

Chapter 11

Connecting the Bench with the Bedside: Translating Life Science Discoveries to Disease Treatments and Vice Versa

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ABSTRACT

Translational research is a branch of researches that attempts to break the barrier between basic science and medical practice, enabling a knowledge flow cycle: basic science discoveries → preclinical/clinical studies → medical practice → health care policy and public awareness → molecular level understanding of disease. In this work, the authors analyze and summarize three aspects of translational research: (1) use cases and opportunities; (2) data types and challenges; and (3) available tools and technologies. They believe that both the opportunities and the challenges of translational research are due to the need to enable knowledge translation between life science and health care domains.

Even though numerous tools and technologies have been developed to meet this need with various degrees of success, a conceptual framework is needed to fully realize the value of those tools and technologies. The authors propose Complex System (CS) to be the logical foundation of such a framework. Since translational research is a spiral and dynamic process. With the CS mindset, they designed a multi-layer architecture called HyGen (Hypotheses Generation Framework) to address the challenges faced by translational researchers. In order to evaluate the framework, the authors carried out heuristic and quantitative tests in the Colorectal Cancer disease area. The results demonstrate the potential of this hybrid approach to bridge silos and to identify hidden links among clinical observations, drugs, genes and diseases, which may eventually lead to the discovery of novel disease targets, biomarkers and therapies.

DOI: 10.4018/978-1-61350-435-2.ch011

INTRODUCTION

A vision of future medicine shared by many researchers is “3R”—to provide the Right treatment to the Right patient at the Right time, in other words, to predict the risk of a clinical event during the course of an individual’s lifetime, diagnose the event as early as possible and apply the most effective treatment (Webb CP, 2004). To achieve this goal, scientific discoveries must be translated into practical applications. Such discoveries typically start from “lab bench”, where basic researches are conducted at a molecular or cellular level, then progress to the patient’s “bedside” as therapies (Pizzo, 2002). On the other hand, knowledge gained by “bedside” is important for the researchers at “lab bench” to future their understanding of human disease and pre-clinical models (Dauphinée 2000).

Over the past decade, the fields of “bedside” and “lab bench” have generated extremely large amount of data. As life science and medical practice continue their exponential growth in complexity and scope, the need for collaboration among experts across different disciplines becomes inevitable. Investigators from worldwide have been trying to establish knowledge mappings and sharing between discovery researchers, practitioners, and end users (Robert Molitor AS, 2003; Ruttenberg, 2007). One solution, translational research, is a branch of research that attempts to develop insight into such cross-disciplinary knowledge transformation and collaboration (Ruttenberg et al., 2007). Translational research provides a systematic way to identify implicit associations and insights “hidden” in large and heterogeneous datasets. Recent decades have witnessed many examples of the important roles that translational research plays in life science and health care practice.

One example is the use of translational approach in drug repositioning. Identifying new indications for existing drugs is an important strategy of drug discovery. For example, Atorv-

astatin is an FDA approved drug used to lower cholesterol (Refolo et al., 2001). An investigator may want to find other possible diseases that might be treated by Atorvastatin. Using a non-translational approach, the investigator would query for pathways related to Atorvastatin in KEGG and would retrieve no result from KEGG. Using a translational approach, the drug hunter would first search for the indications of Atorvastatin. The drug hunter would then search for genes that are associated with those indications. Next the drug hunter would look for pathways associated with those genes in KEGG and would find one of the pathways to be the Alzheimer’s Disease (AD) pathway. He may consider AD as a possible new indication for Atorvastatin. This hypothesis is supported by other studies that show clinical benefit of Atorvastatin in AD patients (Blain & Poirier, 2004; Sparks et al., 2005). The drug hunter can rapidly identify such opportunities because clinical and genomic disciplines are effectively connected in a translational approach.

Discovering novel disease targets is another application of translational research. Identifying the disease gene is often the first step towards discovering the cure. For example, a scientist, looking for AD treatment, may first search for all drug-able genes associated with AD. A non-translational approach is to search against various biological databases for drug-able genes associated with AD. Since the disease has few known pathway steps, this approach yields limited success and no drug-able GPCR target can be identified. Qu et al. described a translational approach in (Qu et al., 2007). They first retrieved all genes participating in the AD pathway. Next they searched for all pathways associated with those genes. Then they repeated the first two steps by searching for genes participated in all pathways found in the previous iteration. Using this approach, the authors reported that they could identify more novel targets. For instance, they found eight GPCR targets that are implicitly associated with AD at the second iteration. Those associations are supported by evidence

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