

Translational research – it takes two to tango!

Abstract

In this opinion article, a basic scientist and a clinical scientist have expressed views on the challenges that exist today in the world of translational research. We highlight differences between the basic scientist and the clinical scientist perspective on translational research, and discuss how these differences are perhaps rooted in the training in each of these disciplines. We also highlight the increasing pressures on both basic scientists and clinical scientists to integrate and come up with solutions for complex diseases, and the dialogue that is necessary to facilitate this interaction robustly. Some suggestions for improving dialogue are included but these are mere starting points for a larger discussion on this topic.

Keywords: ctsi, translation research, basic scientist, clinical scientist

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Introduction

From a basic scientist perspective, translational research is defined as the ability to use knowledge of basic mechanisms responsible for fundamental cellular processes to understand the causative mechanisms underlying human disease. From the perspective of a clinical scientist, translational research implies use of data from human studies and clinical trials to enhance our understanding of human disease and improve health outcomes. A broader definition of translational research would encompass use of all data (clinical or basic research) to understand human disease and improve health outcomes. In this era of the global information explosion, the obstacle in translating research is not primarily in the availability of or the accessibility to information, but rather in the application of information to solve real world problems. Basic scientists have been educated and trained to be minimalist by nature to design simple experiments with hypotheses grounded on solid preliminary data. However, this approach is counterintuitive to the majority of disease processes, which by nature are multi-faceted, and evolve over time. On the other hand, clinical scientists understand complexity but feel challenged in understanding the molecular mechanisms that drive disease pathogenesis; a key to identifying the molecular targets and mechanisms for pharmacological intervention. An amalgamation of both these approaches is needed for science to be translated successfully.

On face value, the basic scientist attempts to deconstruct the disease process by simplifying the tangles and approaches it in a stepwise fashion. The clinical scientist on the other hand approaches the problem with investigating trends, correlations and statistical analysis of significance. There lies the basic difference in approaches, which eventually leads to the two worlds that look at the same problem in isolation. Grant writing and funding pressures for basic scientists, and extensive clinical responsibilities with increasing pressures to generate revenue pushes the two worlds further apart into their

respective comfort zones. One might then ask why is translational research important? Interestingly, the same pressures that keep the basic scientists and clinical scientists apart are now ironically working actively to make them work together. For the basic scientists, the National Institutes of Health (NIH), the main funding agency has increasingly focused its efforts on the “health,” portion of its acronym. Scientists are no different than other professionals – where the money goes so goes the research priority of basic scientists. The same “health,” push from NIH has concomitantly fueled clinicians who have been frustrated with minimal options in the clinic for their patients to get into research. Institutions and administrations have increasingly seized upon this opportunity and pressure has increased at all levels for both basic scientists and clinicians to perform “translational research.” Unfortunately, this economic push has not coincided with an important factor that is necessary to achieve success in this arena, which is the availability of a workforce that is ready to take on this challenge. Although MD/PhD dual degree clinical scientists are ideally poised to take advantage of this critical push, the numbers of such investigators are not at a critical mass to take full advantage of the opportunities in medicine. Importantly, the range of their professional options is broad, and only 39% devote more than 75% effort to research.¹ Therefore, we are left with the breed of PhD’s and MD’s who, understanding the limitations of their own science, become cheerfully “uncomfortable” to get the job done. Unless we find a way to work together, and understand each other’s language and code, the road ahead is likely to be challenging. Elias Zerhouni, MD (former Director of NIH)² summarized this elegantly - “*At no other time has the need for a robust, bidirectional information flow between basic and translational (clinical) scientists been so necessary*”.

Before we find ways to work together, it is perhaps important to define the differences between basic research and clinical research. We hypothesize that differences in how basic and clinical scientists approach research, and the end-points that are important to them

respectively, may play a role in their challenges to communicate. In our view, these differences take root during formal years of research training as a PhD or MD, and become entrenched because there is

minimal exposure or participation in alternative forms of research. The Table 1 show highlights of some of these differences.

Table 1 Differences in basic and clinical scientists approach research

| Variable | Bench Scientist | Clinical Scientist |
|----------------|---|---|
| Scope of study | Relationship between molecule or molecular pathway to phenotype - Microscopic | Relationship between exposure/treatment/variable to disease outcome - Macroscopic |
| Approach | Mechanism-driven: widespread use of genetic manipulation technologies <i>in-vitro</i> or animals. | Phenotype-driven: data collection, risk-factor/exposure/treatment manipulation. |
| Validation | Burden of proof - Additive and subtractive experiments. Version of Koch's postulates. | Burden of proof - Statistical, (exposed vs. unexposed; treated vs. untreated), repeatability. |

Clearly, there are differences, and obstacles are plenty. How do we overcome this? We offer some suggestions, which are by no means comprehensive but are meant to initiate a discussion on this subject.

In our opinion, all researchers have to:

- i. Understand the language - For robust and efficient growth of translational research it is necessary that clinical scientists understand the importance of mechanisms and disease models to prove causation and identify molecular targets. For example, inferences based solely on associations can lead to wrong hypothesis. Similarly, basic science researchers have to concede the restrictive nature of *in-vitro* or animal models when it comes to human disease applicability. For example, knockout animal models may not always serve as great surrogates for disease because in most diseases the gene is not knocked out.
- ii. Forum - A better understanding of the scope and limitations of each type of research is a key step in facilitating constructive dialogue that will break stereotypical research barriers. Establishment of regional Clinical and Translational Sciences Institutes (CTSI) across the country to facilitate novel, interdisciplinary research is one important landmark, and is the forum for such dialogue to start. For institutions not part of the CTSI network, we encourage creating a local chapter. Investigator-driven initiatives at each institution based on diseases being probed can also launch fruitful collaborations.
- iii. Conference – Attending weekly conferences (for basic scientist) and departmental seminars (for clinicians) on a regular basis is a must. This Brownian motion is likely to stimulate collaborations, and exchange of scientific ideas. Importantly in the long run, it contributes to understanding the language (bullet point one above).

Conclusion

In the 21st century, complex diseases represent a major challenge

as they are multifactorial in nature and involve a complex interplay of genetic, epigenetic, and environmental risk factors. There is little doubt that clinical and basic scientists have to work together to create Genotype-Envirotype-Phenotype maps using available human, environmental exposure, and animal data.³ Although ambitious in nature, this is feasible only with strong collaborations between talented clinical and basic scientists who complement themselves and visualize their expertise as part of the whole.

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Conflict of interest

The author declares no conflict of interest.

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