Landscape of Innovation for Cardiovascular Pharmaceuticals: From Basic Science to New Molecular Entities

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ABSTRACT

Purpose: This study examines the complete timelines of translational science for new cardiovascular therapeutics from the initiation of basic research leading to identification of new drug targets through clinical development and US Food and Drug Administration (FDA) approval of new molecular entities (NMEs) based on this research.

Methods: This work extends previous studies by examining the association between the growth of research on drug targets and approval of NMEs associated with these targets. Drawing on research on innovation in other technology sectors, where technological maturity is an important determinant in the success or failure of new product development, an analytical model was used to characterize the growth of research related to the known targets for all 168 approved cardiovascular therapeutics.

Findings: Categorizing and mapping the technological maturity of cardiovascular therapeutics reveal that (1) there has been a distinct transition from phenotypic to targeted methods for drug discovery, (2) the durations of clinical and regulatory processes were significantly influenced by changes in FDA practice, and (3) the longest phase of the translational process was the time required for technology to advance from initiation of research to a statistically defined established point of technology maturation (mean, 30.8 years).

Implications: This work reveals a normative association between metrics of research maturation and approval of new cardiovascular therapeutics and suggests strategies for advancing translational science by accelerating basic and applied research and improving the synchrony between the maturation of this research and drug development initiatives. (*Clin Ther.* 2017;▪:▪▪▪–▪▪▪) © 2017 Elsevier HS Journals, Inc. All rights reserved.

Key words: cardiovascular disease, cardiovascular therapeutics, drug development, drug discovery, innovation, quantitative modeling.

INTRODUCTION

There have been significant decreases in morbidity and mortality from cardiovascular disease (CVD) in developed nations during the last half century. Although it has been estimated that half of this improvement may be attributable to public health measures, such as reduced smoking, half of this reduction is also attributable to the emergence of evidence-based medical therapies, including new biopharmaceutical products; improved diagnostics; surgical interventions, such as coronary artery bypass; and noninvasive interventions, including coronary angioplasty and stents.[1]

In this article, we examine the landscape of innovation that has led to approval of >150 new molecular entities (NMEs) for the prevention or treatment of CVD since 1960, many of which are now the standard of care. A 2012 study reported that 27% of the adult US population took antihypertensive medications on a regular basis and that 18% took

lipid-lowering drugs.[2] Nevertheless, CVD continues to be a leading cause of death in the United States[3] and is estimated to be responsible for >17.5 million deaths worldwide.[4] Although much has been accomplished, much more remains to be done.

Recent reports suggest that discovery and development of new cardiovascular therapeutics is stagnating.[5–7] This view was encapsulated in a 2015 report from a meeting attended by stakeholders from academia, industry, and government titled "Cardiovascular Drug Development: Is it Dead or Just Hibernating?"[5] The group's report expressed concern that the number of NMEs approved for cardiovascular indications between 2000 and 2009 notably decreased compared with previous decades. It called attention to underinvestment in cardiovascular drug development relative to other fields, such as oncology and inflammatory disease, despite the greater burden of cardiovascular disorders.[5] Factors identified as impediments to new drug development include the already crowded market for cardiovascular therapeutics, which both raises the bar for new product performance and limits market potential, uncertainty about the regulatory process, and the escalating cost of drug development.[5,7,8] These views echoed the recommendations of the President's Council of Advisors on Science and Technology[9] to streamline clinical trials to reduce timelines and development costs, to implement new clinical trial designs and accelerate approval pathways, and to improve communication among academic experts, industry, and regulatory bodies to accelerate new drug discovery and development.

There is also evidence of barriers to new drug development in the earliest stages of basic science, where mechanisms of disease are described and new drug targets and therapeutic concepts are identified. This is sometimes referred to as the T0 stage of translational science.[10] The US Food and Drug Administration (FDA) has called attention to the paucity of products in the earliest stages of the clinical pipeline as the major factor limiting the number of new drug approvals.[11] The National Institutes of Health roadmap of 2002,[12] the creation of the Clinical and Translational Science Awards program in 2006,[13,14] and the FDA's Critical Path Initiative in 2004[15] focused on the need for more translational research and the building of these capabilities in Clinical and Translational Science Awards–funded academic research centers.[16,17]

Building on these findings, the 2012 President's Council of Advisors on Science and Technology report pointed to "rate-limiting knowledge gaps" between basic science and the earliest stages of the translational process as limiting the pipeline of new entities in development,[9] and a report from the Institute of Medicine identified a "translational block" in the "transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention, and their first testing in humans."[18] In response, various initiatives have been undertaken aimed at reengineering the translational process to more efficiently translate advances in basic biomedical science, genomics, bioinformatics, and instrumentation into cures.[19,20]

For effective reengineering of the translational process for cardiovascular drug discovery and development, it is necessary to have data on all phases of the translational process, from the initial scientific insights that give rise to new areas of research, to the discovery and development of drugs based on this research, and finally to regulatory approval. The clinical and regulatory stages of this translational sequence have been extensively characterized.[16,21–24] These studies found that there continues to be a high failure rate for compounds entering clinical trials, with the most recent data suggesting that only 19% of all candidates entering Phase I trials are approved,[23] that clinical trials are becoming substantially more complex,[25] and that the cost of clinical development is increasing exponentially.[9,18,23,26–28] At the same time, initiatives aimed at accelerating development have substantially reduced the timeline of regulatory review[22,29,30] and led to a rapid increase in the number of drugs receiving orphan designation and qualifying for ≥1 expedited development pathway.[31–33]

The earliest stages of basic research leading up to development are less characterized.[5,8,34,35] A 2006 US Congressional Budget Office report described an economic model for the association between public funding for basic drug research and development (R&D) that incorporated an 18-year lag between funding and NME approvals but did not explore the reasons for this lag.[26] Eder et al[36] identified publications that experts consider critical milestones in the discovery and development of first-in-class NMEs, estimating that the mean time from the first publication defining a therapeutic concept, target, or