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## **The advantages of frontotemporal degeneration drug development (part 2 of frontotemporal degeneration: The next therapeutic frontier)**

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## The Advantages of FTD Drug Development (Part 2 of FTD: The Next Therapeutic Frontier)

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## Abstract

Frontotemporal Degeneration (FTD) encompasses a spectrum of related neurodegenerative disorders with behavioral, language and motor phenotypes for which there are currently no effective therapies. This manuscript is the second of two articles that summarize the presentations and discussions that occurred at two symposia in 2011 sponsored by the Frontotemporal Dementia Treatment Study Group (FTSG), a collaborative group of academic and industry researchers that is devoted to developing treatments for FTD. This manuscript discusses the current status of FTD clinical research that is relevant to the conduct of clinical trials and why FTD research may be an attractive pathway for developing therapies for neurodegenerative disorders. The clinical and molecular features of FTD, including rapid disease progression and relatively pure molecular pathology, suggest that there are advantages to developing drugs for FTD as compared to other dementias. FTD qualifies as orphan indication, providing additional advantages for drug development. Two recent sets of consensus diagnostic criteria will facilitate the identification of patients with FTD, and a variety of neuropsychological, functional and behavioral scales have been shown to be sensitive to disease progression. Moreover, quantitative neuroimaging measurements demonstrate progressive brain atrophy in FTD at rates that may surpass Alzheimer's disease (AD). Finally, the similarities between FTD and other neurodegenerative diseases with drug development efforts already underway suggest that FTD researchers will be able to draw upon this experience to create a roadmap for FTD drug development. We conclude that FTD research has reached sufficient maturity to pursue clinical development of specific FTD therapies.

## 1. Introduction

This is the second of two articles on FTD drug development that summarize the discussions that took place at two meetings in 2011 sponsored by the Frontotemporal Dementia Treatment Study Group (FTSG), an organization dedicated to promoting therapeutic development for FTD. The previous article discusses the clinical and neuropathological subtypes and molecular biology of FTD, as well as animal models that have been developed to study this group of diseases.

This manuscript summarizes the advantages of pursuing drug development in FTD as compared to Alzheimer's disease (AD), as well as clinical research literature on FTD that is relevant to drug development. These topics were discussed at a FTSG meeting in March, 2011 at the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, NV, and at a symposium on FTD drug development that was held as part of the Clinical Trials in Alzheimer's Disease (CTAD) meeting in San Diego, CA in November 2011. This second symposium focused on clinical aspects of FTD drug development including the epidemiology, current experience with clinical trials and potential outcome measures for clinical trials.

## 2. Attracting the pharmaceutical industry to FTD drug development

Although the majority of FTD research to date has been done in academic laboratories and clinical research centers, rapid development of successful therapies will require the involvement of the pharmaceutical industry with its large therapeutic compound libraries, translational medicine and clinical trials experience, as well as funds to help support such large scale endeavors in FTD. The following sections outline arguments for increased industry involvement in FTD drug development research.

### 2.1. FTD and related disorders have no FDA-approved therapies and few interventions with any symptomatic benefit

There is great unmet medical need to develop effective therapies for FTD. Although anti-dementia and psychiatric drugs are often used off-label for symptomatic treatment of FTD, there is little evidence to suggest that these medications are efficacious (See Section 4)<sup>1, 2</sup>. While particularly difficult for patients and their families, the lack of effective therapies is advantageous for the conduct of clinical trials in FTD because FTD patients and their families are highly motivated to participate in clinical trials. Moreover, because few drugs are beneficial for these patients, concomitant medications seldom exclude patients from participating in clinical trials and experimental medications can be tested in treatment of naïve patients. Finally, the absence of approved FTD therapies allows a new product (or the first of several products) to be strongly positioned in the market.

### 2.2. Drug development for FTD may de-risk AD drug discovery since both disorders have substantial tau pathology

Insoluble tau protein deposits are key neuropathological findings in AD, but are also present in approximately 50% of behavioral variant FTD patients and all patients with an autopsy diagnosis of Corticobasal Degeneration (CBD) or Progressive Supranuclear Palsy (PSP), where they are even more closely linked to disease pathology (see Part I of this series). In both AD and PSP the anatomical distribution and overall burden of tau pathology at autopsy is correlated with specific clinical features of disease during life. Moreover, from a genetic perspective, FTD and related disorders are even more closely tied to tau pathology since tau gene mutations typically lead to FTD, CBD or PSP phenotypes, but not to AD phenotypes. Although there are differences between AD and FTD in tau isoforms and cell types affected, tau is hyperphosphorylated and aggregates in both disorders. Drugs targeting tau protein

abnormalities, including hyperphosphorylation (kinase inhibitors), aggregation, and overall expression (tau immunotherapy) are present in many industry therapeutic pipelines.<sup>3</sup> Based on these proposed mechanisms, such drugs might be predicted to be equally or more efficacious for FTD and related disorders than for AD.

### **2.3. Tau pathology in FTD is less frequently accompanied by other pathogenic processes that could mask beneficial effects of tau-directed therapies**

Increasingly, it is recognized that only a minority of clinically-diagnosed AD cases have pure amyloid and tau AD pathology at autopsy without concurrent vascular or Lewy body disease<sup>4</sup>. One implication of this finding is that amyloid, vascular, Lewy body and TDP-43 co-pathologies<sup>5</sup> could mask therapeutic effects of tau-directed treatments in humans with AD. The presence of such co-pathologies in many human patients with AD might also be a potential reason why some amyloid-targeted drugs for AD developed in amyloid-producing transgenic mouse models have failed in recent human clinical trials. To avoid a similar experience with new tau drugs, FTD spectrum disorders with pure tau pathology, such as PSP, may be a better population for initial development efforts. Because patients with FTD and related disorders are younger at disease onset than AD patients, usually in their 50s or 60s, concurrent amyloid, vascular, or Lewy body pathology is less common than in AD.<sup>6</sup> Moreover, there is a much stronger genetic link between tau and FTD than AD – mutations in the tau (*MAPT*) gene lead to FTD, CBD and PSP clinical syndromes, but not to AD. Together, these findings suggest therapeutic signals with tau-related therapies may be easier to demonstrate in FTD than in AD, and may help to predict the likelihood of success in future AD studies.

### **2.4. Orphan drug development incentives can be applied to FTD**

Orphan drug indications are those for which there are 200,000 or fewer patients in the U.S. who will be treated with a drug.<sup>7</sup> The Orphan Drug Act and FDA Office of Orphan Products Development provide a variety of grant mechanisms and regulatory incentives for approval of orphan medications. Moreover, other accelerated approval mechanisms (e.g., 21 CFR 314.510; subpart H) relying on surrogate outcome measures, such as progressive brain atrophy, could also be applied to FTD. Based on the prevalence of FTD and related disorders (see Section 3), these qualify as orphan indications. Rapid approval of a FTD drug with potential applications in another disease such as AD could thus substantially “de-risk” the financial liability associated with a medication's future development.

### **2.5. FTD clinical trials are feasible, and multicenter, randomized, placebo-controlled trials have been conducted**

Refined diagnostic criteria for the different FTD clinical syndromes, including behavioral variant (bv) FTD<sup>8</sup>, the primary progressive aphasia (PPA) variants of FTD<sup>9</sup> and PSP<sup>10</sup>, have been developed and are widely accepted by the academic community. Currently, *clinicaltrials.gov* lists three active interventional trials in FTD (Phase II or IV), and four in PSP, of which two are Phase III. As outlined below (in Section 5), a variety of cognitive, behavioral and functional measurements have been validated in multicenter studies and translated into multiple languages for use in FTD. One or more of these measurements or combinations of such measurements could form the basis for approval for FTD. Other advantages to industry include the concentration of patients in specialty centers facilitating clinical trial recruitment and eventually assisting marketing of approved compounds.

## 2.6. Rapid disease progression in FTD will allow for shorter duration trials with fewer subjects

Experience from recent AD clinical trials suggests modest declines in cognitive status among patients randomized to placebo over the course of six months to one year, which raises concerns about the power to detect small to moderate treatment effects in shorter duration AD clinical trials.<sup>11</sup> The rate of disease progression in FTD is faster than in AD,<sup>12</sup> suggesting that clinical trials with potential disease-modifying agents targeting pathogenic proteins common to both disorders (such as tau) could read out more quickly and with fewer subjects in FTD than in AD. For example, the median survival from symptom onset in FTD was  $8.7 \pm 1.2$ , whereas survival was  $11.8 \pm 0.6$  years for AD in one study.<sup>13</sup> The FTD-related disorder PSP progresses to death at least as rapidly as the core FTD syndromes.<sup>10, 14</sup>

Neuroimaging studies provide further evidence that disease progression is faster in FTD than AD. Longitudinal volumetric MR imaging demonstrates rapid global and regional brain atrophy rates in FTD, which approach twice the rate of brain atrophy in AD<sup>15, 16</sup>. Together, power estimates based on clinical measurements and volumetric MRI<sup>15, 17</sup> suggest that faster rates of global brain atrophy in FTD relative to AD could increase power to detect disease-modifying medication effects in future clinical trials. In PSP, recent work suggests that the rate of brain atrophy, particularly when focused on brainstem regions of interest, may be sufficient to allow for adequately powered clinical trials of anti-tau drugs over 6 months<sup>18</sup>. There are two longitudinal neuroimaging initiatives underway in FTD that will provide data that are directly comparable to Alzheimer's Disease Neuroimaging Initiative (ADNI) and will further improve the utility of imaging and fluid biomarkers for FTD (see Section 5.2).

## 2.7. Drug development for progranulin-related FTD may inform other more common indications such as rheumatoid arthritis, neuroinflammatory diseases and AD

FTD has a stronger genetic component than AD, and one of the most common genetic alterations associated with autosomal dominant FTD are mutations in the progranulin gene (*GRN*), accounting for up to 5–10% of all FTD cases.<sup>19</sup> Progranulin (PGRN) is a growth factor previously implicated in wound repair that has recently been found to act as an antagonist of the Tumor Necrosis Factor alpha signaling and has potent anti-inflammatory effects in animal models of arthritis.<sup>20</sup> Haploinsufficiency of *GRN* gene expression in humans due to a variety of different mutations leads to FTD phenotypes. In all affected subjects, peripheral blood PGRN levels are decreased, providing a readily accessible diagnostic biomarker for interventions that restore PGRN levels might be effective treatments for FTD.<sup>21</sup> A number of PGRN-elevating drugs (that are FDA approved for use in other indications) have recently been identified.<sup>22, 23</sup> Since FTD is the only known phenotype associated with low PGRN, FTD-PGRN would be an ideal population for testing the efficacy of such drugs. Such treatments could then be fast-tracked into clinical trials for other inflammatory conditions.

## 3. Epidemiology of FTD

Epidemiological studies of the prevalence and incidence of the FTDs have been challenging. FTD encompasses three core clinical syndromes: a behavioral variant (bvFTD) and two primary progressive aphasia (PPA), a semantic variant (svPPA), and a non-fluent variant (nfvPPA).<sup>8, 9</sup> The frequent overlap of FTD with amyotrophic lateral sclerosis (ALS), PSP or CBD has led many authors to consider these disorders as part of the FTD spectrum (further discussed in Part 1 of this series). The diagnoses of bvFTD and PPA have historically required a high level of expertise in behavioral neurology. Equally daunting for epidemiological studies is the rarity of the FTDs. In dementia clinics and neuropathological

series, they are considerably less common than AD when considering all dementia patients; however, when focused on early onset dementias, i.e. individuals with disease onset before age 65, FTD is roughly as common as AD. Because the age of onset of the FTDs extends from the fourth to the eighth decade of life, the number of persons to be examined in an epidemiological survey using prospective examinations and diagnoses performed by a research team, referred to as active surveillance, would be enormous.

As an alternative approach, several research groups in the US, Europe and Japan have used passive surveillance methods to estimate prevalence or incidence of the cognitive syndromes of the FTDs, bvFTD and PPA. With passive surveillance, case detection depends upon the availability of neurological expertise in the community; medical records are reviewed to enumerate cases of clinically diagnosed disease. There are five prevalence and three incidence studies of FTD that have been performed using passive surveillance. Two of the prevalence estimates and all three incidence studies<sup>24,25-27</sup> evaluated both bvFTD and PPA.

The prevalence estimates in the age categories of 45 – 64 years old have ranged from 15 to 22 per 100,000 person-years in studies where both bvFTD and PPA were identified. The incidence estimates for the same age group range from 2.7 to 4.1 per 100,000 person-years. By comparison, the prevalence of PSP based on clinical diagnoses is estimated to be 1.9 to 6.5 cases per 100,000.<sup>28, 29</sup> There are no published studies of CBD prevalence; however, clinical experience suggests the prevalence is similar to that of PSP.

The incidence estimates are very comparable to the prevalence estimates if one assumes a survival from FTD onset of 6 – 9 years. Unfortunately, the prevalence and incidence estimates are more variable in persons under age 45 years or over 65 years. As a consensus estimate from clinics specializing in FTD and clinical neuropathological studies, about 10% of all FTD cases are under the age of 45 years and 30% are 65 years and older. These values imply that there are approximately 20,000 to 30,000 cases of the cognitive syndromes of FTD in the US.

#### 4. Current treatment practice and clinical trials in FTD and related disorders

There have been several recent reviews of off-label medication use in patients with FTD.<sup>2</sup> There are a limited number of randomized, placebo-controlled trials in FTD and related disorders to date. There is evidence from autopsy, imaging, and cerebrospinal fluid that FTD patients show deficiencies in the serotonergic neurotransmitter system.<sup>2</sup> In a meta-analysis, the use of antidepressants that increase serotonergic transmission appeared to reduce behavioral, but not cognitive, symptoms in FTD, although the evidence was weak due to small and mostly uncontrolled trials<sup>2</sup>. Antidepressants that increase serotonergic transmission are the most common psychiatric medication used in FTD<sup>1</sup>. Of the randomized trials for serotonergic agents, only those for trazodone have shown clear benefit over placebo,<sup>30</sup> while paroxetine showed positive results in one trial (N = 8)<sup>31</sup> and negative in another (N = 10).<sup>32</sup> Smaller numbers of FTD patients are taking anxiolytic medicines and antipsychotic medications<sup>1</sup>. The reasons for the off-label use of medications used to treat psychiatric illnesses or AD in patients with FTD are not clear, but might include attempts to ameliorate symptoms, uncertainties about underlying diagnosis, and patient or caregiver preference, or a desire to institute a treatment for this progressive illness<sup>1</sup>.

The cholinergic system appears relatively intact in FTD compared to the deficits observed in AD. Trials of cholinesterase inhibitors, which have shown effects on apathy and other symptoms shared with FTD and AD, showed only a potential trend towards benefit for those FTD patients with the language presentation disorder primary progressive aphasia (PPA), some of whom may have had underlying AD pathology.<sup>33</sup>

Memantine, which is approved for use in AD, was well-tolerated in open-label studies of patients with FTD<sup>34</sup>. However, no significant benefit was seen in a recent randomized clinical trial (RCT) of memantine for bvFTD<sup>35</sup>. A second, larger RCT of memantine for the svPPA and bvFTD subtypes of FTD is underway at nine centers throughout the US (clinicaltrials.gov NCT00545974). Results from this trial are expected in mid-2012. In summary, off-label medication treatments are commonly used in FTD and may have limited efficacy in reducing behavioral symptoms. However, no treatment has gathered enough evidence to recommend for use in all FTD patients.

Recently, the hormone oxytocin, which is known to have potent effects on human social interactions, has been shown to improve social interactions and neuropsychiatric inventory scores over the course of one week in FTD patients when delivered intranasally.<sup>36</sup> While it is unlikely that oxytocin will have long term effects on disease progression, an effective symptomatic agent for FTD-associated behaviors would be welcomed by clinicians.

The majority of clinical trials in FTD-related disorders have been performed in PSP and ALS. Multiple placebo-controlled, randomized clinical trials in PSP have been completed.<sup>37</sup> In the Neuroprotection and Natural History in Parkinson's Plus Syndromes (NNIPPS) study, the largest study in PSP (n=362) and MSA (n=398), patients received riluzole for up to 36 months. Riluzole had no significant benefit on survival or rate of decline.<sup>14</sup> In a 6-week randomized trial (n=21), donepezil had no significant beneficial effects with worsening in ADL and mobility scores.<sup>38</sup> In a 6-week randomized trial with coenzyme Q10 (CoQ10) (n=21), CoQ10 improved MRS signal in the occipital lobe and the right basal ganglia. CoQ10 also improved PSP rating scale and the Frontal Assessment Battery.<sup>39</sup> Three multicenter, randomized long-term (24 weeks to 1 year) Phase II/III trials are in progress to assess the efficacy of rasagiline, a MAO inhibitor (n=112); NP031112, a GSK3b inhibitor (n=146), and davunetide, a neuroprotective peptide (n=300) in mild to moderate PSP patients.

Randomized treatment trials in ALS have been more numerous, but have not addressed any associated behavioral or cognitive syndromes shared with FTD.<sup>40</sup> Only riluzole, through an unclear mechanism of action, has prolonged survival in ALS. With the discovery of the *C9ORF72* gene, which causes bvFTD, ALS or FTD-ALS,<sup>41</sup> it may be possible to extend the use of successful ALS therapeutics into a subset of FTD patients who are known gene carriers.

## 5. Tools for measuring disease progression in FTD

### 5.1. Clinical Rating Scales

Although there have been only a small number of randomized, placebo-controlled trials in FTD and related disorders, these studies, as well as a growing number of natural history studies, are providing clinical tools that have been sufficiently validated in multicenter studies to use in FTD clinical trials (Table 1). For measurement of general cognition, the Mini Mental State<sup>42</sup> is moderately sensitive to disease progression, however, the Addenbrooke's Cognitive Examination Revised (ACE-R) has been more extensively studied longitudinally in FTD, and is a more sensitive measure.<sup>43</sup> Moreover, since versions of the ACE-R have been validated in a variety of languages, including French, Spanish, German, Japanese and Korean, this tool could be applied to multinational studies.<sup>44</sup> A multi-domain composite of standard neuropsychological tests of executive function, language and memory is also sensitive to disease progression in FTD.<sup>17</sup> Using this composite or the ACE-R, approximately 35 – 70 subjects per arm would give 80% power to detect a moderate (40 – 50%) reduction in cognitive decline in a one year trial.<sup>17, 43</sup> FTD patients often display profound deficits in executive function, and more specialized tests of executive function

have been studied in FTD. These include the Frontal Behavior Inventory,<sup>34</sup> the EXAMINER battery (<http://examiner.ucsf.edu/>)<sup>45</sup> and EXIT25 scale.<sup>34</sup> More work will be necessary to establish whether these batteries are more sensitive to disease progression than multi-domain composites.

Because behavior and daily function are frequently more impaired than cognition in FTD, functional scales, such as the Clinical Dementia Rating (CDR) scale, for which a FTD-specific version has been developed, and clinical global impression of change (CGIC) scales may be more sensitive to disease progression than cognitive tests<sup>17</sup>. Other functional rating scales such as the Disability Assessment in Dementia (DAD) and a composite FTD Rating Scale (FRS) that adds behavioral questions to the DAD, are also sensitive to FTD disease progression.<sup>46, 47</sup> In PSP, functional scales such as the Schwab and England ADL scale, most commonly used to study Parkinson's, have been shown to be sensitive to disease progression.<sup>48</sup>

Although FTD patients display prominent neuropsychiatric abnormalities on the neuropsychiatric inventory (NPI),<sup>49</sup> it is important to note that many individuals' NPI scores will improve over time without any treatment, presumably due to increasingly levels of apathy and withdrawal in advanced FTD. This suggests that the NPI may be less sensitive to therapeutic effects on disease progression in FTD clinical trials than functional rating scales.<sup>17</sup> However, for symptomatic therapies such as trazodone and oxytocin, the NPI has been shown to be sensitive to change over short periods of time.<sup>30, 36</sup>

Motor impairments are common in FTD and may reflect the emergence of underlying ALS, CBD or PSP pathology. The Unified Parkinson's Disease Rating Scale (UPDRS) has been used longitudinally in FTD,<sup>34</sup> and specialized rating scales such as the PSP Rating Scale<sup>50</sup> and the Neuroprotection and Natural History in Parkinson's Plus Syndromes - Parkinson's Plus Scale (NNIPPS-PPS)<sup>48</sup> have been developed to capture change in individuals with PSP.

## 5.2. Imaging and fluid biomarkers

FTD is a neuropathologically heterogeneous group of disorders. As discussed in Part 1 of this series, the two predominant neuropathologic subtypes of FTD are frontotemporal lobar degeneration with underlying tau protein pathology (FTLD-tau) and FTLN with underlying Tar DNA binding protein 43 kDa (TDP-43) pathology (FTLD-TDP). Although certain clinical phenotypes are strongly linked to one type of molecular pathology, such as PSP with FTLN-tau and svPPA with FTLN-TDP, the most common FTD clinical phenotype, bvFTD, is approximately split evenly between these two molecular subtypes.

Most FTD biomarker studies to date have focused on developing assays that can differentiate FTD from AD or identify specific molecular subtypes of FTD during life. A number of biomarkers, including CSF beta amyloid and tau which are commonly used in AD trials, are helpful for differentiating FTD cases from AD, because in FTD, levels are indistinguishable from controls.<sup>51</sup> Similarly, amyloid-sensitive PET scans with Pittsburgh Compound B (PIB) may also be useful for distinguishing FTD from AD, since most FTD patients do not show appreciable PIB uptake.<sup>52</sup> New work suggests that other CSF proteins may potentially be useful for differentiating FTD with underlying tau pathology from that with underlying TDP-43 pathology.<sup>53</sup> As noted, serum and CSF progranulin levels are likely to be useful pharmacodynamics biomarkers in clinical trials of progranulin elevating drugs. Genetic tests may also prove useful in identifying subsets of FTD patients with specific types of underlying pathology. For example, the newly identified gene, *C9ORF72*, accounts for a significant proportion of both familial and sporadic FTD cases, and is associated with FTLN-TDP pathology. Genotyping for *C9ORF72* and other FTLN-TDP associated genes such as *GRN* may also help to define FTD subpopulations for therapeutic trials.

Although no fluid biomarkers have yet been identified that are sensitive to disease progression, global and regional atrophy rates that sometimes surpass those in AD have been documented in FTD, and brain atrophy on structural MRI scans will likely be useful for tracking disease progression in clinical trials.<sup>54</sup> Using standard longitudinal volumetric imaging techniques, such as boundary shift integral (BSI) sample size, estimates have been derived for disease modifying clinical trials in FTD that demonstrate the potential utility of volumetric imaging as an outcome measure, with smaller sizes to detect treatment effects than those relying only on clinical measures.<sup>15, 55</sup> Recent work in PSP has demonstrated a similar advantage of structural neuroimaging measures over the standard clinical PSP rating scale.<sup>18</sup> The new NIH funded neuroimaging initiatives, Neuroimaging in FTD (NIFD) and the Four Repeat Tauopathy Neuroimaging Initiative (4RTNI), will further develop multicenter MR imaging techniques for use in FTD and related disorders. These projects are designed to generate data that will be directly comparable to the Alzheimer's Disease Neuroimaging Initiative (ADNI), allowing for further between disease comparisons and refinements of analysis methods.

## 6. Collaborative drug development models from other neurological diseases

Successful drug development for neurodegenerative disease depends not only on a thorough understanding of disease-related brain mechanisms and the course of illness, but also on development of specific tools (animal models, compound libraries, etc.) not readily available to all researchers. Academia or industry (pharmaceutical or biotech) will not provide tool development of high quality on their own to facilitate drug development, although each has its own strengths and clear areas of expertise. Innovation will be painstakingly slow if left to individual investigators, and it is becoming increasingly apparent that extensive collaborations will be necessary to develop these tools. Examples of such tools include: identification of novel targets, standardized dynamic (vs. static) animal models, biometrically well-designed clinically meaningful endpoints (e.g., rating scales), validated disease progression and target engagement biomarkers (as endpoints and for dose finding), and, finally, rapid access to clinical investigators and patients. A neutral third party that acts as an intermediary between different academic, industry and other organizational groups could greatly facilitate such collaborative efforts.

It is imperative that only the best compounds proceed into clinical trials in order to give patients affected by FTD the best possible chance to preserve their health and quality of life. Given the various points of attack along the pathological cascade, there are many potential therapeutic approaches. However, the FTD community cannot afford the kind of failure rate seen in recent studies of putative disease modifiers in AD.<sup>56</sup> The consequences of those failures, in terms of increased skepticism about the value of developing novel treatments for neurodegenerative disorders, mandates that we try a different approach. Importantly, the relative paucity of FTD patients could potentially lead to a surplus of preclinical models and investigational agents, leading to a potentially pharma-cidal competition for subjects in clinical trials.

Precompetitive collaborative efforts focused on FTD could have a major impact on accelerating drug development. Such collaborative efforts should bring together academic and industry researchers in partnerships that assure each party benefits. One potential collaborative model to optimize the entry of promising compounds into clinical trials is a "clearinghouse model". A clearinghouse organization would have leadership, funding and representation from the various stakeholders critical to the development of novel compounds. These stakeholders would agree to share information about their respective compounds or models in a pre-specified way that respects proprietary information. This

organization would develop and maintain intellectual property and contractual criteria in order to allow those with novel compounds to interact with those with preclinical models to determine which model(s) would be most appropriate to test a given compound in a time and cost-efficient way.<sup>57</sup> Furthermore by sponsoring clinical data collections and by establishing global longitudinal observation and biomarker studies, large enough standardized clinical data sets could be available to lead to valid conclusions, even among rare disorders. At the same time, supporting global patient registries and clinical investigator networks would speed up clinical development trials as needed. One can envision additional functions that such a clearinghouse could develop, including developing regulatory guidance for pre-clinical and clinical trials, as well as fostering the development of new clinical and biomarker outcome measures.

One example of a successful clearinghouse is run by the Cure Huntington Disease Initiative (CHDI) Foundation. The CHDI Foundation is a well-funded, not-for-profit virtual Biotech, set up to rapidly develop drug treatments that will delay onset or slow progression of Huntington's disease (HD). Several years ago before establishing the management foundation, alone does not lead to novel treatments; this requires an active role of neutral third party, such the anonymous donors who fund CHDI realized that providing money to academic investigators as the foundation, to get there. CHDI is staffed by basic and clinical scientists recruited from Industry. Among their approaches to speed up drug development are: 'collaborative enablement', standardization, and industrial type quality control. CHDI has developed, standardized and distributed research tools, such as dynamic animal models, antibodies, cell assays and out-sourced tool development. CHDI also established bio-sample repositories.

To facilitate discussion among HD researchers, CHDI has developed Research Crossroads, an interactive, web-based tool that presents data from papers, public databases, and CHDI research reports ([www.hdresearchcrossroads.org](http://www.hdresearchcrossroads.org)). Moreover, CHDI has its own HD treatment pipeline and assists biotech companies in developing theirs, and publishes PLoS HD Currents for rapid publication, including negative study results. The Foundation believes that sharing information will accelerate their goal of finding treatments for HD, and is committed to making such data exchanges as easy as possible, while striking a balance between the free exchange of information, researchers' interest in publication and the creation of desirable intellectual property.

A more clinically-oriented clearinghouse is run by the Coalition Against Major Diseases (CAMD; <http://www.c-path.org/CAMD.cfm>), which focuses on neurodegenerative diseases such as Alzheimer's and Parkinson's disease. CAMD was formed by the Critical Path Institute in September of 2008, in collaboration with the Engelberg Center for Health Care Reform at the Brookings Institution. The Coalition is based on the value of sharing precompetitive patient-level data from the control arms of legacy clinical trials, and transforming those data into generalizable and shareable knowledge in the form of drug development tools for AD and Parkinson's diseases.<sup>58</sup>

A common dataset of 4,000 patients from pharmaceutical AD trials was opened in 2010. It is the first effort of its kind to share anonymized patient data from trials over time, creating a voluntary industry data standard that will help accelerate new treatment research on brain diseases. The level of detail and scope of this database will enable researchers to more accurately predict the true course of Alzheimer's, Parkinson's and other neurodegenerative diseases, thereby enabling the modeling and design of more efficient clinical trials. CAMD supports biomarker qualification for patient selection and model development for disease progression. These tools are being developed with the hope of gaining acceptance by the EMA and FDA.

The Dominantly Inherited Alzheimer's Network (DIAN) is a NIA-sponsored, international effort to study individuals with autosomal dominantly inherited AD (ADAD)<sup>59</sup> Although less of a clearinghouse than a collaborative research effort focused on understanding and treating inherited forms of AD, DIAN has developed research tools that could readily be adapted to FTD to facilitate clinical trials. The project has recruited both symptomatic and asymptomatic carriers of presenilin and amyloid precursor protein mutations that lead to early onset AD, and is rigorously characterizing the earliest features of disease prior to the onset of symptoms in preparation for clinical trials of amyloid lowering drugs aimed at preventing or slowing the onset of disease. DIAN has recruited industry partners and plans clinical trials of amyloid-lowering therapies funded through a combination of industry, NIH and other funding sources. The currently planned clinical trials may incorporate novel adaptive clinical trial models based on biomarker responses, a strategy modeled after a collaborative effort to accelerate clinical trials for breast cancer called I-SPY (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis; [www.ispy2.org](http://www.ispy2.org)).<sup>60</sup> Such adaptive designs have the ability to compare multiple compounds in the same trial using fewer subjects due to the incorporation of Bayesian analysis that allow for alterations in the trial procedures once it is underway. Since it is estimated that autosomal dominant FTD is approximately as common as ADAD, approaches to development of biomarkers and clinical trials from DIAN should be readily applicable to the design of clinical trials for genetic forms of FTD, particularly the most common forms of autosomal dominant FTD, *MAPT*, *GRN* and *C9ORF72* mutations.

## 7. Conclusion

FTD and related disorders are common causes of neurodegeneration for which there are no effective treatments. Knowledge of the molecular causes of FTD has reached sufficient maturity to create a variety of drug targets, animal models and early stage compounds that could be tested in human clinical trials. At the same time, FTD clinical research has achieved key milestones that will allow definitive clinical trials to be carried out, including the development of well-validated clinical criteria, genetic and clinically-defined patient populations with known underlying pathology, and clinical and neuroimaging outcome measures. Although less common than other neurodegenerative diseases such as AD, there are a variety of advantages to developing therapies specifically for FTD that should make this group of disorders attractive to pharmaceutical companies. Development of academic-industry partnerships such as clearinghouses for new therapies, animal models, clinical tools and regulatory policy information could greatly accelerate the identification of successful FTD therapies. Based on similar ventures in other neurodegenerative diseases, a roadmap exists for all aspects of FTD drug development. Over the next decade, organizations such as the FTSG will follow this roadmap to develop effective therapies for FTD and related disorders.

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**Table 1**

Clinical outcome measures for FTD clinical trials

Domain	Clinical Syndromes	Data collected from	Test	Longitudinal Data in FTD?	Reference
General Cognitive	bvFTD, SD, PNFA, CBS, PSPS	Patient	Addenbrooke's Cognitive Examination –Revised (ACE-R)	Yes	1 2 3 4
Executive function	bvFTD, SD, PNFA	Patient	Mini Mental State (MMSE)	Yes	5,6
	bvFTD, SD, PNFA, CBS, PSPS	Patient	EXAMINER	Yes	7
	bvFTD	Informant	Frontal Systems Behavior Evaluation (FrSBc)	No	8
	bvFTD, SD, PNFA, CBS, PSPS	Patient	Frontal Behavior Inventory	Yes	6,9,10
ADL, IADL	bvFTD, SD, PNFA	Informant	Disability Assessment for Dementia (DAD)	Yes	11 12
	bvFTD, SD, PNFA,	Informant	Clinical Dementia Rating Scale (CDR)	Yes	5
	bvFTD, SD, PNFA	Patient	Test of Everyday Functional Activities (TEFA)	Yes	6
General	bvFTD, SD, PNFA, PSPS	Informant and Patient	Clinicians Global Impression of Change (CGIC)/Clinical Global Impression of Severity (CGIS)	Yes	5,13
Multiple Domains	bvFTD, SD, PNFA	Informant	Frontotemporal Dementia Rating Scale (FRS)	Yes	14
Neuropsychiatric	bvFTD, SD, PNFA, CBS, PSPS	Both	Neuropsychiatric Inventory (NPI)	Yes	6
	bvFTD, SD, PNFA	Informant	Cambridge Behavior Inventory	No	15
Motor	bvFTD, SD, PNFA, CBS, PSPS	Patient	Unified Parkinson's Disease Rating Scale	Yes	6