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Review – Part of the Special Issue – Pharmacology in 21st Century Biomedical Research

Translational paradigms in pharmacology and drug discovery

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ABSTRACT

The translational sciences represent the core element in enabling and utilizing the output from the biomedical sciences and to improving drug discovery metrics by reducing the attrition rate as compounds move from preclinical research to clinical proof of concept. Key to understanding the basis of disease causality and to developing therapeutics is an ability to accurately diagnose the disease and to identify and develop safe and effective therapeutics for its treatment. The former requires validated biomarkers and the latter, qualified targets. Progress has been hampered by semantic issues, specifically those that define the end product, and by scientific issues that include data reliability, an overt reductionistic cultural focus and a lack of hierarchically integrated data gathering and systematic analysis. A necessary framework for these activities is represented by the discipline of pharmacology, efforts and training in which require recognition and revitalization.

Contents

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1. Introduction

The goals of the biomedical research enterprise that is generally associated with Vannevar Bush's post-WWII, "Endless Frontier" of science initiative [1] are two-fold. Firstly to understand human disease causality, its progression and prognosis; and, secondly, to identify safe and effective therapeutics that can ameliorate disease by restoring normal tissue function. Accordingly, research in the absence of any considered intent to provide tangible benefit to society cannot be justified [2].

To efficiently and productively execute the goals of biomedical research requires a series of hierarchical translational frameworks that can provide necessary structure to focus and prioritize research activities in order to make informed decisions. At the preclinical level, this occurs by using data from investigating disease causality, to identifying targets and beginning the process of their validation, through animal testing. The aggregate data derived is then used at the clinical interface to transition drug-like new chemical entities (NCEs) to the clinical trial process, a process termed T1 translational medicine [3,4]. This involves considerations of NCE efficacy, selectivity and safety together with animal PK/PD (pharmacokinetic/pharmacodynamic) properties that facilitate the design of Phase I safety and Phase II proof of concept trials as well as predicting human exposure. The final translational processes is that of moving approved therapeutics into clinical practice and health care decision-making to enhance the adoption of "best practices" within the community [5], the T2 translational medicine process [4]. Of the three translational processes, that termed T1, is probably the most controversial as it is thought to be the weakest link and is a key factor in the Phase II attrition rate [6]. However, none of these processes should be unidirectional, since the clinical studies can be invaluable in informing the research component e.g., defining the appropriate phenotype and/or relevant genotype, identifying active metabolites in human tissues while "best practices" aid in understanding what type of therapeutic is acceptable in the marketplace.

From a preclinical research perspective, The American Society of Pharmacology and Experimental Therapeutics (ASPET), has defined T1 translational research in terms of developing "methods and systems to integrate molecular, cellular, tissue, organ and clinical information so that the response to experimental therapeutics in model disease systems and patients is fully understood" [7] in essence describing the discipline of applied pharmacology [8]. The present article, in using this research-centric definition, focuses on the many challenges, and some potential solutions to improving T1 translation and making it the more effective component of the biomedical research enterprise that was envisaged in its conceptualization as part of the "Endless Frontier" [1,4,9].

2. Biomedical research funding in the decade of the 21st century

In 2013, the biomedical research enterprise, federal, academic and industrial in the US, is anticipated to spend more than $220 billion on research, both preclinical and clinical, with the majority of the funding coming from the biopharmaceutical industry [9]. While the precise split between basic/preclinical research and preclinical development and clinical trials is generally a moving target depending on the organization, these resources will support many hundreds of thousands of experiments that include: chemical synthesis [10–12]; target [13–16] and biomarker [17] selection and validation; assessment of target engagement and function [18,19]; animal disease model testing [20]; various preclinical development activities that include absorption, distribution, metabolism and excretion (ADME [21]), the formulation and scale up of new chemical entities (NCEs), early stage toxicology and safety pharmacology [22,23] and, ultimately, clinical trials [24,25].

The $220 billion to be spent on biomedical research in 2013 comes from a variety of sources, in addition to the biopharmaceutical industry [9] and includes taxpayers via federal government allocations, philanthropic organizations like the Juvenile Diabetes Research Foundation (JDRF), the Huntington's Disease Foundation (HDF) and the Multiple Myeloma Research Foundation (MMRF) and from investors both in stock markets and venture capital.

As noted [2], the principal outcome that is anticipated from these investments is an improvement in societal health. Ancillary outcomes that are often likely to precede tangible improvements in health care, and are also necessary for these to occur, involve the economic contributions to national competitiveness in knowledge-based economies with the financial benefits to society reflected in public funding to universities and research institutes to support research and to "for profit" organizations and investors with concomitant collateral economic benefits to local communities [26,27]. Thus the NIH and the FDA are vital to the economy in the Bethesda/Rockville MD area with universities, pharma and biotech being critical to the local economies in Boston/Cambridge, San Diego, San Francisco, Research Triangle Park, Medicon Valley, Rehovot, Cambridge UK, etc. [28]. Witness the impact on the local economy when Pfizer sequentially closed research operations in