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# Translational Medicine: A two-way road

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#### **Abstract**

The purpose of translational research is to test, in humans, novel therapeutic strategies developed through experimentation. Translational research should be regarded as a two-way road: Bench to Bedside and Bedside to Bench. However, Bedside to Bench efforts have regrettably been limited because the scientific aspects are poorly understood by full time clinicians and the difficulty of dealing with humans poorly appreciated by basic scientists. Translational research would be most useful to the scientific community at large if journals would foster specific interest for the publication of ex vivo human observation. The review process for such work should be assigned to clinical scientists competent not only in the intricacies of molecular or cell biology but also intimate with the reality of Internal Review Boards, ethics committees, Governmental Regulatory Agencies and most importantly the humane aspects of dealing with sick individuals and their families. This approach may focus both basic and clinical scientists and those struggling to fill the gap between them on the effective treatment of diseases affecting women, men and children making translational research more than an interesting concept.

## Introduction

The purpose of translational research is to test, in humans, novel therapeutic strategies developed through experimentation. This concept is so popular that Bench to Bedside Awards were developed within the NIH to encourage collaboration between clinicians and basic scientists across institutes. But a more realistic approach would be to encourage opportunities to pursue Bedside to Bench research since our understanding of human disease is still limited and pre-clinical models have shown a discouraging propensity to fail when applied to humans. Translational research should be regarded as a two-way road: Bench to Bedside and Bedside to Bench. However, Bedside to Bench efforts have regrettably been relegated to a Cinderella role because the scientific aspects are poorly understood by full time clinicians and the difficulty of dealing with humans poorly appreciated by basic scientists. In practice, Bedside to Bench information, though

conceptually valuable, is often frustrated by an unsympathetic review process.

### Specific hurdles

Indeed, the scientist attempting to dissect scientifically human diseases as they evolve has to confront unique challenges related with the genetic polymorphism of our species, the extreme and evolving heterogeneity of some diseases (such as cancer or viral disease) and often external constraints posed by ethical and practical considerations. Thus, some prefer to pre-fabricate animal models resembling human diseases to enable the mathematical prediction of a given treatment outcome by simplifying its biology through standardization of the genetic makeup of animals and diseases. These models, however, do not represent the basic essence of human diseases: they represent attempts to put the bull's eye in the trajectory of the projectile rather than designing a weapon capable of hitting a

moving target. "Clean" studies can be performed in humans following Phase III and some Phase II trials where clinical conditions are carefully designed and consistently maintained. However, such trials do not represent the primary purpose of translational research: the simple necessity to assess the effectiveness of a therapeutic modality in a Phase III context suggests minimal if any benefit.

The heart of translational research resides in Phase I trials where novel treatments are tested for feasibility and toxicity in preparation for a Phase II trial in which therapeutic effectiveness is tested. In the wake of a potential "breakthrough" in the lab, the Phase I trial offers great temptation to test what could be a pioneering therapeutic effect and learn from the novel concepts derived from clinical experience that could be shared with those bench scientists who originally conceived the treatment. But, since, unfortunately, minimal clinical benefit is usually seen in the context of exploratory studies, enthusiasm fades and a Phase II study does not materialize; attention turns to new therapeutic modalities brought to the clinical shore from a new Bench to Bedside wave.

#### How science fails us

Here is where the scientific community drops the ball. Often scientists that designed new potential therapies based on fundamental scientific breakthroughs are not inclined to learn why things did not work as well in humans as they did in the pre-clinical settings because there is no room in prestige journals for negative results. Indeed, the scientific community is not generally interested in negative results. In addition, difficulty in publishing results derived from phase I studies is compounded by the fact that often data are of compromised quality and not of the pristine quality achievable in the pre-clinical setting. Also, Phase I clinical studies in particular are characterized by evolving treatment strategies such as dose escalations and modifications dictated by regulatory agencies or demanded by clinical realities. For example, the patient population enrolled in phase I studies is primarily constituted of individuals who failed standard therapy and face terminal disease. In these individuals, therapies often need modification according to acute need for palliation and/or life saving procedures due to clinical emergencies. Finally, Phase I studies are limited in patient accrual and sample population. Yet, information derived from these pilot studies may offer precious insight for the rethinking of therapeutic strategies particularly when a Phase II study will not take place due to the failure of a Phase I study to meet expectations. Prestigious journals, however, appear more fascinated with the modern mythology of transgenic and knock-out mice than the humble reality of human disease. Thus, new ideas and related therapies based on genetically engineered results

of ever growing complexity are continuously published to compensate for previous failures.

#### More effective collaboration

Translational research would be most useful to the scientific community at large if journals would spare some precious space for ex vivo human observation or a specialized journal would be envisioned. The review process for such work should be assigned to clinical scientists competent not only in the intricacies of molecular or cell biology but also intimate with the reality of Internal Review Boards, ethics committees, Governmental Regulatory Agencies and most importantly the humane aspects of dealing with animals who can talk and have a life outside of a cage. This deeper approach may keep all of us honest by focusing both basic and clinical scientists and those struggling to fill the gap between them on the endgame: the effective treatment of diseases affecting women, men and children. The scientific process is meant, after all, to alleviate human misery and this ultimate goal could be facilitated by connecting basic scientists with the reality of human disease and making translational research more than an interesting concept.

# A new journal

We are therefore, starting a new open access Journal devoted to the appropriate peer review and rapid publication of results obtained through human investigation that may be of benefit to the scientific community and vice versa. The uniqueness of the journal will reside in the selection of a specialized editorial board composed of individuals with expertise in both the clinical as well as the basic aspects of science. Hopefully, the Journal of Translational Medicine will contribute to the advancement of clinical care through sympathetic collaboration between scientists and clinicians.

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