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Review Articles

Frontotemporal degeneration, the next therapeutic frontier: Molecules and animal models for frontotemporal degeneration drug development

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Abstract Frontotemporal degeneration (FTD) is a common cause of dementia for which there are currently no approved therapies. Over the past decade, there has been an explosion of knowledge about the biology and clinical features of FTD that has identified a number of promising therapeutic targets as well as animal models in which to develop drugs. The close association of some forms of FTD with neuropathological accumulation of tau protein or increased neuroinflammation due to progranulin protein deficiency suggests that a drug's success in treating FTD may predict efficacy in more

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common diseases such as Alzheimer's disease. A variety of regulatory incentives, clinical features of FTD such as rapid disease progression, and relatively pure molecular pathology suggest that there are advantages to developing drugs for FTD as compared with other more common neurodegenerative diseases such as Alzheimer's disease. In March 2011, the Frontotemporal Degeneration Treatment Study Group sponsored a conference entitled "FTD, the Next Therapeutic Frontier," which focused on preclinical aspects of FTD drug development. The goal of the meeting was to promote collaborations between academic researchers and biotechnology and pharmaceutical researchers to accelerate the development of new treatments for FTD. Here we report the key findings from the conference, including the rationale for FTD drug development; epidemiological, genetic, and neuropathological features of FTD; FTD animal models and how best to use them; and examples of successful drug development collaborations in other neurodegenerative diseases.
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1. Introduction

Frontotemporal degeneration (FTD), sometimes referred to as frontotemporal dementia or frontotemporal lobar degeneration (FTLD), in the case of the neuropathology associated with the clinical syndrome, is a common form of dementia in individuals who are <65 years old at time of diagnosis. Once poorly understood and thought to be rare, there has been a rapid growth of knowledge about the biology of FTD over the past decade that has identified a number of potential therapeutic targets in different forms of FTD. FTD encompasses three clinical syndromes: behavioral variant frontotemporal degeneration and two primary progressive aphasias, a semantic variant and a nonfluent variant [1,2]. These syndromes frequently overlap with amyotrophic lateral sclerosis (ALS), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP), such that FTD, ALS, CBD, and PSP are often considered as a related spectrum of diseases. Although FTD basic science has advanced rapidly over the past decade, there are no Food and Drug Administration-approved treatments for these disorders, and there are few data to suggest that any medications are effective in treating the symptoms of FTD or altering the progression of disease, highlighting the enormous unmet medical need of FTD patients. Moreover, because of significant overlap in pathogenic processes between FTD and other neurodegenerative diseases such as Alzheimer's disease (AD) and ALS, development of disease-modifying therapies for FTD may help to accelerate drug development for more diseases, and conversely, therapies initially developed for AD and ALS, but not pursued, might be successfully exploited to treat FTD.

With this in mind, the Frontotemporal Degeneration Treatment Study Group was formed in 2010 to promote collaborations between academic and pharmaceutical industry researchers focused on drug development for FTD and related disorders. On March 25 and 26, 2011, the Frontotemporal Degeneration Treatment Study Group sponsored a meeting entitled "FTD: the Next Therapeutic Frontier" at the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Nevada. This meeting focused on preclinical models for FTD drug development, examples of successful academic–industry drug development collaborations in other neurodegenerative diseases, and development of tools, such as a Web site, to promote drug development for FTD. One of the goals of the meeting was to produce position papers focused on the rationale for and preclinical aspects of FTD drug development. This article summarizes the presentations and discussions that took place surrounding animal models for FTD drug development at the March 2011 meeting. The clinical and regulatory rationale for FTD drug development is discussed in the companion article.

2. Neuropathology of FTD

The neuropathology underlying the clinical syndromes of FTD is heterogeneous; however, there are a number of common themes and molecules that relate FTD to other neurodegenerative diseases, including AD and ALS. Autopsy usually demonstrates relatively selective degeneration of the frontal and temporal lobes, and FTLD has become the accepted general terminology for FTD-related pathologies. In addition to nonspecific microscopic changes of chronic neurodegeneration, most cases are found to have abnormal accumulation of protein within neurons and glia (inclusion bodies). The identity of the pathological protein varies among cases. The current classification of FTLD neuropathology is based on the predominant molecular abnormality, in the belief that this most closely reflects the underlying pathogenic process (Figure 1) [3].

In approximately 45% of FTLD cases, abnormal inclusion bodies contain the microtubule-associated binding protein tau (*MAPT*), which is ubiquitinated and hyperphosphorylated. This molecular pathology overlaps with, but is distinct from, that seen in AD. In the adult brain, there are normally six isoforms of tau: three isoforms with three microtubule-binding repeats (3R tau) and three isoforms with four microtubule-binding repeats (4R tau). Tau protein in both FTLD and AD is relatively insoluble, and these insoluble species can be detected by biochemistry. In AD, all six isoforms are abnormally hyperphosphorylated and migrate as three major bands and one minor band when visualized by

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