Clinical Therapeutics/Volume ▮, Number ▮, 2015

Commentary

Patterns of Innovation in Alzheimer's Disease Drug Development: A Strategic Assessment Based on Technological Maturity

Jennifer M. Beierlein, PhD; Laura M. McNamee, PhD; Michael J. Walsh, PhD; and Fred D. Ledley, MD

Center for Integration of Science and Industry, Department of Natural and Applied Sciences and Department of Management, Bentley University, Waltham, Massachusetts

ABSTRACT

Purpose: This article examines the current status of translational science for Alzheimer's disease (AD) drug discovery by using an analytical model of technology maturation. Previous studies using this model have demonstrated that nascent scientific insights and inventions generate few successful leads or new products until achieving a requisite level of maturity. This article assessed whether recent failures and successes in AD research follow patterns of innovation observed in other sectors.

Methods: The bibliometric-based Technology Innovation Maturation Evaluation model was used to quantify the characteristic S-curve of growth for AD-related technologies, including acetylcholinesterase, *N*-methyl-D-aspartate (NMDA) receptors, B-amyloid, amyloid precursor protein, presenilin, amyloid precursor protein secretases, apolipoprotein E4, and *transactive response DNA binding protein 43* kDa (TDP-43). This model quantifies the accumulation of knowledge as a metric for technological maturity, and it identifies the point of initiation of an exponential growth stage and the point at which growth slows as the technology is established.

Findings: In contrast to the long-established acetylcholinesterase and NMDA receptor technologies, we found that amyloid-related technologies reached the established point only after 2000, and that the more recent technologies (eg, TDP-43) have not yet approached this point. The first approvals for new molecular entities targeting acetylcholinesterase and the NMDA receptor occurred an average of 22 years after the respective technologies were established, with only memantine (which was phenotypically discovered) entering clinical trials before this point. In contrast, the 6 lead compounds targeting the formation of amyloid plaques that failed in Phase III trials between 2009 and 2014 all entered clinical trials before the respective target technologies were established.

Implications: This analysis suggests that AD drug discovery has followed a predictable pattern of innovation in which technological maturity is an important determinant of success in development. Quantitative analysis indicates that the lag in emergence of new products, and the much-heralded clinical failures of recent years, should be viewed in the context of the ongoing maturation of AD-related technologies. Although these technologies were not sufficiently mature to generate successful products a decade ago, they may be now. Analytical models of translational science can inform basic and clinical research results as well as strategic development of new therapeutic products. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮)

Key words: Alzheimer's disease, Amyloid, Drug development, Innovation, Quantitative modeling.

INTRODUCTION

Alzheimer's disease (AD) has proved to be a challenging target for drug discovery. It has been 12 years

This research was presented, in part, at a conference ("Learning From Cancer to Advance Neurodegeneration Drug Discovery and Development") presented by the New York Academy of Sciences, June 2015.

Accepted for publication July 8, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.07.003
0149-2918/$ - see front matter

since the last approval of a new molecular entity (NME) aimed at treating the core symptom complex of AD. Moreover, there is a paucity of both validated drug targets and advanced-stage clinical candidates with the potential to modify the essential pathogenesis of the disease or its associated disabilities.

The challenge has been exacerbated in recent years by the Phase III failures of several lead compounds (most recently, bapineuzumab and solanezumab in 2012 and gammagard in 2013) designed to reduce β-amyloid plaque formation. These high-profile failures led many to conclude that β-amyloid may not be a viable target for AD.[1–7] The subsequent successes of a Phase I trial with aducanumab in prodromal (or mild) AD,[8] as well as optimism regarding the ongoing trial of crenezumab in a Columbian cohort of early-onset AD,[9] have rekindled interest in β-amyloid as a drug target.[10]

The meager product pipeline and limited number of validated targets for drug discovery seems incongruous with the dramatic advances in understanding AD that have come from positional cloning, genomics, transgenic disease models, positron emission tomography scanning, and sophisticated biomarkers. Perhaps the most important pathologic insight occurred when the protein comprising the amyloid plaques was identified as β-amyloid,[11] a cleaved form of the known genetic risk factor, amyloid precursor protein (APP).[12] It was hypothesized that the accumulation of β-amyloid plays a central role in the pathogenesis of the disease and its symptoms. Dubbed the "amyloid hypothesis," targeting β-amyloid with immunotherapies to reduce amyloid plaques has become a dominant strategy for treating AD.[13,14]

Other targets have also been identified. In addition, drug discovery efforts have focused on APP secretase enzymes, which are responsible for cleavage of APP to form β-amyloid.[15] Presenilin 1 and 2, components of λ-secretase, have also been identified as genetic risk factors for the disease[16] and are a significant focus of interest. The neurofibrillary tangles, which are a characteristic pathologic feature in diseased brains, have been identified as tau protein, a microtubule-binding protein that stabilizes the long microtubules involved in structural support of neurons.[17] AD research continues to identify putative pathways that impact the pathogenesis or core symptoms of the disease and propose novel targets for interventions.

Five NMEs have been approved for treating the core symptom complex of AD. These compounds, however, were not generated from recent molecular insights but originated from older research in other fields. Specifically, NMEs that target acetylcholinesterase (AChE)[18] or *N*-methyl-D-aspartate (NMDA) receptors[19] were discovered through research on these neurotransmitter pathways and were only later applied to AD therapy. Moreover, the most common genetic risk factor for both sporadic and familial forms of AD, the apolipoprotein E4 allele,[20] was first described as a risk factor for cardiovascular disease and is now considered an important biomarker in AD. In fact, 1 of the important strategies for current research is repurposing drugs from other indications.

The goal of the present article was to examine the status of innovation in AD by using an analytical model for the maturation of technology and the relationship between technological maturation and successful product development. We assessed whether the paucity of therapeutic products and recurrent failure of lead compounds arising from recent scientific advances are consistent with the time course of translational science observed in other therapeutic areas. Specifically, an analytical model of technology maturation was used to determine whether the recent failures of drugs designed to reduce β-amyloid should be interpreted as invalidating the amyloid hypothesis or whether amyloid-related technologies are not yet sufficiently mature to expect efficient generation of successful lead and therapeutic products.

PATTERNS OF INNOVATION IN BIOPHARMACEUTICAL DEVELOPMENT

Research on innovation in different technology sectors suggests that technologies mature through a characteristic, sigmoid growth cycle (S-curve) (**Figure 1**) and that the ability to generate successful products is predictably related to technology maturity.[21–26] The key feature of the technology S-curve is a stage of exponential growth sparked by a scientific insight or invention. This "initiation" event is followed by exponential advances that continue until limits are encountered and growth slows. At this point, the technology is considered "established." Although new insights and inventions offer the promise of new product opportunities, nascent technologies commonly fail to generate products that can meet the standards set by previous, established technologies.[21,22] Only as the nascent technologies mature to the point of being established are they able to generate