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GUEST EDITOR'S PAGE

Partnerships Promote Translation in Biomedicine

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The term "translational research" trips lightly off the tongue, but the actual practice often proves elusive. I argue here that partnerships can prove pivotal in promoting the translation of laboratory studies to advances in clinical medicine. I focus particularly on what I will define as "horizontal" and "vertical" partnerships. "Horizontal" partnerships pertain to the relationships between laboratory investigators with more patient-based or clinically-oriented participants in the biomedical enterprise. "Vertical" partnerships refer to interactions between academic investigators and those involved in biotechnology and pharmaceutical enterprises.

"Horizontal" partnerships in translational research usually involve an individual dedicated principally to laboratory research who has made discoveries that hold promise for clinical application and clinical trialists. Few laboratory researchers have the skill set necessary for taking a laboratory finding through all the phases of clinical investigation and development to establish a new therapy or indication in the clinic. What key ingredients can foster partnership between these too often disparate types of individuals?

Mutual respect comprises one essential component. Laboratory-based researchers must accord equal esteem to their more clinically-oriented colleagues as to peers in the basic research community. The practice of clinical medicine and investigation at the highest level requires many of the same attributes that enable success in laboratory undertakings. These qualities include intelligence, investment in training, judgment, and of course the sine qua non: hard work. For the laboratory-based physician-investigator, maintaining clinical contact can heighten appreciation of the talents and dedication of their more clinically-oriented colleagues. Taking a turn in caring for hospitalized patients keeps the laboratory-based partner in touch with the problems posed by patients in actual practice. As opposed to the laboratory world, the care of patients involves making decisions and judgments in the absence of precise prior information, rigorous controls, or abundant data that apply directly to the patient in front of them. While the practitioner has clinical guidelines and the results of trials as touchstones, in actual practice the individual face-to-face with the physician often does not meet the entry criteria for the pivotal clinical trials, and each patient's care requires a good deal of individual judgment. For the laboratory-based physician, confronting the uncertainties and ambiguities of actual practice can foster humility and also engender deep respect for the seasoned clinician and clinical investigator whose partnership proves essential to enable effective translation.

Beyond mutual respect, a shared language can facilitate translational partnerships. Often more clinically-oriented partners in translational relationships have trained in some aspect of more fundamental research. Individuals who have spent some time grappling with the delayed gratification common in the laboratory can appreciate better the travails of the experimental investigator. In addition, an acquaintance with the concepts involved in research beyond that which can be gleaned from textbooks provides a common language: a Rosetta stone that facilitates communication in translational partnerships.

In addition, institutional culture can catalyze translational research. Leadership that fosters, enables, and rewards partnerships along the lines described above can stimulate and sustain the types of interactions that enable success in translational research. In many great institutions, a cultural divide

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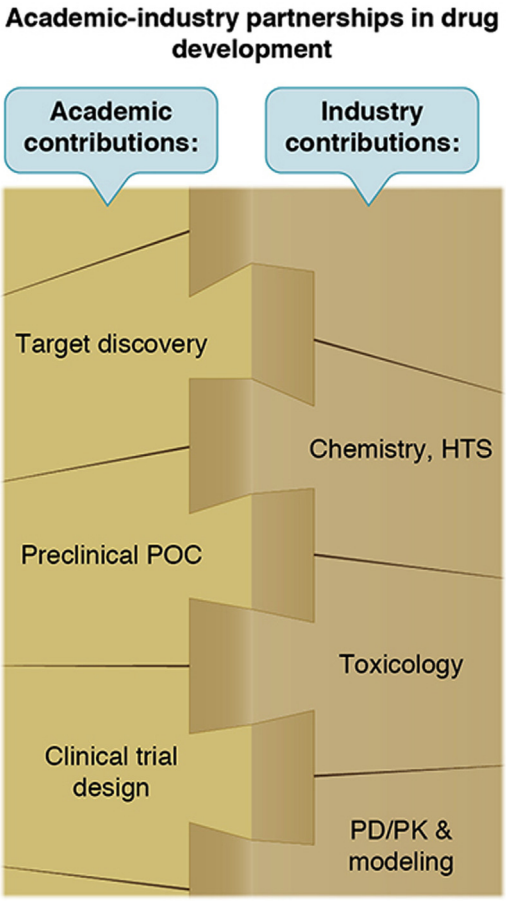
FIGURE 1 Interlocking Skills and Platforms Provided by Partners in Clinical Translation



HTS = high-throughput screening; PD = pharmacodynamics; PK = pharmacokinetics; POC = proof-of-concept.

exists between the clinically-oriented faculty and those engaged in basic research. Such a "twin tower" environment can present a barrier to the very types of interactions that cultivate effective translation. Leadership that values contributors along the entire spectrum of translation from the most fundamental through to master clinicians can inspire the types of interactions that kindle success in translation. An environment that encourages laboratory researchers to attend clinical conference and participate actively can enhance the likelihood of successful translation. Including in clinical conferences laboratory-oriented individuals who can communicate the concepts of their basic science findings clearly and understandably to more clinically-oriented individuals and trainees can nurture the culture of cooperation in translation.

Many laboratory-based investigators do not appreciate the extent of the inner workings of large-scale clinical trials. Such investigations are delicate, intricate, and arduous undertakings that involve multiple trade-offs and compromises foreign to the formulation of laboratory experiments. Clinical trials require incredible dedication and effort for successful completion. The clinical trialist lacks the ability to repeat an experiment, a luxury available in the laboratory environment.

While successful clinical trials entail many mechanical aspects which must perform correctly for success, the judgment and scientific discernment of the clinical trialist also participates pivotally in the design, execution, analysis, and mining of the data from clinical trials. On the other hand, input from the more laboratory-based investigators can contribute to the design and interpretation of trials. Input from the laboratory investigator can help prioritize subsidiary analyses and provide advice regarding what biomarkers or genetic studies would enable the most productive use of the biobanks and databases acquired by contemporary large-scale clinical trials. The remarks above provide some personal observations regarding the value of partnerships in maximizing opportunities for translational advances within academic institutions.

"Vertical" partnerships provide another key to successful translation. The best academic-industrial partnerships maximize the opportunities afforded by interlocking skill sets, strengths, expertise, and platforms (Figure 1). Academic investigators excel at defining biological pathways that can identify new targets for therapeutics as well as enlightening understanding of the pathogenesis of disease. Yet potential targets lie fallow without the application of skillful medicinal chemistry, access to compound libraries, or biological agent development to generate therapeutics based on the targets identified in academic research. High-throughput screening with large libraries and robotic technology most often exceed the resources of any single academic laboratory and many academic institutions. The medicinal chemistry and high-throughput screens of compound libraries, as well as the development of biological agents, represent strengths of industry that complement discovery research conducted in the academic laboratory.

The design of preclinical "proof-of-concept" studies can benefit enormously from input from academic investigators. The choice of target populations, biomarkers, and surrogate endpoints in early clinical development thrives when true partnership prevails between industry and academic physicians

acquainted with the disease processes based on close clinical contact. These clinical insights—coupled with the strong pharmacokinetic and pharmacodynamic modeling expertise of industry—can help to avoid some of the pitfalls of early clinical development.

Such challenges commonly include issues related to dosing, enrollment criteria, and the choice of outcome measures. The conduct of toxicology studies for new chemical entities in drug development not only lies outside the expertise and resources available to academic investigators, but also does not provide a fertile field for training in academic laboratories. This consideration limits the appropriateness of involvement of students or fellows in such projects in academic laboratories. Yet, toxicology studies including *in vitro* mutagenesis and animal toxicity studies must precede bringing a compound into the clinic. These undertakings lie well within the expertise and resources of the industrial partner, and illustrate the necessity of joining the interlocking expertises of academia and industry to achieve effective translation.

The design and execution of clinical trials at its best involves a balletic coordination between academic investigators and the pharmaceutical sponsor. As in earlier clinical development, a great deal of discernment and judgment can maximize the possibility of obtaining a clear answer from a clinical trial. Collaboration between academic and industrial statisticians can help assure the most rigorous approach to the all-important development of the trial protocol, choice of endpoints, dosages for study, and the all-important statistical analysis plan. The tension between resources allocated by the sponsor to the trial and the academic partner's interest in maximizing power (for example, for subsidiary, subgroup, or exploratory analyses beyond the primary endpoint) provides another example of the intricacy and importance of the partnership between academia and industry.

Of course, academic-industry partnerships in development of novel therapies and their translation to the clinic require safeguards. There must be transparency regarding financial relationships between academic investigators and industry. The right of the academic investigators to publish even negative data or possible adverse effects requires rigorous preservation. Academic investigators should have a duplicate of the database of clinical trials and have access to the biobanks generated during the investigation. Academic investigators should have the ability to perform independent statistical analyses of the study database. The steering committees of clinical trials and the data and safety monitoring board must have sufficient independence to assure the rigor of the conduct of an analysis of a trial and protect the participants.

Many look askance at partnerships between academic investigators and their institutions and the biotechnology or pharmaceutical industry. I argue that such partnerships not only enable or speed translation, but can actually provide substantial societal benefit by enhancing the public health. With adequate safeguards, partnerships between academia and industry can hasten the development of novel therapies and also provide pathways for the development of careers of physician investigators. The rich databases generated by contemporary clinical trials not only inform the primary endpoint, but should give rise to many subsidiary analyses which prove hypothesis-generating, and can provide mechanistic insight or increased knowledge of pathophysiology.

Thus, both horizontal and vertical partnerships can help promote translational medicine. Like many human enterprises, these partnerships require considerable care and curation. Yet, at the end of the day they help to increase human knowledge and understanding of disease, and provide advances in clinical care that can alleviate suffering and prolong life.

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