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Bridging the Gap Between Basic and Clinical Investigation

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This article focuses on the increasing importance of effective communication between basic bench scientists and their colleagues in clinical investigation, and some recent and innovative programs to facilitate these interactions.

When I entered the MD/PhD program at Rockefeller University and Cornell Medical School in 1973, I very naively imagined a future of encountering interesting diseases in the clinic and running to my laboratory to solve mysteries and discover cures by the dozens. It was of course not long before I realized that medicine and research were two separate worlds, and that jumping back and forth between the lab bench and patient's bedside was not a trivial matter. In fact, in the exciting world of the laboratory of a Nobel laureate (Gerald Edelman, himself an MD/PhD), I fell in love with basic science and began a career that for over twenty years never dealt with a human in a research context, although my work was connected with diabetes. Only in the past ten years did I begin human studies in diabetes, finding a rewarding and productive niche in the world between mouse models and clinical research. Rapidly developing hypotheses using mouse models, testing the hypotheses in humans, and returning to the mouse for mechanistic studies is exhilarating but not always easy. It is increasingly difficult to maintain expertise across a spectrum of research that reaches from molecules to organisms to societies. The tools have increased in complexity, as have the hurdles (regulatory and funding, for example). At the same time, the tools bring with them new possibilities to actually understand and cure disease as could not have been imagined even a few years ago, making this an exciting time to be involved in translational research efforts. This brief article focuses on some of the difficulties of translational research, the crucial importance of training a new generation of scientists that can participate in such research efforts, and new programs that will facilitate such efforts.

Are there in fact problems with translating basic science to the doctor's office or patient's bedside under the current system? There are numerous examples that would suggest the system has worked quite well. For example, pathologists had long observed cholesterol in atheromatous plaques and epidemiologic studies in the 1960's demonstrated associations between serum cholesterol and coronary artery disease. Based on knowledge of the biochemical pathway of cholesterol synthesis and the cell biology of cholesterol transport, inhibitors of HMG-CoA reductase ("statins") came to the market in the 1980's. Subsequent clinical trials revealed efficacy and safety, the public and physicians were appropriately educated, the drugs were widely adopted, and this contributed in a major way to a decrease in mortality from coronary disease. Thus, the entire spectrum of clinical research from basic

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science to clinical trials, population science and public policy worked together and generated a remarkable success story ¹. Numerous similar stories exist wherein basic science knowledge spawned effective therapies such as inhibitors of angiotensin converting enzyme, inhibitors of oncogenic tyrosine kinases ², insulin derivatives with more favorable pharmacokinetic profiles, and many others.

Although such success stories exist, the complexities of and the specialized expertise required for successful research across the chasm between molecules and populations has multiplied immensely. Thus, it is very difficult in these times to imagine one laboratory, let alone one person, having all of the knowledge to cover the huge gulf between a basic discovery to the development of a disease therapy and its implementation in a community doctor's office. Furthermore, there exist unique hurdles in translational science that may even become more problematic as our technical prowess increases and outpaces our ability to move the advances in knowledge to therapeutic reality. One answer is to build research teams that span at least sections of the chasm. Alternatively, individuals at various points across the spectrum can be trained to speak the language of investigators who are a step closer than they to the molecular end or the translational end of the spectrum. Thus, even if a formal team does not exist, the investigator at any one point in the continuum will be able to more easily move along the continuum to enlist help at the next stage in the process. A separate need is to create a home for translational investigators where they can more easily access the educational and core support services that are unique to the translation process.

The National Center for Research Resources (NCRR) of the NIH recognized these needs at the beginning of this century and created the Clinical and Translational Science Awards (CTSA, see <http://www.ctsaweb.org/>). These supplanted the General Clinical Research Centers and instead funded support for a much broader infrastructure for translational investigation, including core support in the areas of biostatistics, translational technologies, study design, community engagement, biomedical informatics, education, ethics and regulatory knowledge, and clinical research units. Forty-six such Centers have been funded, and ultimately sixty are planned. Among the bridging mechanisms for the earlier stages of translation:

- Training of individuals across the translational spectrum, including educating MDs to become clinical investigators. Equally important, however, is educating PhDs in medical pathophysiology and the translation process so that they will have at least a starting point when and if they come across a basic finding that might have direct translatability.
- Simplification of the translational process. The goal is to accelerate and simplify the regulatory processes as much as is feasible while maintaining research subject safety. Expertise is made accessible to investigators in areas such as Institutional Review Boards, contracting, FDA regulations and Investigational New Drug applications.
- Applying advances in informatics, imaging, and data analysis to translational research to allow investigators to fully exploit their findings and apply the latest technologies such as whole-genome sequencing, proteomics, and metabolomics to their studies.
- Determining mechanisms to nurture the careers of translational researchers. The MD/PhD programs are the prototype mechanism for training investigators that can bridge the translational divide. The success of those programs is at least partly attributable to the tuition support given to trainees such that when they finish training they are not saddled with the burden of huge loans. Further training of these individuals can also be streamlined, with "short track" residency and fellowship programs ³.

- Team mentoring and support of junior clinical scientists through programs such as K12 awards.
- Cataloguing research resources in such a way as to make specialized technologies, animal models, and analytic tools available to the widest possible set of users.

Other institutions, such as the Howard Hughes Medical Institute, have also joined in similar efforts. Its “Med into Grad Initiative,”

<http://www.hhmi.org/grants/institutions/medintograd.html> has a goal of bringing medical knowledge and an understanding of clinical practice into the curricula of biomedical Ph.D. programs.

These mechanisms should enhance the translational research enterprise, and efforts of the CTSA consortium have already borne considerable fruit. As team science focused on translation becomes more heavily supported by our government and private foundations, however, new challenges will emerge. Among the many:

- As large teams form to tackle the complexities inherent in translational research in a system that still largely functions on the basis of individual grant awards, there are questions of how these efforts will be rewarded. Who gets the first authored paper, the grant, the promotion and tenure? How can the stability and productivity of these teams be insured in a system fueled by five-year awards that wax and wane with the economic and political winds? Can we create career paths for translational scientists outside of the current “principal investigator” model?
- What will happen to the pipeline of basic science findings that fuel the enterprise as more money is shifted to later translational efforts? Many or most of our greatest advances in biomedical science have not come as the result of research targeted to a specific medical end. Who would have guessed that investigators of bacteriophage host restriction would make the discoveries that made possible the entire molecular biology revolution? At the other extreme, how could we have expected a “war on cancer,” declared in 1971, to be won when we did not know of the existence of oncogenes, apoptosis, or transcription factors? The lesson would seem to be that it is still crucial to give bright and dedicated individuals support to explore the unknown without expectations that their work will necessarily lead to a drug or product in five years.
- How will the capital-driven pharmaceuticals industry respond to the explosion of knowledge and opportunities? To follow an example of translational success mentioned above, as we become able to design molecules that can inhibit specific oncogenes and other molecules that can bypass common mutations that result from the first line therapies, will pharma take on the enormous task of bringing such compounds to market knowing that the use of the compounds will be in tens of thousands of patients rather than in tens of millions? Will we need a “National Institute of Pharmaceuticals” to support such drug development?

Although we face numerous daunting challenges, with the support brought by entities such as the CTSA consortium, there have never been grounds for greater optimism that the most significant health problems of the world can be brought to within reach of complete understanding and even eradication.

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