Translating Research into Clinical Practice: Deliberations from the American Association for Cancer Research

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Abstract

Translational research is difficult to define but recognizable to all who engage in it. Academic medical centers struggle to participate effectively, in contrast to the biotechnology or pharmaceutical industry, which are designed for nothing else. The process of translational research can be viewed as a cycle with defined phases and identifiable checkpoints. From the original hypothesis, through early scientific testing, investigators with different skill sets are required to move a fundamental observation through preclinical tests of clinical relevance then ultimately into the clinic. The various investigators must be able to organize effective research teams, whose compositions will differ as one moves closer to treating patients. Each phase, from discovery through application, has a set of barriers that can be summarized as culture, human resources/education, infrastructure, and regulatory. At a retreat of the Clinical Translational Research Committee of the American Association for Cancer Research, many of the issues facing academic centers were discussed and several recommendations are summarized here.

“If it sounds good, it is good.”
— Duke Ellington

All involved in translational research agree on one thing—it is difficult to define. Several organizations and individuals have made valiant attempts, and so will I.

“Translational research is the application of a discovery to the practice of medicine.”

(Personally, I like Duke Ellington’s better). But as a distinguished colleague stated recently “We are all translational researchers!” consistent with the feelings of Pasteur who wrote, “To the individual who devotes his or her life to science, nothing can give more happiness than when the results immediately find practical application. There are not two sciences. There is science and the application of science and these two are linked as the fruit is to the tree.”

Although often considered “bench to bedside,” the origins of translational research were not necessarily in the laboratory. One of the most notable examples was the work of Sir Edward Jenner (1749-1823) who observed that dairymaids who had contacted cowpox through milking did not get smallpox. Jenner then tested the hypothesis that vaccination with cowpox could protect versus smallpox, leading to the first successful vaccination against an infectious disease of humans (1).

However, Jenner could not have imagined the complexities he would encounter if today he were to attempt similar vaccination against an infectious disease of humans (1). Could protect versus smallpox, leading to the first successful vaccination against an infectious disease of humans (1).

The Translational Research Cycle

Figure 1 depicts the “translational research cycle”, which includes several identifiable stages and clearly defined checkpoints. Each phase has its unique features. For example, the resting phase (T0) requires the generation of a great idea and the formulation of that idea into a testable hypothesis.

The testing phase (T1) is when the great idea is subjected to interrogation through scientific inquiry. This hypothesis testing requires the assembly of a research team that includes students, postdoctoral fellows, and more established scientists. The principal investigator or team leader must acquire funding for the project and show that progress is being made. With a combination of luck, skill, and tenacity, a discovery will occur that may become the basis for translation.

The synthesis phase (S) requires the ability to identify the potential importance of a discovery to a clinical problem. This is often dependent on mechanisms to place fundamental information in front of people who understand the scientific basis of medicine and are familiar with medical problems.

Movement into the application phase (T2) requires the ability of researchers to determine the importance of a discovery to deconstruct. Much of what follows was discussed at a recent retreat of the American Association for Cancer Research and through meetings of the AACR Clinical Translational Research Committee. I thank and credit my many distinguished colleagues who participated in these activities for refining these comments.

1Participants in the AACR retreat on Clinical Translational Research held January 6 to 7, 2003 included: Dr. Karen H. Amtman, Dr. Frederick R. Appelbaum, Dr. Robert J. Arceci (invited but did not attend), Dr. Tom Benthin, Dr. Michael A. Caligiuri, Dr. Michele C. Christian, Dr. William S. Dalton, Dr. Raymond D. DuBois, Dr. William E. Evans, Dr. Margaret Foti, Dr. Stephen H. Friend, Dr. William N. Hait, Dr. John A. Hickman, Dr. Susan Band Horwitz, Dr. H. Kim Lyerly, Dr. Joyce O'Shaughnessy, Dr. David R. Parkinson, Dr. Joel E. Tepper, and Mr. Robert Mittman, facilitator.
human biology. Here, the team of investigators must have access to human tissue and body fluids, predictive animal models, as well as pathologists, pharmacologists, surgeons, and biostatisticians.

The movement phase (M) is where preclinical studies enter the clinic. Now the research team must expand to include practicing physicians, nurses, research coordinators, toxicologists, informaticians, regulatory experts, lawyers, and a variety of other seemingly unrelated species. Ironically, as the discovery moves closer to human application, the science tends to get less expensive).

**Translational Research Checkpoints**

The translational research cycle has barriers or checkpoints that must be overcome to allow progression from one phase to the next. These checkpoints can be described as follows:

- **The T0/T1 checkpoint** stands between a bright idea and an important discovery. Components of this checkpoint include lack of creativity, innovation, methodologies, skill, funds, space, and the ability to assemble an effective research team.

- **The T1/S checkpoint** is the barrier between the new discovery and understanding its importance to clinical medicine. This checkpoint is fortified by the cultural differences between scientists and clinicians. As one colleague stated, "Clinicians know all of the problems, but none of the solutions; scientists know all of the solutions, but none of the problems." Although I believe this may be less true today than 10 years ago, this cultural gap remains substantial. Institutions such as cancer centers encourage, whereas pharmaceutical and biotechnology companies demand, team interactions. Components of the checkpoint include lack of a properly trained workforce, lack of appropriate venues for interdisciplinary discussions, and academic disincentives to participation in team research. Scientists who are interested in understanding human biology and pathology, and clinicians able to understand the methodologies and significance of laboratory findings are the critical components of this workforce.

- **The T2/M transition** is the most daunting of all. The T2/M checkpoint blocks the movement from preclinical research into the clinic. Its components include the lack of role models, mentors, models of human disease, access to human tissues, funding, and powerful tools for conducting research with human subjects and evaluating interventions (e.g., imaging, innovative trial design, serial sampling of tissues, etc.). This checkpoint is fortified by the culture of most academic organizations that encourage individual science but fail to support team-based research, and by funding agencies where translational grants have fared poorly. Several important advances in this area have been made including the creation of Specialized Programs of Research Excellence, formation of clinical study sections, improvement in training or K awards, and the recently announced "Paul Calabresi Award for Clinical Oncology (K12)". Translational research requires both the tenacious individual scientist and effective teams to be successful.

Trumping all of these barriers may be a regulatory environment that is intimidating to even the most seasoned translational investigator. The T2/M transition requires knowledge of the policies and procedures regulating the conduct of research on human subjects and the ability to overcome obstacles to material transfer and intellectual property rights. To enter clinical trial, a validated discovery must leap over a seemingly interminable series of hurdles such as Food and Drug Administration, Institutional Review Board, Protocol Review and Monitoring System, and Health Insurance Portability and Accountability Act regulations, intellectual property discussions, not to mention the practical scientific needs of toxicology and manufacturing. In the wake of recent events regarding cyclooxygenase-2 inhibitors, this environment will surely worsen as well-intentioned public servants strive to protect the American public from adverse side effects of new and approved drugs.

Translational research should not end with the first clinical trial. Rather, the initial clinical experiment should be viewed as the first of a series of experiments designed to test an important hypothesis; the re-entry point into the "testing phase" where data can be evaluated and new ideas generated. Thus, the M/T0 checkpoint is created by the lack of scientifically astute physicians, clinically astute scientists, and rigorous design of clinical trials. Just as a laboratory scientist would not depend on the first experiment to be the last one, so should not the clinical investigator feel that the first trial would provide definitive conclusions. Rather, clinical trials like laboratory experiments should be designed with proper positive and negative controls to provide information that guides more sophisticated future experiments that will give more definitive answers.

To overcome this checkpoint I suggest a "war games" approach, where the vested laboratory and clinical scientists meet before a clinical protocol is designed to ask the following question: "What if after completion of phase I and II clinical testing, we see not a single indication of drug activity?" My experience is that investigators/companies get so caught up in the excitement of moving into the clinic, (or so relieved by finally knocking down all the barriers and struggling over the hurdles) that they become more convinced than ever that their new treatment would actually work! In other words, blockbuster blindness. As one scientist recently told an external advisory board, "...our target is important in virtually all cancers, so we predict activity against most." In fact, most targets for anticancer drugs (e.g., DNA, microtubules, and...
growth factor receptors) are present in most tumors, yet the drugs that target these molecules are inactive in most patients. If before designing a clinical trial we asked, “What are the 10 most likely reasons our drug won’t work?,” and go back and define these preclinically, we will be better prepared to design rational, informative, early phase clinical experiments.

**Recommendations**

This discussion points to certain barriers to translational research in academic centers (workforce, culture, infrastructure, regulations) and logically leads to recommendations that could improve the process. The translational research cycle has identifiable activators including committed mentors, protected time, critical mass of scientifically sophisticated physicians, medically sophisticated scientists, nurses, and advocates, who share interests, goals, rewards, venues, seminars, retreats, societies, and resources (e.g., tissue retrieval, chemistry, informatics, imaging, GCRC, GMP facilities).

The AACR working group drafted recommendations for alleviating four major barriers.

**Culture**

**Primary objective.** Establish mechanisms for people from across disciplines to work effectively together.

 Expedite the process by (a) identifying models used by others that reward a team approach to science; (b) exploring innovative mechanisms/relationships between academia, industry, and government; (c) funding genius grants designed to identify and develop innovative partnerships; (d) offering fellowships/sabbaticals to individuals in academia who wish to spend time in industry (potential for exchange programs); (e) writing a white paper on the barriers to translational research present within academic institutions.

**Human Resources/Education**

“...research can be no more divorced from medical education than can medical education be divorced from research” (2).

**Primary objective.** Create a stable, effective army/orchestra of translational researchers to better link biology and medicine.

Help achieve this primary objective by (a) making the AACR national meeting attractive to the best and brightest translational researchers; (b) exploring ways to influence the medical school curricula to develop pathways for training translational scientists (different from the M.D., Ph.D. programs); (c) creating educational series at its meetings; and (d) producing a handbook on the “Fundamentals of Clinical Translational Research.”

**Infrastructure**

**Primary objective.** Define best practices that are known, approved, and implemented.

Many of the shared resources that make up the infrastructure for clinical translational research may not be available to some investigators wishing to enter the field. Create an electronic clearinghouse to help identify where these resources exist and how they can be accessed. In addition, AACR could publish guidelines that attempt to define standards for developing and reporting clinical/translational research for publications or for presentations at national meetings and to regulatory agencies.

**Regulatory**

**Primary objective.** Create simple, streamlined, efficient processes that protect patients, and promote research.

(a) Convene a working group to share or create best-practice guidelines; (b) involve international Food and Drug Administration representatives through the AACR meetings; (c) support a national Institutional Review Board to expedite institutional approval of national cooperative group protocols; (d) educate the public on the negative impact of over-regulation on the development of effective new treatments; (e) engage advocates to help combat the media-driven image that clinical trials and clinical researchers are “evil”; (f) stress the importance to the press of balanced reporting on the successes and mishaps of clinical research through press briefings, taking advantage of the AACR national meeting.

In the months ahead, Clinical Cancer Research will publish a series of articles that address in more detail the recommendations outlined above. The Editors would be pleased to receive comments, manuscripts, and advice in this most important area.

**References**

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