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Featured Article

The price of progress: Funding and financing Alzheimer's disease drug development

Jeffrey Cummings[a,*], Carl Reiber[b], Parvesh Kumar[b]

[a]*Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA*
[b]*University of Nevada, Las Vegas, NV, USA*

Abstract

Introduction: Advancing research and treatment for Alzheimer's disease (AD) and the search for effective treatments depend on a complex financial ecosystem involving federal, state, industry, advocacy, venture capital, and philanthropy funding approaches.

Methods: We conducted an expert review of the literature pertaining to funding and financing of translational research and drug development for AD.

Results: The federal government is the largest public funder of research in AD. The NIA, National Institute of Mental Health, National Institute of General Medical Sciences, and National Center for Advancing Translational Science all fund aspects of research in AD drug development. Non-National Institutes of Health federal funding comes from the National Science Foundation, Veterans Administration, Food and Drug Administration, and the Center for Medicare and Medicaid Services. Academic Medical Centers host much of the federally funded basic science research and are increasingly involved in drug development. Funding of the "Valley of Death" involves philanthropy and federal funding through small business programs and private equity from seed capital, angel investors, and venture capital companies. Advocacy groups fund both basic science and clinical trials. The Alzheimer Association is the advocacy organization with the largest research support portfolio relevant to AD drug development. Pharmaceutical companies are the largest supporters of biomedical research worldwide; companies are most interested in late stage de-risked drugs. Drugs progressing into phase II and III are candidates for pharmaceutical industry support through licensing, mergers and acquisitions, and co-development collaborations.

Discussion: Together, the funding and financing entities involved in supporting AD drug development comprise a complex, interactive, dynamic financial ecosystem. Funding source interaction is largely unstructured and available funding is insufficient to meet all demands for new therapies. Novel approaches to funding such as mega-funds have been proposed and more integration of component parts would assist in accelerating drug development.

Keywords: NIH; NIGMS; NCATS; NIMH; NINDS; Venture capital; Advocacy; Philanthropy; Alzheimer's disease; Clinical trials; Pharmaceutical industry; Biotechnology companies; SBIR; STTR

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*Corresponding author. Tel.: 702-483-6029; Fax: 702-722-6584.
E-mail address: cumminj@ccf.org

Alzheimer's disease (AD) is increasing in frequency as the world's population ages and poses a major threat to the public health. AD doubles in frequency every 5 years after the age 65, and the number of individuals in the United States with AD dementia is projected to grow from a current 5.5 million to an estimated 14 million by the year 2050 [1,2]. The world's population of AD dementia will increase from 35 million to an astonishing 135 million by 2050 [3]. The

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corresponding toll in human suffering and socioeconomic costs will be enormous. The identification of milder forms of cognitive impairment and preclinical AD further enlarges considerations regarding the impact of AD on society [2,4,5].

Prevention and treatment of AD by 2025 has been articulated as a goal of the US government and has been endorsed by other countries [6,7]. Prevention and treatment require the development of new treatments that prevent or delay the onset, slow the progression, or improve the symptoms (cognitive, functional, and behavioral) of AD. The failure rate of AD drug development is 99% [8]; the failure rate of the development of disease-modifying therapies for AD is 100%. Despite these discouraging outcomes in drug development programs, the urgent need to address the socioeconomic crisis posed by AD requires that we continue to advance understanding of AD drug development. Lessons learned from AD are likely to generalize to other neurodegenerative disorders (NDDs), given the many similarities in protein aggregation and cell injury across NDD [9]. To advance the research agenda in AD, financial resources are required including funding from government, industry, venture capital, foundations, and philanthropy. Federal research funding programs include the National Institutes of Health (NIH), National Science Foundation (NSF), Food and Drug Administration (FDA), Department of Defense, and Veterans Administration (VA). Private sector funding includes sources in the biopharma industry, venture capital investments, foundations, advocacy organizations, and support from philanthropists. Public-private partnerships have formed to help ameliorate the financial burden to individual entities, and industry collaborations have evolved to de-risk investments [10,11]. Funding and financing resources form a complex financial ecosystem, which is a key to advancing research in AD. Here, we describe major elements of this network of support especially as it pertains to development of new drug treatments for AD.

1. Cost of AD drug development

Total costs of an AD drug development program are estimated at $5.6 billion, and the process takes 13 years from preclinical studies to approval by the FDA [12]. This compares to an estimated cost of cancer treatment development of $793.6 million per agent (assuming 9% cost of capital) [13]. Consider the pharmaceutical industry as a whole bringing a new agent to approval has an estimated cost of $2.8 billion [14]. AD drug development costs substantially exceed most estimates.

Table 1 shows the average cost and duration of each phase of AD drug development. These figures include the cost of capital and the cost of failures that companies must sustain if they work in the AD drug development arena. The high rate of failure of AD drug development is partly responsible for the high costs of advancing AD drug development [8], but out-of-pocket costs for development of a single AD agent approach $500 million (Table 1). Phase III trials are the most costly part of AD drug development, and pharmaceutical companies are among the few enterprises that can sustain such costs.

Table 1
Cost and duration of each aspect of AD drug development

Stage of process	Duration (months)	Cost (billions)* ($)	Cumulative out-of- pocket costs (at end of each stage) (millions) ($)
Preclinical	50.1	1.65	
Phase I	12.8	1.19	71
Phase II	27.7	1.04	126
Phase III	50.9	1.79	413
FDA	18	0.02	
Total	13.3 years	5.69	

Abbreviations: AD, Alzheimer's disease; FDA, Food and Drug Administration.

*Capitalized and including cost of failures of drug development (from Scott et al, 2014) [12].

2. National Institutes of Health

The principle public funder of research is the US NIH, investing more in health research than any other public enterprise in the world with an annual budget of approximately $34 billion U.S. dollars. The federal budget devoted to NIH has had support from both Republican and Democratic parties. There is a mismatch between the cost of disease to society and the amount of research devoted to it. AD, for example, costs the US society more than $216 billion annually, and it has an NIH budget of $1.8 billion; for every $1 spent on AD, less than 1% of that amount is devoted to research [15,16]. AD has a greater impact on the US economy than cancer or cardiovascular disease [15]; it has a smaller NIH research budget than either of these disorders (cancer – $6.0 billion, cardiovascular disease - $2.2 billion; www.nih.gov).

Neuroscience research at NIH is guided by the Neuroscience Blueprint and within that the NIH Neurotherapeutics Blueprint was launched to create a virtual pharmaceutical company aimed at advancing discovery and development of small molecules to treat Central Nervous System disease including NDDs [17]. The goal was to foster the development of potential therapies in Academic Medical Centers (AMCs) and biotechnology companies and to advance new therapies to clinical trials and potential industry partnership. Once funding is approved, lead discovery teams from the National Institute of Neurological Disease and Stroke work collaboratively and guide the grantee's development program. The lead team assists in bioactivity/efficacy hit-to-lead studies, medicinal chemistry and lead optimization, pharmacokinetics and toxicity, data management, manufacturing and formulation, and phase 1 clinical trials [17].

Within the NIH, the major funding agency for AD research is the NIA. To support the development of new