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Commentary

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Lost in Translation: Obstacles to Translational Medicine

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Abstract

When we launched the *Journal of Translational Medicine* a few months ago, we were interested primarily in exploring scientific consideration of this discipline. However, as editors of *JTM*, we have been contacted almost daily to discuss the problems faced by scientists and clinicians around the world who are challenging the traditional boundaries of science and medicine. Through these conversations, we have learned that translational medicine is in fact "lost in translation," inspiring much angst, many promises and some Federal appropriations. However, little has been done to substantively promote this important field. Authoritative reviews on the subject are available to the interested reader [1-7]. In this article, we will address *JTM*'s "constituency" to report what we've learned about the obstacles to translational medicine from the myriad of phone conversations and e-mail interactions.

In addressing issues for Translational Medicine, we categorize the hurdles faced by our colleagues as follows:

Semantics

What's in a name? A name defines a concept which in turn may shape a vision. Therefore, it may behoove us to establish a common understanding of the definition of "translational medicine" to frame our expectations or frustrations. For most, "translational medicine" (or "translational research") describes a uni-directional effort to test in humans novel therapeutic strategies developed through experimentation. This would suffice if animal or other experimental models were representative of human pathology, but this remains to be determined [8-10]. as well summarized by Herbert Slade's: "there are no good animal models, but some are useful." In addition, translational medicine may include the development of new

devices or novel diagnostic tools. Moreover, we suggested in a previous editorial that "translational medicine" is a two-way street where the drive to cure should be complemented by the pursuit to understand human diseases and their complexities [11]. Thus, one important aspect of translational medicine is going back from the bedside to the laboratory with observations made in human studies. This practice might be more constructive, focusing scientific thinking and providing more practical information.

Mario Sznol, a member of *JTM* Editorial Board, suggested that Translational Medicine should be defined as a discipline that encompasses:

1. Basic science studies which define the biological effects of therapeutics in humans

2. Investigations in humans which define the biology of disease and provide the scientific foundation for development of new or improved therapies for human disease
3. Non-human or non-clinical studies conducted with the intent to advance therapies to the clinic or to develop principles for application of therapeutics to human disease
4. Any clinical trial of a therapy that was initiated based on #1-3 with any endpoint including toxicity and/or efficacy.

In addition, in the regulatory arena:

5. Translational research may be defined as appropriate product development for clinical use in various stages of investigational clinical trial. For example, identity, purity and potency of a drug product must be studied during the early stages of the clinical trial. However, these tests must be in place before implementing phase 3 trials as required by the regulations.

Establishing a definition of "translational medicine" has both regulatory and commercial implications. Currently, a large sector of the biopharmaceutical industry is devoted to the development of new therapeutic modalities. However, industry is also concerned with the monitoring of ever-evolving therapeutic strategies by enhancing the quality, efficiency and throughput of available methods. In addition, revolutionary progress in genomics, functional genomics and proteomics may result in the identification of new diagnostic and/or prognostic parameters and define therapeutic end-points based on novel surrogate markers relevant to disease progression and response to therapy [5,12-16]. Are public, government, academic and industry interests united in supporting this important direction of translational medicine?

Advocacy

Translational medicine covers a broad range of scientific, regulatory and clinical disciplines and there is no single organization currently in existence to embrace the field in its globality. Therefore, while scientific and clinical aspects related to individual fields can be addressed within the realm of specialized societies, other practical aspects often related to education, regulation, business and economic issues remain orphaned, with no focused outlet through which to address emerging issues. An organization embracing the complexities of translational medicine should be considered with the goal of contributing information to all arenas of the need for translational efforts.

A translational medicine organization is particularly important in today's era of federal budget constraints. For example, most "standard" therapies for cancer do not affect survival [17], and billions of dollars are spent on drugs and therapeutic interventions that do not impact the natural history of most common diseases. Should advocacy efforts seek to shift funds from other research areas to translational research? Would it be savvier to join with other advocates of medical research to increase public and congressional awareness of the integrated need to understand basic as well as human biology? And who should be responsible for such advocacy? The National Institutes of Health has recently staked a claim on this issue by defining a roadmap to accelerate medical discoveries to improve human health <http://nihroadmap.nih.gov>. Should more institutions join the effort? And how should industry integrate with this effort? To be effective, barriers will only be removed by the collaborative efforts of multiple system stakeholders [7].

Intellectual

We confess to being baffled by some comments from reviewers solicited by the Editorial Board of *JTM* regarding some of the manuscripts submitted. Reviewers often dismiss some *JTM* submissions as not "hypothesis-driven", not "mechanistic", but "just" descriptive or discovery-driven. Such reviewers have often embraced solid hypotheses of their own to which they are strongly attached, like Manzoni's Donna Prassede who "in the matter of ideas followed the policy we are told we should follow with friends – She had only a few, but she was strongly attached to them" [18]. By their own admission, no objective evidence conclusively supports their hypotheses in the context of human disease, yet loyal they remain. Unfortunately, hypothesis-driven research alone cannot meet the needs of translational medicine. This is because hypotheses derived from complex experimental models often simply do not translate to human pathology. Thus, we suggested that discovery-driven research should be promoted in the context of translational medicine and should be better referred to as "reality-driven" research underlining the concept that direct human observation may direct to the study of hypotheses relevant to human reality.

Reality-driven research in humans faces obstacles of its own. First, communication between basic and clinical scientists is rare and sporadic [2]. Few meetings are devoted primarily to bringing the two entities together to promote mutually beneficial exchange. The paradigm between basic and clinical science has oftentimes put these two disciplines at odds with each other. It is not in the interest of basic scientists to accept changes unless publishing and study section standards are realigned to reward clinical relevance. Clinical scientists for their part are often over-

whelmed with information coming from the basic science community. How can such a wealth of information be processed into a useful compendium that might contribute the understanding of human disease? Furthermore, clinical scientists may be too distracted by the intensity of clinical care to be able to seriously help bridge this gap. Are clinical research grants providing sufficient support to academic clinicians to truly promote translational research [19]? For instance, traditionally, R01 grants have been used to measure a scientist's "independence". However, such approach may distance newer basic or clinical investigators from the integrated approach often required for translational efforts. Should advocacy efforts voice the importance of more interdisciplinary grants?

Confounding the whole picture is the fact that translational research is not pristine [11]. This is partly due to the constraints and inconsistencies of dealing with human subjects. It is at once true that review standards for grant applications and publications need to account for this unavoidable "sloppiness", and that clinical studies must be better designed prospectively to address biological questions beyond the routine assessment of safety and clinical efficacy. This could be achieved by prospectively collecting biological material of broad scientific interest at time points relevant to the natural or treatment-induced history of a disease and applying modalities appropriate for the exploitation of modern scientific tools. Clinical scientists, particularly those not extensively and currently exposed to bench research, should receive special training to become at least informed of the ever growing scientific opportunities for translational research [19-23]. This limitation leads to simple lack of manpower. At present there are few training programs that are ideally geared toward teaching all aspects of translational research. Although there are some attempts at developing clinical research training programs as evidenced by the NIH initiative and the Doris Duke Charitable Foundation funding for medical students to spend one year engaged in clinical research programs, it is not clear that this will significantly impact the manpower shortage. Translational investigators must not only be familiar with the regulatory, statistical and administrative issues related to clinical investigation, but must also possess a highly specialized expertise in the basic science underlying the new technology or pharmacologic agents. At a time when there are more agents to test than ever before, it is problematic that medical schools and medical education programs are not ready to train physicians in translational research. Programs providing interested applicants with experience in both basic science and clinical investigation may be necessary to maintain a pool of competent translational researchers. Furthermore, role models need to be developed for students and young investigators to begin to encourage the brightest students to enter this highly rewarding field.

Regulatory

Regulatory requirements provide formidable challenges for investigators. Major efforts have been made by regulatory agencies by releasing guidance documents. However, several obstacles remain. For example, preclinical evidence is usually required despite its unclear relevance to human disease. Similarly, it remains unclear whether toxicity testing in animal models is relevant to humans, particularly when biological agents with strong species-specificity are considered. Perhaps directly testing in humans, particularly for life threatening diseases when standard therapies have failed, should be considered in a limited number of patients. Clinical trial designs for the early development of novel therapies could be simplified according to the anticipated biologic activity of the agent tested [24]. While biopharmaceutical companies employ contractors or staff to address and meet regulatory requirements as required by regulations and the law, many academic institutions do not provide appropriate regulatory support. Most translational research is supported by grants; however, few provide funding for regulatory staff or consultation. Academic institutions do not provide support to non hypothesis driven research such as product development. In addition, a grant application focused on translational research characterizing identity, purity, stability and potency is rarely funded. Yet these characteristics are needed for advance testing of novel agents.

By the time new therapies work their way through preclinical experimentation, clinical studies and Phase III studies, they are often no longer state-of-the art and may even be scientifically obsolete. Therapeutic efficacy in the form of survival advantage remains a pre-requisite for regulatory approval of new therapies for cancer. This requirement is a major financial burden for small industries since the long term costs of clinical testing have to be sustained without economic return. This problem is compounded for tailored therapies such those directed against specific cancer mutations that target smaller market sizes while their development costs remain the same.

Paradoxically, many currently accepted therapies are known to provide no statistically significant survival benefit yet they have both approval for distribution and coverage by insurance companies. The National Cancer Institute leadership has recently put emphasis on "discovery, development and delivery" (NCI Director's report 2003) and, with the purpose of eliminating or reducing obstacles in translational research, the NCI Director's office has appointed new deputies charged with streamlining the discovery to delivery process. This strategy will hopefully yield results, at least in the context of cancer research, in a new modus operandi in clinical research where new agents could be quickly moved through the process and either approved or discarded.

Obviously, regulatory problems are not only limited to the development and distribution of new therapeutics. Institutional Review Boards and other internal review processes implement "ad hoc" rules to protect patients' safety and privacy based on the well established principle of "primum non nocere, i.e. do no harm". Yet, it remains questionable as to whether this theoretical need to protect sufficiently balances the overwhelming desire of patients' to attempt novel therapies when all other options are exhausted.

Economic

The current uni-directional paradigm of bench to bedside translational research is not cost-effective when one considers the long term expenditure of testing new drugs pre-clinically, obtaining regulatory approval for testing in humans and organizing increasingly larger clinical studies to demonstrate long-term clinical efficacy. How can small or medium biotechnology firms justify these costs? Similarly, how can academic institutions seeking to translate ideas of their research faculty take the economical risk of supporting a promising clinical trial? Should the cost of clinical trials be partly covered by insurance? How can Big Pharma justify the price of translational medicine? Academic clinical centers currently have an incentive to re-try combination trials based on permutations of approved treatments. These trials, at best, result in incremental therapeutic and scientific returns. Real and effective academic translational research centers are slowly growing but they have to confront tremendous economic challenges since their funding continues to depend predominantly on industry, grants from federal and non federal agencies and philanthropy.

It may be possible to create a solvent system for translational research if the well-designed but standard biological studies are combined with already approved therapies. For instance, interleukin-2 has been approved for the treatment of renal cell cancer and melanoma, yet the mechanism responsible for cancer rejection remains unknown. Centers could implement studies that generate revenue and provide material for biological studies while at the same time contribute to the support of novel experimental therapies.

Conclusion

There are three major obstacles to effective translational medicine. The first is the challenge of translating basic science discoveries into clinical studies. The second hurdle is the translation of clinical studies into medical practice and health care policy [7]. A third obstacle to effective translational medicine is also philosophical. It is a fact that the available standard therapies for most common diseases are less efficacious than they are believed by the Public to be and significant funds are allocated to main-

tain this "placebo" effect through standard care. Proportionately, very little is spent to identify truly effective therapies. Finally, it may be a mistake to think that basic science, without observations from the clinic and without epidemiological findings of possible associations between different noxes and disease, will efficiently produce the novel therapies that we are eager to test. If we as a body can coordinate efforts by advocacy groups, academia and industry to educate the public and the government of the need for translational medicine, novel and effective therapies could be the significant result.

In the upcoming Translational Research conference to be held September 20–22, 2004 in Princeton (for more information visit: <http://www.iqpc.com/NA-2166-01/translationalresearch>) we will be addressing these critical issues.

Comments are welcome and should be directed to: <http://EMarincola@cc.nih.gov> or directly submitted to JTM at <http://www.translational-medicine.com>.

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