CHAPTER 1

Translational Medicine—A Paradigm Shift in Modern Drug Discovery and Development:
The Role of Biomarkers

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Abstract

The success rate of novel medical entities that are submitted for registration by the regulatory agencies and followed successful marketing has been stagnating for the past decade. Failure in efficacy and safety continue to be the prime hurdles and causes of failure. Translational medicine is a new function within the pharmaceutical industry R&D organization aimed to improve the predictability and success of drug discovery and development. Biomarkers are the essence of the translational medicine strategy focus on disease biomarker, patient selection, pharmacodynamic responses (efficacy and safety) target validation, compound-target interaction). Successful deployment of biomarkers research, validation and implementation is adopted and embraced as key strategy to improved the drug discovery and development towards new medical entities.

Drug Targets—Historical Perspectives

Drugs are natural or designed substances used deliberately to produce pharmacological effects in humans or animals. Drugs have been part of human civilizations for millennia. However, until the very recent modern era, drugs have been introduced to humans by empiricism and largely by serendipitous events such as encounters with natural products in search of food or by avoiding hazardous plants and animal products. The emergence of the scientific era in drug discovery evolved along-side the emergence of physical and chemical sciences at large, first as knowledge to distill, isolate and enrich the desired substance from its natural environment, followed by deliberate attempts to modify natural substances to better serve the human needs and desires.

Scientific evolution throughout the past two centuries enabled identification of biologically active substances in humans (e.g., hormones), which were manipulated chemically to improve (potency, duration of action and exposure), or to mitigate or abrogate undesirable actions. The cumulative knowledge of human, animal and plant biology and chemistry provided the scientific foundation and technical capabilities to purposely alter natural substances in order to improve them. Such evolution marked the era of “forward pharmacology”. The era of forward pharmacology is about drug design that emanates from primary knowledge of the action of the biological target that has clear biological action.

The exponential progress in molecular biology since the mid-20th century, culminating in deciphering the complete human genome in the year 2000, brought the dawn of pharmacogenomics

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and the "reverse pharmacology" era. The "reverse pharmacology" era is defined by the need to first clarify the biology and medical perspectives of the target so as to qualify it as a drugable and pharmaceutically exploitable for drug discovery and development scheme. The pharmacogenomic era provides vast opportunities for selection of new molecular targets from a gamut of approximately 30,000 primary genes, over 100,000 proteins and multiples of their translational and metabolomics products. Thus, the permutations in respect to opportunities for pharmacological interventions are unprecedented, vast and most promising for innovative medicines.

The pharmacogenomics era as a source for drug targets also poses unprecedented hurdles in selection, validation and translation into effective and safe drugs. New technologies continue to drive efficiency and robustness of mining the genomic drug discovery opportunities but physiological and integrated biology knowledge is lagging. In this perspective, translational medicine and biomarkers research have taken center stage in validation of the molecular target for pharmaceutical exploitation.

In this chapter we offer a utilitarian approach to biomarkers and target selection and validation that is driven by the translational medicine prospect of the target to become a successful drug target. We hereby offer classification and analytical process aimed to assess risk, innovation, feasibility and predictability of success of translating novel targets into successful drugs. This manuscript provides clear definitions on the type of biomarkers that are core to translational medicine and biomarkers research in modern pharmaceutical companies.

**Translational Medicine: Definition**

Translational medicine in the pharmaceutical industry is a research discipline aimed to improve the predictability of success of drug discovery and development. Translational medicine research aims to discovery, validate and implement biomarkers in lieu of clinical outcome studies, improve the congruency of preclinical models to clinical reality and establish proof of concept for efficacy and safety based on targeted mechanism of action. In particular, translational medicine aims to establish surrogate biomarkers to aid in early registration and promote personalized medicine for better patients selection for targeted mechanism of action.

**Biomarkers—Utilitarian Classification**

Biomarkers are the stepping-stones for modern drug discovery and development. 1-4 Biomarkers are defined as biological substances or biophysical parameters that can be monitored objectively and reproducibly and used to predict drug effector outcome. This broad definition is however, of little utility to the pharmaceutical process since it carries no qualification for the significance and use of the biomarker. The following classes and definitions of biomarkers are therefore offered (see Fig. 1):

I. **Disease Biomarkers**: disease biomarkers are biomarkers that correlate statistically with the disease phenotype (syndrome) for which therapeutics are developed. Correlation of levels (in the circulation, other fluids or tissue) or expression patterns (gene, protein) in peripheral blood cells or tissues should signify disease initiation, progression, regression, remission or relapse. When we apply these criteria to our empirical approach to current strategies to develop drugs for certain diseases, it becomes apparent that our current approaches employed in clinical testing are sub-optimal. One pertinent example is provided by the way industry has approached the development of treatments in schizophrenia.

   a. **Disease Initiation Misconceptions**: Unfortunately in the past 50 years all marketed therapies have been developed around the dopamine D2 receptor, either in the form of full antagonism or partial agonism. These treatments are only effective on the positive symptoms in around 70% of patients and are associated with treatment resistance and poor side effect profiles. Current clinical practice and drug discovery is based around the concept that the onset of positive symptoms represents the initiation of the disease. Arguably, however, these symptoms arrive late in the chapter of schizophrenia. The focus on the positive symptoms has impeded the development of novel therapeutics