. This work was funded through an NCI R01 grant originally focused on the evaluation of immune responses against melanoma. Patent applications were filed in 1995 through UW claiming immune reactivity to HER-2/neu protein as the basis for diagnosis and treatment of HER-2/neu-associated malignancies. UW scientists co-founded a start-up biotech company, Corixa, which licensed the patent and commenced GMP manufacturing of a series of HER-2/neu peptide vaccines using an NCI SBIR grant as one source of funds.

The initial Phase I trial in 1998 was conducted under a UW IND with Corixa funding. This initial trial led to multiple Corixa-funded Phase I trials in collaboration with UW translational scientists in order to refine the vaccine construct and optimize the immune response. One key refinement was the transition from using smaller portions of the HER-2/neu protein to using the full extracellular domain fused to major portions of the intracellular domain of the protein.

In order to continue development of the vaccine, Corixa partnered with GSK. GSK was essential for financing the project and for manufacturing the vaccine under conditions that maintained the natural folding of the extracellular domain. The vaccine was also formulated with unique combinations of adjuvants available to GSK and not available to academic investigators. Phase I/II testing of this improved vaccine formulation was initiated in 2004 by GSK and Corixa in collaboration with multiple academic translational researchers including those at UW. The vaccine formulation was able to induce substantial antibody and T cell immune responses in breast cancer patients and continues in development at GSK. While Corixa and GSK moved forward with improving the HER-2/neu protein-based vaccine, other UW scientists (funded through NCI R01 and K08 grants) have been successfully working on DNA-based HER-2/neu vaccine approaches.

### Relationship to TRWG Pathway

Development followed the immune response modifier pathway through multiple iterations of vaccine construction and adjuvant formulation, delivery schemes, and vaccine regimens, both in animal models and early-phase human clinical trials. The multiple iterations led to refinements of the HER-2/neu vaccine construct to finally achieve an immune response that was deemed adequate to justify testing of the vaccine in larger-scale trials.

### Bottlenecks

Preclinical development/manufacturing required biotech and large-company financial and technological resources. The final vaccine formulation used a series of adjuvants not commonly available to most academic researchers or biotech companies.

### Key Observations

1. Successful handoff of technology from academia to industry was facilitated by a strong intellectual property position, which led to the co-founding of a small biotech company by the academic inventors.
2. Testing of the vaccine in patients required that the constructed vaccine be “handed back” to academic investigators.

3. Partnership between a small biotech company and a large pharmaceutical company was necessary to overcome financial, manufacturing and adjuvant availability hurdles.
4. Phase I trials of initial vaccine constructs can serve as “validation steps” that assist researchers in refining approaches and developing improved vaccines for subsequent expanded trials.

### Sources

- Interview with Dr. Mac Cheever, Fred Hutchinson Cancer Research Center/University of Washington (February 6, 2006)

### Literature

- Disis ML, Gralow JR, Bernhard H, Hand SL, Rubin WD, Cheever MA. Peptide-based, but not whole protein, vaccines elicit immunity to HER-2/neu, oncogenic self-protein. *J Immunol.* 1996;156(9):3151-8.
- Disis ML, Pupa SM, Gralow JR, Dittadi R, Menard S, Cheever MA. High-titer HER-2/neu protein-specific antibody can be detected in patients with early-stage breast cancer. *J Clin Oncol.* 1997;15(11):3363-7.
- Disis ML, Grabstein KH, Sleath PR, Cheever MA. Generation of immunity to the HER-2/neu oncogenic protein in patients with breast and ovarian cancer using a peptide-based vaccine. *Clin Cancer Res.* 1999;5(6):1289-97.
- Disis ML, Gooley TA, Rinn K, Davis D, Piepkorn M, Cheever MA, Knutson KL, Schiffman K. Generation of T-cell immunity to the HER-2/neu protein after active immunization with HER-2/neu peptide-based vaccines. *J Clin Oncol.* 2002;20(11):2624-32.
- Disis ML, Schiffman K, Guthrie K, Salazar LG, Knutson KL, Goodell V, dela Rosa C, Cheever MA. Effect of dose on immune response in patients vaccinated with an HER-2/neu intracellular domain protein-based vaccine. *J Clin Oncol.* 2004;22(10):1916-25.
- Limentani S, Dorval T, White S, Curigliano G, Campone M, Disis M, Piccart M, Cheever M, Gérard C, Brichard V. Phase I dose-escalation trial of a recombinant HER2 vaccine in patients with Stage II/III HER2+ breast cancer. *J Clin Oncol.* 2005;23(165) Part I of II (June 1 Supplement): 2520.

### Patent Search

- Cheever et al. Immune reactivity to HER-2/neu protein for diagnosis and treatment of malignancies in which the HER-2/neu oncogene is associated (#5,876,712). Filed June 6, 1995; received March 2, 1999.
- Cheever et al. Immune reactivity to HER-2/neu protein for diagnosis and treatment of malignancies in which the HER-2/neu oncogene is associated (#5,846,538). Filed June 7, 1995; received December 8, 1998. Subsequent patents include #6,075,122—University of Washington and #6,379,951—Corixa.



## Cell-Based Vaccine for Pancreatic Cancer

### Summary

In the late 1980s and early 1990s, a number of studies were reported indicating that murine tumor cells transduced to express a wide range of cytokines could induce an immune response against the transduced cells and in certain cases against subsequent challenge with nontransduced cells or a pre-existing tumor. In 1993 a group including researchers from Johns Hopkins University reported that cells transduced with granulocyte-macrophage colony-stimulating factor (GM-CSF) were a particularly potent stimulator of systemic antitumor immunity. Extending this finding, several early-stage clinical trials were conducted in the late 1990s with autologous GM-CSF-secreting tumor vaccines which showed promising results in patients with prostate and renal cell carcinoma and melanoma. Based on these results and the inherent technical and regulatory difficulties associated with autologous vaccines, the Johns Hopkins group began pursuing development of an irradiated, allogeneic GM-CSF-transduced cellular vaccine against pancreatic cancer. Pancreatic cancer was chosen as the target based on both clinical need and the association of the investigators with the Johns Hopkins GI SPORE.

Development of the allogeneic vaccine required establishing new methods for generation of *in vitro* cell lines from primary tumors as well as animal models and *in vitro* assays. For the initial Phase I trial begun in 1997, the new allogeneic lines were genetically modified to express GM-CSF and clinical grade vaccine was produced by a contract manufacturer using funds provided by a private donor. The vaccine development and clinical trial costs were funded by a combination of NCI R01, SPORE, and training awards. A Phase II trial was initiated in 1999 under the Hopkins GI SPORE using vaccine prepared by the NCI Rapid Access to Intervention Development (RAID) program.

As development progressed, the Johns Hopkins group applied for and received U.S. patents covering a broad method for treating pancreatic cancer using allogeneic pancreatic tumor cell lines modified to produce a cytokine that stimulates an antitumor response as well as specific cell lines and cell line production methods. These patents and the underlying vaccine technology were licensed in 2001 to Cell Genesys, who provided additional funding for the initial Phase II trial. Cell Genesys then supported a second Phase II trial in metastatic patients comparing the vaccine alone with vaccine plus immune modulating doses of cyclophosphamide to deplete regulatory T cells. Two additional Phase II trials are also now under way—one examining the value of booster vaccinations and the second testing the vaccine in combination with cyclophosphamide and cetuximab.

Based on the success of this cell-based vaccine development program, in 2001 Johns Hopkins began to develop a GMP vaccine manufacturing capability as a Cancer Center P30-supported core resource. This facility became fully operational in 2004 and has facilitated refinement of several other vaccine development concepts and expanded the pool of Johns Hopkins investigators developing vaccines for clinical trials.

### Relationship to TRWG Pathway

Development of the vaccine followed the immune response modifier pathway through multiple iterations starting with autologous vaccines tested in Phase I trials for several different cancers before focusing on an allogeneic vaccine for pancreatic cancer as the primary developmental focus.

### Bottlenecks

The primary bottleneck identified by the investigator was manufacturing. Funds from private sources were needed for initial Phase I manufacturing and without involvement of the NCI RAID program the vaccine may never have proceeded to Phase II trials. This experience led the Cancer Center at Johns Hopkins to develop a GMP vaccine manufacturing facility as a core resource.



## Key Observations

1. In the area of immune response modifiers, it can be difficult to obtain R01 funding for “credentialing” a discovery for entry into the TRWG developmental pathway. Because the approaches can be quite novel, researchers often must use training awards, SPORE funds, or other funding sources to conduct the necessary studies.
2. Completing the later stages of development (e.g., manufacturing and early-stage trials) required the investigator to assemble funds from several different government programs as well as private sources.
3. Multiple Phase I trials of initial vaccine concepts were necessary to provide proof of principle and identify developmental bottlenecks to be overcome (i.e., promising results with autologous vaccines lead to development of a more practical allogeneic version).
4. Successful handoff to industry for further development was facilitated by a strong intellectual property position, RAID funding of vaccine production, and SPORE funding of an initial Phase II trial.
5. An academic medical center’s investment in GMP manufacturing capabilities can lead to substantial expansion of related translational research at the institution.

## Sources

- Interview with Dr. Elizabeth Jaffee, Johns Hopkins University (February 1, 2006)

## Literature

- Dranoff G, Jaffee E, Lazenby A, Golumbek P, Levitsky H, Brose K, Jackson V, Hamada H, Pardoll D, Mulligan RC. Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony-stimulating factor stimulates potent, specific, and long-lasting anti-tumor immunity. *Proc Natl Acad Sci.* 1993;90(8):3539-43.
- Jaffee EM, Schutte M, Gossett J, Morsberger LA, Adler AJ, Thomas M, Greten TF, Hruban RH, Yeo CJ, Griffin CA. Development and characterization of a cytokine-secreting pancreatic adenocarcinoma vaccine from primary tumors for use in clinical trials. *Cancer J Sci Am.* 1998;4(3):194-203.
- Jaffee EM, Abrams R, Cameron J, Donehower R, Duerr M, Gossett J, Greten TF, Grochow L, Hruban R, Kern S, Lillemoe KD, O’Reilly S, Pardoll D, Pitt HA, Sauter P, Weber C, Yeo C. A phase I clinical trial of lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene for the treatment of pancreatic adenocarcinoma. *Hum Gene Ther.* 1998;9(13):1951-71.
- Jaffee EM, Hruban RH, Biedrzycki B, Laheru D, Schepers K, Sauter PR, Goemann M, Coleman J, Grochow L, Donehower RC, Lillemoe KD, O’Reilly S, Abrams RA, Pardoll DM, Cameron JL, Yeo CJ. Novel allogeneic granulocyte-macrophage colony-stimulating factor-secreting tumor vaccine for pancreatic cancer: a phase I trial of safety and immune activation. *J Clin Oncol.* 2001;19(1):145-56.

## Patent Search

- Jaffee et al. Method of treating cancer with a tumor cell line having modified cytokine (#6,033,674). Filed December 26, 1996; received March 7, 2000.
- Jaffee et al. Purified pancreatic tumor cell lines and related compositions and method (#5,985,290). Filed March 18, 1998; received November 16, 1999. Subsequent patents include #6,193,970 and #6,350,445.
- Jaffee et al. Growth medium for primary pancreatic tumor cell culture (#6,087,174). Filed March 18, 1998; received July 11, 2000.

## Radiofrequency Ablation

### Summary

Radiofrequency (RF) ablation uses electromagnetic energy to heat and destroy tissue. The technique was initially developed for use in cardiology, primarily as a treatment for arrhythmias, and the FDA approved cardiac RF ablation devices in 1994. In early 1995, Italian clinicians presented a series of case reports on using RF ablation to treat liver cancer and researchers at the University of California Davis reported results from RF ablation of prostate tissue in dogs. During the period 1995-1997, investigators at multiple institutions in the United States and Europe reported a number of animal, phantom, and exploratory human studies examining RF ablation for use in cancer intervention. The majority of this work was supported by ad hoc local funding rather than by a traditional grant mechanism.

The first formal Phase I trial, performed by researchers at Case Western Reserve University, was reported in 1998. Even after this first Phase I trial, multiple research groups worldwide continued to examine RF ablation in both phantom and animal studies in order to refine procedures. Although some of these studies were NCI funded through R01 and SBIR awards as well as one SP0RE project, most of the preclinical work was funded by industry. Multiple NCI-funded Phase II trials, primarily in patients with liver or renal cancer who were not candidates for surgical resection, were carried out beginning in the late 1990s. A Phase III trial comparing surgery directly with RF ablation in renal carcinoma was initiated in 2005 in France and is still accruing patients.

### Relationship to TRWG Pathway

As RF ablation devices were originally developed and FDA approved for a nononcology purpose, translation into oncology proceeded with clinical studies being conducted in parallel with studies on phantoms and animals rather than in sequential fashion as described by the pathway.

### Bottlenecks

There were no significant bottlenecks encountered.

### Key Observations

1. Interventional device development often proceeds through a learn-by-doing approach whereby clinical trial-and-error is used to refine the technique rather than proceeding through a structured preclinical validation process leading to definitive clinical trials.
2. Because interventional device development is strongly driven by industry, particularly small companies, devices are often moved forward into clinical trials and clinical practice without substantial optimization. Once a device is approved, it is difficult to obtain either industry or government funding for optimizing its use (e.g., optimizing the time, size, and precision of RF ablation therapy).
3. Development of a stronger preclinical testing infrastructure for interventional devices may be beneficial in the long run as more effort would be paid to optimization (and the utility of the technique relative to competing approaches) before the device is brought into the clinic.
4. Development of a stronger early clinical testing infrastructure for interventional devices (comparable to the Cooperative Groups) and mechanisms for multicenter database reporting will be important to ensure efficient translation of preclinical studies and robust evaluation of safety and efficacy.

### Sources

- FDA Center for Devices and Radiological Health, Devices@FDA database

- Interview with Dr. Nahum Goldberg, Beth Israel Deaconess Medical Center (February 7, 2006)

### Literature

- Manolis AS, Wang PJ, Estes NA III. Radiofrequency catheter ablation for cardiac tachyarrhythmias. *Ann Intern Med.* 1994;121(6):452-61.
- Buscarini L, Rossi S, Fornari F, Di Stasi M, Buscarini E. Laparoscopic ablation of liver adenoma by radiofrequency electrocautery. *Gastrointest Endosc.* 1995;41(1):68-70.
- McGahan JP, Griffey SM, Budenz RW, Brock JM. Percutaneous ultrasound-guided radiofrequency electrocautery ablation of prostate tissue in dogs. *Acad Radiol.* 1995;2(1):61-5.
- Djavan B, Susani M, Shariat S, Zlotta AR, Silverman DE, Schulman CC, Marberger M. Transperineal radiofrequency interstitial tumor ablation (RITA) of the prostate. *Tech Urol.* 1998;4(2):103-9.
- Lewin JS, Connell CF, Duerk JL, Chung YC, Clampitt ME, Spisak J, Gazelle GS, Haaga JR. Interactive MRI-guided radiofrequency interstitial thermal ablation of abdominal tumors: clinical trial for evaluation of safety and feasibility. *J Magn Reson Imaging.* 1998;8(1):40-7.
- Ahmed M, Liu Z, Afzal KS, Weeks D, Lobo SM, Kruskal JB, Lenkinski RE, Goldberg SN. Radiofrequency ablation: effect of surrounding tissue composition on coagulation necrosis in a canine tumor model. *Radiology.* 2004;230(3):761-67.
- Goldberg SN, Bonn J, Dodd G, Dupuy D, Geschwind J, Hicks M, Hume KM, Lee FT, Lewis CA, Lencioni RA, Omary RA, Rundback JH, Silverman S, Dorfman GS, Society of Interventional Radiology Interventional Oncology Task Force. Interventional oncology research vision statement and critical assessment of the state of research affairs. *J Vasc Interv Radiol.* 2005;16:1287-94.

## Three-Dimensional Conformal Radiation Therapy for Prostate Cancer

### Summary

Radiation therapy requires careful planning to direct the radiant energy to tumor tissue while largely sparing surrounding healthy tissue. In the 1970s, the arrival of CT scan technology gave clinicians, for the first time, detailed anatomical information about the location of a tumor and its surrounding tissue. Three-dimensional (3-D) visualization was performed manually by using multiple 2-D CT images to determine the optimal geometry for radiation delivery. Although computers were applied to radiotherapy treatment planning as early as 1955, the huge growth in computer power through the 1970s and 1980s made possible the development of algorithms for accurate three-dimensional visualization of a tumor and creation of more optimal radiation treatment plans, offering the potential for decreased error rates and increased doses of radiation to cancerous tissue.

During the late 1970s and early 1980s, development of computer-assisted three-dimensional tumor visualization and radiation therapy treatment planning was undertaken simultaneously by many groups of investigators. The first 3-D planning developments were reported by McShan et al. at Rhode Island Hospital (later relocated to the University of Michigan) and Goitein, et al., at Massachusetts Institute of Technology and Massachusetts General Hospital (MGH). By 1987, many groups were developing 3-D planning systems.

The earliest use of 3-D systems occurred in the particle therapy efforts at MGH and the University of California at Berkeley, while routine clinical use of a fully integrated 3-D planning system started in 1986 at the University of Michigan. During the mid and late 1980s, NCI used the N01 contract mechanism to fund development and comparison studies of both photon and electron 3-D planning at a number of institutions. These studies further documented the potential value of 3-D planning by testing the methodology in parallel at multiple institutions in order to demonstrate reproducibility when used by different machines and operators.

The first Phase I trial of the three-dimensional tumor localization and treatment planning system began in 1987 at the University of Michigan with dose escalation trials in prostate and liver cancer, followed by a larger dose escalation prostate cancer trial in 1991 at Memorial Sloan-Kettering Cancer Center using NCI P01 funding. During the late 1980s and early 1990s, investigators at several institutions, some using N01 or P01 funding, continued to make improvements in the algorithms and capabilities of the systems and to extend their use in clinical settings. A number of Phase I/II trials were performed in single institution settings through the late 1990s, some with NCI funding.

### Relationship to TRWG Pathway

Development of three-dimensional conformal radiation therapy followed the interventional device pathway closely. However, because of the nature of the technology, it was possible to introduce use of three-dimensional conformal radiation therapy into clinical practice in advance of controlled Phase I and II testing of its utility in guiding enhanced therapy regimens such as dose escalation.

### Bottlenecks

No significant early translational bottlenecks were reported.

### Key Observations

1. Development required that multiple institutions be involved in both the validation phase and in clinical trials to ensure that operator/machinery characteristics did not bias the results.
2. A combination of NCI contract and grant funding was used to support both the validation and early clinical trial phases.

## Sources

- Interview with Dr. Ted Lawrence, University of Michigan (December 29, 2005)

## Literature

- DL McShan, A Silverman, D Lanza, LE Reinstein, AS Glicksman: A computerized three-dimensional treatment planning system utilizing interactive color graphics. *Brit J Rad.* 1979;52:478-81.
- Goitein M, Abrams M, Rowell D, Pollari H, Wiles J. Multi-dimensional treatment planning: II: Beam's eye-view, back projection, and projection through CT sections. *Int J Radiat Oncol Biol Phys.* 1983;9(6):780-97.
- GW Sherouse, CE Mosher, K Novine, J Rosenman, E Chaney: Virtual simulation: concept and implementation. In: Bruinvis IAD, van der Giessen FH, van Kleffens HJ, Wittkamper FW, eds. *The Use of Computers in Radiation Therapy.* North-Holland: Elsevier; 1987, pp. 423-36.
- Mohan R, Barest G, Brewster LJ, Chui CS, Kutcher GJ, Laughlin JS, Fuks Z. A comprehensive three-dimensional radiation treatment planning system. *Int J Radiat Oncol Biol Phys.* 1988;15(2):481-95.
- McShan DL, Fraass BA, Lichter AS. Full integration of the beam's eye view concept into computerized treatment planning. *Int J Radiat Oncol Biol Phys.* 1990;18(6):1485-94.
- TS Lawrence, RJ Tesser, RK TenHaken: An application of dose volume histograms to treatment of intrahepatic malignancies with radiation therapy. *Int J Rad Oncol Biol Phys.* 1990;19:1041-7.
- Simpson JR, Purdy JA, Manolis JM, Pilepich MV, Burman C, Forman J, Fuks Z, Cheng E, Chu J, Matthews J, et al. Three-dimensional treatment planning considerations for prostate cancer. *Int J Radiat Oncol Biol Phys.* 1991;21(1):243-52.
- Sandler HM, Perez-Tamayo C, TenHaken RK, Lichter AS. Dose escalation for stage C (T3) prostate cancer: Minimal rectal toxicity observed using conformal therapy. *Radiother Oncol.* 1992;23:53-4.
- Leibel SA, Zelefsky MJ, Kutcher GJ, Burman CM, Kelson S, Fuks Z. Three-dimensional conformal radiation therapy in localized carcinoma of the prostate: interim report of a phase 1 dose-escalation study. *J Urol.* 1994;152(5 Pt 2):1792-8.

## Exercise, Diet, and Breast Cancer

### Summary

In the early 1990s, several observational studies were reported indicating that excess weight and obesity are associated with poorer prognosis and survival for breast cancer patients. Additionally, as part of an NCI-funded cohort study that has followed 1,185 breast cancer cases for 10 years, the McTiernan group at the Fred Hutchinson Cancer Research Center interviewed study participants to determine physical activity both pre- and postdiagnosis. In preliminary analyses, they noted that women who were physically active both pre- and postdiagnosis had lower recurrence of breast cancer, which suggested that increasing activity could potentially improve prognosis.

However, because weight, diet, and physical activity are highly correlated, it was difficult to assess their independent contributions to breast cancer prognosis from such observational studies. Therefore, the McTiernan group conducted a pilot diet-exercise intervention study (funded by a Clinical Research Center award from the National Center for Research Resources) in nine overweight, sedentary breast cancer patients to test the feasibility of such a trial. The results reported in 1998 indicated that recruitment success and compliance were very high and that significant reductions in weight, body fat, blood pressure, and pulse were achieved.

Based on the feasibility demonstrated by this pilot study, the McTiernan group obtained an NCI R01 grant in 1997 which funded randomized controlled studies examining the effect of a 1-year, moderate intensity exercise program on hormone levels (as a potential surrogate for outcome) of approximately 170 sedentary, overweight postmenopausal women. Results showed decreases in serum estrogen, testosterone, and insulin, which may explain the association of exercise with reduced cancer recurrence. Large observational studies on the relationship of exercise, diet, and sex hormone or insulin levels on breast cancer risk continue to be reported, but no further large, controlled interventional studies have been published.

### Relationship to TRWG Pathway

Assessing effectiveness of exercise and diet on breast cancer risk followed the lifestyle intervention pathway closely.

### Bottlenecks

The primary bottleneck reported was a perceived low priority for lifestyle intervention research at NCI. Other Institutes such as the National Institute of Diabetes and Digestive and Kidney Diseases and the National Heart, Lung, and Blood Institute were characterized as being more accustomed to funding this type of research.

### Key Observations

1. Small, carefully controlled pilot studies of lifestyle interventions are critical to establish feasibility of patient recruitment and compliance.
2. It is difficult to fund pilot lifestyle intervention studies with traditional NCI grants. It is often useful to use Cancer Center or other infrastructure resources to fund such pilot studies and build the premise for more definitive trials.

### Sources

- Interview with Dr. Anne McTiernan (February 7, 2006)

### Literature

- McTiernan A, Ulrich C, Kumai C, Bean D, Schwartz R, Mahloch J, Hastings R, Gralow J, Potter JD. Anthropometric and hormone effects of an eight-week exercise-diet intervention in breast cancer patients: results of a pilot study. *Cancer Epidemiol Biomarkers Prev.* 1998;7(6):477-81.

- Chlebowski RT, Aiello E, McTiernan A. Weight loss in breast cancer patient management. *J Clin Oncol.* 2002;20(4):1128-43.
- McTiernan A, Tworoger SS, Rajan KB, Yasui Y, Sorenson B, Ulrich CM, Chubak J, Stanczyk FZ, Bowen D, Irwin ML, Rudolph RE, Potter JD, Schwartz RS. Effect of exercise on serum androgens in postmenopausal women: a 12-month randomized clinical trial. *Cancer Epidemiol Biomarkers Prev.* 2004;13(7):1099-105.
- McTiernan A, Tworoger SS, Ulrich CM, Yasui Y, Irwin ML, Rajan KB, Sorensen B, Rudolph RE, Bowen D, Stanczyk FZ, Potter JD, Schwartz RS. Effect of exercise on serum estrogens in postmenopausal women: a 12-month randomized clinical trial. *Cancer Res.* 2004;64(8):2923-8.



## Smoking Cessation and Lung Cancer

### Summary

Because of the well-documented causal effect of smoking on lung cancer and previous studies of smoking cessation intervention in other types of cancer, a randomized trial of a smoking cessation intervention for early-stage lung cancer patients was designed by Drs. Gritz (M. D. Anderson Cancer Center) and Albain (Loyola University) in the Cancer Control Research Committee of the Southwest Oncology Group (SWOG). The trial was implemented in SWOG and other affiliated cooperative oncology groups. Because previous work had identified interventions that would facilitate smoking cessation, a pilot study was not conducted in advance of starting this Phase III trial in 2002. However, members of the SWOG Lung Committee were surveyed regarding their support of this trial prior to its inception and the response was extremely positive. Smoking status data were also sampled from a prior clinical trial in lung cancer patients to estimate smoking prevalence in the relevant population. The investigators obtained support from a pharmaceutical company to carry out this study.

After 2 years of implementation, active training at two SWOG meetings/year, and significant outreach to other cooperative groups, the trial was closed due to lack of accrual. Accrual barriers included (a) difficulty in accessing patients, as stage I and II lung cancer patients are generally treated by surgeons, not by medical oncologists; (b) lack of incentives for investigators to participate, due to low-level reimbursement per patient; and (c) perceived difficulties in conducting the intervention and follow-up, as nurses and SWOG patient coordinators are more accustomed to medical interventions which require less patient-completed assessment.

### Relationship to TRWG Pathway

Development of the smoking cessation intervention did not follow the pathway in that a pilot study to assess feasibility was not conducted.

### Bottlenecks

The primary bottleneck was extreme difficulty in accruing patients to this intervention trial. Significant delays in receiving NCI approval to conduct the trial and the need to obtain external funding were also barriers.

### Key Observations

1. Pilot studies to assess feasibility of patient recruitment and compliance as well as other logistical aspects of a large definitive trial are critical elements in successful lifestyle intervention development.
2. Lifestyle intervention studies in cancer survivors are not a high priority for oncology cooperative groups and require intensive efforts to develop, fund, accrue patients, and successfully complete. In this case, the latter two objectives were not achieved.

### Sources

- Interview with Dr. Ellen Gritz, The University of Texas M. D. Anderson Cancer Center (February 7, 2006).

### Literature

- Gritz ER, Nisenbaum R, Elashoff RE, Holmes EC. Smoking behavior following diagnosis in patients with stage I non-small cell lung cancer. *Cancer Causes Control*. 1991;2(2):105-12.

- 
- Gritz ER, Carr CR, Rapkin D, Abemayor EA, Chang LJ, Wong WK, Belin TR, Calcaterra T, Robbins KT, Chonkich G, Beumer J, Ward PH. Predictors of long-term smoking cessation in head and neck cancer patients. *Cancer Epidemiol Biomarkers Prev.* 1993;2(3):261-70.
  - Gritz ER, Schacherer C, Koehly L, Nielsen IR, Abemayor E. Smoking withdrawal and relapse in head and neck cancer patients. *Head Neck.* 1999;21(5):420-7.
  - Gritz ER, Dresler C, Sarna L. Smoking, the missing drug interaction in clinical trials: ignoring the obvious. *Cancer Epidemiol Biomarkers Prev.* 2005;14(10):2287-93 (and references cited therein).

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## Appendix F: TRWG Meeting Dates

<b>2005</b>	<b>2006</b>	<b>2007</b>
November 15-21 TRWG Conference Calls	February 23-24 TRWG First Public Roundtable Phoenix, AZ	January 17-18 TRWG Face-to-Face Meeting Millbrae, CA
December 4-5 TRWG Face-to-Face Meeting Baltimore, MD	March 23-24 TRWG Face-to-Face Meeting Bethesda, MD	
December 7 Presentation to National Cancer Advisory Board Bethesda, MD	April 24 TRWG Industry, Foundation, Society Roundtable Philadelphia, PA	
	May 30-31 TRWG Face-to-Face Meeting Houston, TX	
	June 14 Interim Report to National Cancer Advisory Board Bethesda, MD	
	June 30 Interim Report to NCI Board of Scientific Advisors Bethesda, MD	
	August 16-17 TRWG Face-to-Face Meeting Chicago, IL	
	September 14-15 TRWG Face-to-Face Meeting Herndon, VA	
	October 16-17 TRWG Second Public Roundtable Atlanta, GA	
	November 27-28 TRWG Face-to-Face Meeting Bethesda, MD	