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An analysis of global research funding for the frontotemporal dementias: 1998–2008

Christopher D. Walentas[a], Diana W. Shineman[a], Antony R. Horton[b], Bradley F. Boeve[c,d], Howard M. Fillit[a,*]

[a]*Alzheimer's Drug Discovery Foundation, New York, NY, USA*
[b]*International Rett Syndrome Foundation, New York, NY, USA*
[c]*Department of Neurology, Mayo Clinic, Rochester, MN, USA*
[d]*Medical Advisory Council of the Association for Frontotemporal Dementia, Radnor, PA, USA*

Abstract

Background: To better understand the status of frontotemporal dementia (FTD) research, and identify opportunities to accelerate translational research, we analyzed international funding for FTD and related dementias between 1998 and 2008.

Methods: Search terms were compiled to define the clinical spectrum of FTD and all known mechanisms. Funders were asked to return grants that contained these search terms in the title or abstract. Grants were classified according to the most reasonably achieved stated aim using a classification scheme of research activities that was developed to map grants along the continuum from basic research to clinical trials of treatments.

Results: This analysis captured 613 grants ($432,167,275), from 19 private and public funders from 7 countries and the European Union. National Institutes of Health contributed $360 million (MM), 53% of grants and 83% of total funding. Foundations contributed $43 MM, 35% of grants and 10% of total funding, an increase in recent years. A total of $319 MM (74%, funding) went toward basic research, of which 10% was dedicated to preclinical treatment development, clinical treatment evaluation, and developing detection, diagnostic, and imaging technologies and reagents.

Conclusions: FTD received moderate funding over the past decade, which has decreased almost five-fold during this period. A sizable proportion of FTD funding supported mechanisms shared with Alzheimer's disease. Few programs advanced past validating target models and into drug discovery and preclinical development, indicating that the knowledge gained from recent research has still not advanced into treatment development. Quantitative analysis of funding highlighted underresourced areas as well as redundant efforts, enabling a more strategic approach toward advancing FTD drug discovery and development.

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1. Introduction

This report provides an overview of global research funding for frontotemporal dementias (FTD) and related disorders using a biomedical research activity classification system. This data-driven analysis of research funding includes public and private agencies worldwide; exploring patterns of research spending and determining where gaps and opportunities exist to develop future programs for the development of treatments for FTD. The original full-length report of this international funding landscape is available on the Alzheimer's Drug Discovery Foundation's (ADDF) Web site [1].

1.1. Overview of the FTD spectrum of dementias

FTD encompasses a clinical spectrum of progressive neurodegenerative disorders that share pathological features of

*Corresponding author. Tel.: 212-901-8000; Fax: 212-901-8010.
E-mail address: hfillit@alzdiscovery.org

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frontotemporal lobar degeneration. For purposes of this report, FTD will be used to represent both the FTD-related clinical syndromes and the histopathologically defined frontotemporal lobar degenerations. FTD is considered to be the second most common form of early-onset dementia after Alzheimer's disease (AD), representing 5% to 10% of all dementias. However, its prevalence rate is at a minimum of 10% to 20% in patients aged <65 years [2,3].

Most neurodegenerative disorders are characterized by the accumulation of abnormally folded proteins in the central nervous system that are thought to be pivotal to pathogenesis by resulting in cell death. Some patients with FTD can exhibit intracellular neurofibrilliary tangles, such as those seen in AD, composed of the microtubule binding protein, tau. Because FTD and AD both exhibit neurofibrilliary tangles, this analysis captured research on tau irrespective of disease. Grants were excluded if their focus was on other protein aggregates not typically seen in FTD, such as amyloid.

The majority of "frontotemporal-spectrum dementias" are characterized by either tangles, and other tau-positive (tau+) inclusions, or aggregates of trans-activating response RNA DNA-binding protein (TDP-43) [4]. Pick's disease, the historical name for FTD, multiple system tauopathy, and FTD with Parkinsonism linked to chromosome 17 (FTDP-17) with mutations in the microtubule associated protein, tau (*MAPT*), are among the tau-positive FTDs. Corticobasal degeneration and progressive supranuclear palsy are also considered "tauopathies." FTD with ubiquitin-positive and tau- and α-synuclein-negative inclusions, FTD with motor neuron disease, and FTDP-17 because of mutations in progranulin (*PGRN*) represent the tau-negative FTDs [5,6]. As noted previously, these ubiquitin-positive, tau-negative inclusions also contain TDP-43, a nuclear protein involved in transcriptional regulation [7]. Other FTD-related disorders include primary progressive aphasia, semantic dementia, and progressive nonfluent aphasia [8]. Patients with progressive nonfluent aphasia usually exhibit tau+ pathology, whereas TDP-43 inclusions are typically present in semantic dementia [9]. Mutations within the *MAPT* gene are thought to lead to FTDP-17, and are also strongly associated with an increased risk for progressive supranuclear palsy and corticobasal degeneration [10]. These FTD-spectrum disorders were all included as search terms in this analysis.

1.2. Molecular targets for FTD intervention

Several proteins have been associated in the FTD disease process and were included as search terms in this analysis. The heat shock proteins (hsp70 and hsp90) and ubiquitin, owing to their central roles in protein folding and turnover, have been actively studied [11]. Cyclin-dependent kinase 5 (Cdk5) and glycogen synthase kinase 3 beta (GSK3β) have both been implicated in catalyzing the overphosphorylation of tau. Peptidyl-prolyl cis/trans-isomerase 1 (Pin1), a prolyl isomerase, modifies tau and provides greater access for these kinases to phosphorylate tau [12]. Inhibiting these enzymes could potentially block tau overphosphorylation and the subsequent formation tangles, representing promising targets for translational research programs.

A recent genetic study found mutations in a new candidate gene mapped to chromosome 17 that were strongly associated with FTD, in the absence of tau mutations or pathology [13]. This candidate, adjacent to *MAPT*, codes for a secreted precursor protein, *PGRN* or progranulin, which has growth factor-like properties and weak anti-inflammatory activity. Extracellular proteolytic cleavage of *PGRN* generates a family of granulin peptides (6–25 kDa.) that are strongly proinflammatory; however, their exact function in the brain remains undetermined [2,7].

In addition to TDP-43, another protein, valosin-containing protein (VCP), has been shown to be associated with FTD. VCP is involved in multiple systems, including protein transport and ubiquitin-proteosome-dependent degradation. Although rare, *vcp* mutations are now known to cause FTD with inclusion body myopathy and Paget's disease of the bone. However, as seen in FTD and amyotrophic lateral sclerosis, brains of these patients also contain pathological inclusions of ubiquitinated TDP-43 [14].

1.3. Background to drug discovery and development

For the purposes of this overview, drug discovery and development has been subcategorized into target discovery/validation, lead discovery/validation, preclinical development, and clinical evaluation. Although risk declines, an increasingly substantial commitment of funding is required during each progressive stage. Recent studies estimate the average cost of developing a single drug to be $1.3 to 1.7 billion (B) and that the process takes on average 10 to 15 years [15–17].

Because strategic funding is essential to translate new biological research findings through drug discovery into potential clinical candidates, this analysis was designed to identify gaps and redundancies in drug discovery and development funding for FTD and address other key nondrug research related to the care and well-being of patients with FTD.

2. Methods

2.1. Data sources: International biomedical research funders

Consultations with opinion-leading researchers and clinicians, and senior directors from a range of medical research foundations, as well as Internet searches, helped to compile the list of relevant funding agencies for FTD. The grants data requested included grant title and abstract with a minimum of one search term, awarded within the time frame (1998–2008), as well as investigator name, recipient institute, start year, end year or duration, and award amount. The absolute minimum fields required for inclusion were title and/or abstract, dates or start date and duration, and award amount.

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