Process Analysis for the NCI Translational Research Working Group

INTRODUCTION AND SUMMARY

In order to inform its deliberations, the NCI Translational Research Working Group (TRWG) has developed five developmental pathways to clinical goals encompassing agents, immune response modifiers, risk assessment devices, interventive devices and lifestyle alterations. At the December 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 and the summarized results of the analysis.

METHODOLOGY

Identification of Case Study Candidates

After the December 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, early-stage clinical trial abstracts, and funding data (including 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.

- **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
- **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
- **Interventive Devices**
  - Radiofrequency Thermal Ablation (RFA)
  - Conformal Radiotherapy
  - 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., SPORE, EDRN), others funded through a series of individual-investigator awards (e.g., R01, K-series, SBIR/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., NIGMS, NIDDK, 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 FDA approval or patient recruitment issues.

3. A range of interactions among stakeholders were 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 interventive 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 new candidate biomarker of biological response).

   - The TRWG developmental pathways are idealized representations of the translational research process. For example, several cases in the interventive 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.