SYMPOSIUM

Translational Research in Academia and Industry

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Research that bridges between scientific insights and clinical application is one of the most active and exciting areas of current biomedical activity. Much of this translational work occurs through collaborations between academic and industrial institutions, taking advantage of the respective strengths and resources of the two sectors. However, such collaborations sometimes can be challenging due to differences between the cultures and priorities of the two parties. This article discusses the nature of translational research, with a focus on the academia–industry interface, analyzes the factors important for effective collaborations, and describes specific examples of successful translational research programs. Exp Biol Med 231:1685–1689, 2006

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Translational research is one of the most satisfying and exciting areas of current scientific and medical endeavor. It is the conduit through which pure scientific insights can be connected with direct patient benefits. It also is a field that is rapidly changing, constantly being reshaped by the advent of new technologies and scientific breakthroughs. As such, it represents a challenging but highly rewarding area to occupy as a researcher and/or clinician.

A fascinating aspect of translational research is its location squarely on the boundary between academe and industry, a consequence of the ultimate aim of bringing (marketed) therapies to patients. This is simultaneously one of the greatest attractions and potential headaches of the field. On the positive side, great synergies can result from combining the respective strengths and resources of the two sectors. However, complications associated with cultural differences and intellectual property (IP) rights often can impede efficient progress.

This article will discuss the nature of translational research, with an emphasis on the issues associated with the interface between academia and industry. Some of the characteristics, challenges, and pitfalls of the field will be described, along with case studies that illustrate its great potential for improving biomedical innovation and medical practice.

What Is Translational Research?

Like many fields, translational research has as many definitions as it does practitioners. In the past, it has represented one step on a fairly linear path between a scientific discovery and its clinical application—often the bridge between a definitive scientific report and first-in-man clinical studies. Thus, the process of validating a newly identified drug target and developing a drug to it would be considered translational. This remains a valid categorization, but the current understanding of what constitutes translational research is both broader and more diffuse (Table 1). Some activities that could be described as translational—for example, the development of a new drug delivery technology—might be completely nonclinical in nature. In other cases, translational research could take clinical findings as a starting point and address resulting questions using laboratory analysis—for example, the identification of predictive biomarkers. Thus, translational research does not have rigid boundaries, either with basic research on one side or with clinical research on the other.

These examples also illustrate another very important feature of current translational research practice: it is no longer linear or unidirectional. The translation can occur

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Table 1. Examples of Translational Research Programs

	Program	Description
1	Validating a protein as a target for a particular disease, and developing a drug that hits the target	Bench to bedside
2	Taking a new technology (e.g., for drug delivery) and rebuilding/fine-tuning it for the clinic	Bench to bedside
3	Molecular profiling of patients in clinical trials to identify those who respond best for a drug (biomarker development)	Bedside to bench to bedside

from the bench to the bedside (example 1 in Table 1) or from the bedside to the bench (example 3), and in many cases it can include multiple journeys in both directions. Some of today's most exciting translational research involves the rapid analysis of clinical findings using cutting-edge molecular analysis, followed by the equally rapid application of those findings back into clinical practice (bedside to bench to bedside), as exemplified later in this article.

Another key characteristic of translational research is its complexity. Its execution usually requires working across different disciplines (biology, chemistry, development sciences, clinical research) as well as institutions (universities, hospitals, biotech and pharma companies, and contract research organizations), many of which will have equally different cultures. Progressing research efficiently across these multiple divides requires an understanding of the strengths, priorities, and limitations on each side.

Academia and Industry

Translational research projects can be initiated or principally based in either an academic institution or a company. From a purely technological point of view, most kinds of translational research could, in principle, take place in either setting. What are the differences between the two, and how do they influence the way that research is conducted?

In many ways, the differences between academia and industry are getting smaller. Academic institutions are increasingly aware of the potential commercial value of scientific breakthroughs, and companies increasingly embrace the importance of internal curiosity-driven research as a source of commercially important innovation. But there also are key differences between the two. For example, experimental product candidates that enter human testing will invariably come only from the industrial sector, due to realities such as manufacturing and regulatory requirements. This means that translational research involving such product candidates will necessarily have a major industrial involvement.

What are the pros and cons of undertaking translational research in an academic or an industrial institution? A major advantage of academic translational research, particularly in a hospital setting, is direct access to patients for clinical studies. Allied to the cutting-edge science present in academic centers, this can provide a formidable platform for high-quality translational studies. On the other hand, such studies face the challenges of securing grant funding, and investigators need to find or build the organizational structure required to orchestrate complex collaborations. And in the end, in many cases academic translational researchers can find themselves dependent on an industrial partner for access to reagents, such as drug candidates.

Translational research based in or coordinated by an industrial institution typically can benefit from access to the resources and organizational structure of that institution. In addition, most industrial institutions will have an inherent operational focus on product development, meaning that the infrastructure for managing complex interdisciplinary interactions already exists. However, funding challenges still may be encountered, particularly in smaller and/or early-stage companies, where there may be competition for resources with other endeavors. In addition, in many cases collaborations with academic institutions will be needed in order to obtain access to critical technologies or to patients.

Bridging the Divide: Intellectual Property

Some of the best translational research takes advantage of the strengths of each of the sectors. What are the factors behind successful collaborations of this kind? A very important requirement is that the two (or sometimes more) parties in the collaboration are fully aligned with respect to aims, priorities, and plans. Problems can arise if there are different expectations for the scientific direction of the research, or the anticipated timelines. It is also important to maintain communication when unexpected results suggest new directions. Often there is a clear scientific case for changing course, yet, for example, the industrial partner may have key product development milestones linked to the original goals. Another potentially thorny issue is the question of publication policy. Academic researchers, quite reasonably, expect and often need to be able to publish their findings promptly, whereas a company may be reluctant to release potentially valuable information to its competitors.

Undoubtedly, the single most important issue dominat-

ing translational collaborations between academic and industrial institutions is IP. IP and legal considerations are viewed with suspicion and distrust by many scientists, and yet they critically underpin the ability to effectively translate novel findings into therapies. For example, much translational research starts with a basic research insight at an academic institution that results in a patent filing and is then licensed to an industrial partner that collaborates with them to translate the finding into the clinic. This will only happen if the original insight or invention is sufficiently protected to warrant the company's investment. To ensure a path to commercialization and therefore to patients, it is critical that the possibility of solid patent protection is not thwarted by, for example, pre-filing disclosure or inadequate documentation. To this end, most academic institutions have technology transfer offices that work with investigators to protect emerging inventions.

In the many translational partnerships between industry and academia that involve studies with a specific reagent, such as a drug candidate, the key document is the materials transfer agreement, or MTA. MTAs govern all aspects of the use of a drug candidate in a collaborative setting, including the scope of studies, ownership of any inventions that result, publication policy, and the procedure to be followed in case of deviations from the MTA. Sometimes MTAs can seem to impose restrictions on curiosity-driven research: A very common example is the difficulty of combining two reagents or technologies governed by mutually incompatible MTAs (for instance, exploring whether two drugs from different companies act synergistically). However, the clarity provided by an MTA is key to the ultimate success of the collaboration in achieving its goals.

Case Studies

With these considerations as background, it is instructive to review two successful examples of translational research involving both academia and industry. Each represents a specific case of the general scenarios outlined in Table 1: the first is an example of a clinically driven biomarker discovery project, and the second is an example of taking a new technology and rebuilding it for clinical use.

Epidermal Growth Factor Receptor Biomarkers

A classic example of reiterative "bench to bedside" translational research is the discovery in 2004 of mutations of the epidermal growth factor receptor (EGFR) in patients with non–small cell lung cancer (reviewed in Refs. 1, 2). EGFR can be detected by immunohistochemistry in 40%–80% of such cancers, a finding that prompted the development of small molecule and antibody inhibitors of the protein, a receptor tyrosine kinase. This in itself represents a translation of research findings into the clinic. It was generally expected that tumors detectably expressing EGFR would be those sensitive to the drug, affording a potential predictive biomarker for response. Therefore, a diagnostic test was developed based on immunohistochemistry to allow such tumors to be identified (another translational activity). However, when clinical efficacy data were obtained for small molecule EGFR inhibitors in patients, it was found that only ~10% of patients in U.S. trials had clinical responses—but these responses were dramatic and long lived. There did not seem to be a correlation with EGFR expression as measured by immunohistochemistry.

These clinical findings prompted several academic groups to investigate the molecular nature of the highly responsive tumors, taking advantage of direct access to tumor samples taken from the patients. In 2004—by which time an EGFR inhibitor was already approved for marketing in the United States—several papers independently described how those tumors that responded dramatically to the drugs were distinguished by specific mutations in the kinase domain of EGFR (3, 4). These mutations were shown to render the enzyme more susceptible to inhibition by the drug. These findings immediately explained why fewer patients than expected benefited from the treatment, and why those patients had a striking response. Thus, the sequence, not the expression level, of the target is the critical determinant of tumor sensitivity.

The results of this laboratory-based insight into clinical data are now being translated back into the clinic. New trials are underway in which patients are being prescreened by DNA sequencing so that only those whose tumors harbor the mutated EGFR (and are therefore predicted to benefit) are enrolled. The institutions in which the mutations were discovered have licensed the resulting IP to a company that is developing a diagnostic test for commercialization. Most excitingly, rapid translation of insights to and from the clinic, and cooperation between academic institutions and industry, has resulted in a major step toward tailored treatments that maximize the chances of a patient receiving a beneficial therapy. The discovery of EGFR mutations represents a new paradigm for molecularly targeted cancer drugs that is likely to be repeated many times as more targeted therapies enter clinical development, and this progress will undoubtedly benefit from close collaborations between industry and academia (5).

Chemical Dimerization Technology

A more upstream example of reiterative translational research comes from our own experience developing a platform technology for controlling protein–protein interactions (6). In the early 1990s, academic researchers discovered that many cellular processes are triggered by the induced interactions between signaling proteins. Examples include the clustering of cell surface receptors by extracellular growth factors and the subsequent stepwise recruitment and activation of intracellular signaling proteins. In a 1993 paper published in *Science*, researchers at Harvard and Stanford described a general method to bring such

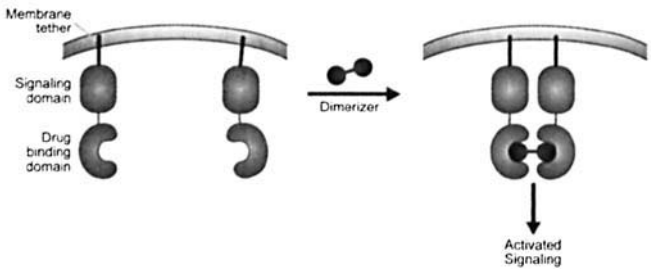

Figure 1. Scheme for control of protein–protein associations and cellular signaling using chemical inducers of dimerization. Signaling proteins of interest are expressed in cells as chimeric proteins, fused genetically to a drug-binding domain. Addition of a bifunctional organic dimerizer clusters the proteins together, mimicking the natural activation of the protein and initiating signaling. In this example, the chimeric proteins are tethered to the cell membrane through a short lipidated peptide tag.

interactions under chemical control (7). The technique involved the use of chemical inducers of dimerization, or dimerizers, cell-permeant organic molecules with two separate motifs that each bind with high affinity to a specific protein module. Any cellular process that is activated by protein–protein interactions can be brought under dimerizer control by fusing the protein(s) of interest to the binding domain(s) recognized by the dimerizer. Addition of the dimerizer then noncovalently links the chimeric signaling proteins, activating the cellular event that it controls (Fig. 1).

Chemical dimerization had obvious potential utility in biological research; for example, allowing the roles of individual signaling proteins and pathways to be dissected. Work continued in academic labs on these applications, but it was immediately apparent that the technology might also have broad therapeutic potential in gene and cell therapy by offering a way to control gene expression or cell fate using a small molecule drug. To exploit this potential, ARIAD licensed the technology from the universities, which had filed patent applications on the invention. A team of biologists and chemists at ARIAD embarked on an extensive program to rebuild and optimize the technology for clinical use; for example, generating dimerizers with optimal pharmacology and specificity, and "humanizing" each protein module. A dimerizer drug was advanced into the clinic, where it was found to be safe and well-tolerated in a Phase I trial (8).

Although the ARIAD scientists were highly successful in optimizing the dimerizer technology, to explore the potential uses in gene and cell therapy it was necessary to forge collaborations with key academic laboratories in order to access technology outside of the company's areas of expertise. For example, one potential application is the use of dimerizers to control expression of therapeutic proteins delivered *via* a gene therapy approach by using dimerizer-regulated gene transcription. However, ARIAD lacked expertise in the gene delivery vectors needed to insert a dimerizer-regulated construct into the tissues of experimental animals (and, in due course, humans). Therefore, ARIAD entered into an agreement with the University of Pennsylvania, governed by an MTA, that has blossomed into a highly productive translational research collaboration. By

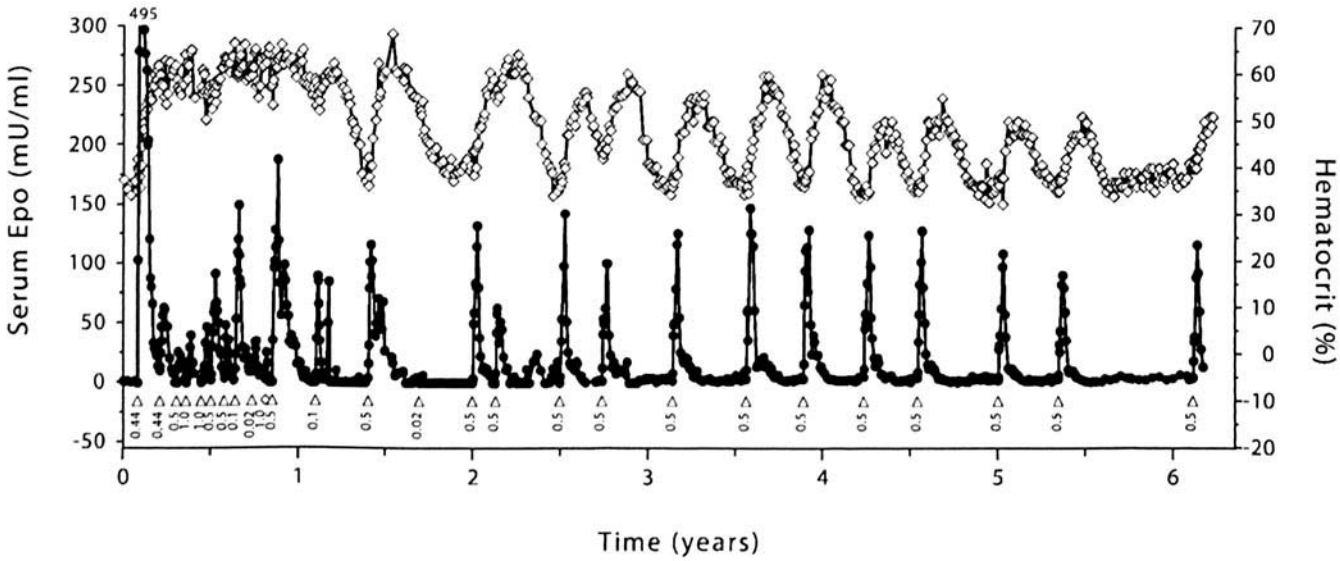

Figure 2. Use of dimerization technology to achieve long-term regulation of gene expression in a nonhuman primate. Adeno-associated viral vectors harboring a primate erythropoietin gene under the control of a dimerizer-regulated transcriptional control system were injected into the muscle of a nonhuman primate on Day 0. Subsequent injections of the dimerizer drug rapamycin (open triangles) induced a strong and reversible production of Epo (closed symbols) and consequent transient elevations in hematocrit (open symbols). No protein was produced in the absence of induction. Inducibility has persisted for more than 6 years to date following a single vector injection (10). This research was originally published in *Blood*: Rivera VM *et al.* Long-term pharmacologically regulated expression of erythropoietin in primates following AAV-mediated gene transfer. *Blood* 2005;105:1424–1430. © The American Society of Hematology.

combining the dimerizer system with adeno-associated viral (AAV) vectors, it has been possible to demonstrate very long-term, drug-regulated delivery of therapeutic proteins such as Epo in experimental rodents and nonhuman primates (Fig. 2; Refs. 9, 10). Similar collaborations with the Istituto Scientifico H. S. Raffaele (Milan, Italy), the Fred Hutchinson Cancer Research Center and the University of Washington (Seattle, Washington) have allowed the combination of dimerizer technology with methods for preparing genetically modified hematopoietic cells. These have again led to proof-of-concept studies showing drug-regulated cell elimination (11, 12) or cell proliferation (13) in rodents and nonhuman primates.

In all these examples, the industry and academic collaborators each contributed key insights and technology, and the sum was much greater than the parts—progress was made that could not have been made by either party alone. The result has been the translation of the original invention to the cusp of the clinic (although ultimate clinical testing has been slowed by the general clinical and commercial complexity of gene therapy). Key in each collaboration has been close communication and cooperation between the two research teams.

An additional reverse translational aspect to this program relates to the research uses of dimerizer technology. The optimized reagents developed at ARIAD for clinical use also were ideal for robust applications in the laboratory. To make the reagents broadly available, ARIAD scientists assembled them into kits that contain vector constructs and dimerizer drugs. These regulation kits are available free of charge to researchers in the academic community under the terms of a standard MTA. Access is through a dedicated website environment where users can register, obtain information, request kits, and provide usage updates (14). Researchers benefit from the availability of the reagents, and ARIAD potentially benefits from any insights or inventions that emerge. To date more than 1000 laboratories worldwide have received kits under this scheme, and more than 300 publications have appeared describing the use of the technology. It is entirely possible that findings from some of these studies will in turn be translated back into the clinic.

Conclusion

Translational research clearly is a vibrant field and the source of many of the important medical advances of the future. Some of the most compelling examples of its practice happen at the interface between academia and industry. Although there can be challenges in carrying out research across this boundary, the rewards are also great, and unexpected benefits can result for both parties. Therefore, active engagement between academic and industrial translational researchers is to be encouraged wherever possible.

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