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New Approaches to the Treatment of Frontotemporal Lobar Degeneration

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Abstract

Purpose of review—Treatment approaches for frontotemporal lobar degeneration (FTLD) are rapidly evolving with improved understanding of the disease. This brief review highlights recent advances.

Recent findings—Early-onset dementia has a devastating impact on families and rids its victims of their most productive and rewarding years. Over the past ten years, FTLD has emerged as the commonest cause of dementia under the age of 60 years, outstripping even Alzheimer's disease in prevalence. Remarkable progress has occurred in our understanding of FTLD both as a set of distinctive clinical syndromes and as a set of disorders with unique genetic and pathological profiles. While there are no Food and Drug Administration approved medications for FTLD, new evidence of specific genetic and neurochemical defects are beginning to provide a strong rationale for pharmacological treatment.

Summary—Behavioral changes, which are common in behavioral variant FTD and semantic dementia, often respond to treatment with selective serotonin inhibitors. Memantine also holds promise to treat neuropsychiatric symptoms, but more prospective trials are needed. With better understanding of pathogenic molecular pathways involving microtubule associated protein tau, progranulin and TDP-43, potential disease-modifying therapies are being studied in animal models and approaching human trials.

Keywords

frontotemporal; tau; progranulin; TDP-43; treatment

Introduction

Once considered a rare disorder, frontotemporal lobar degeneration (FTLD) is now recognized as a common cause of early-onset dementia. Patients typically present in their 50s to 60s with impairments in social comportment, language production or semantic knowledge. Because there are no Food and Drug Administration-approved medications for FTLD, treatment choices have been mostly culled from therapies that are available for Alzheimer's disease and for psychiatric disorders. In the absence of large-scale placebo-controlled clinical trials, the treatment of FTLD does not have a strong rational basis, although, with recent breakthroughs in our understanding of the biology of FTLD along with improved diagnostic accuracy, new approaches to FTLD are likely to emerge.

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FTLD subtypes

In 1998, Neary and colleagues established research criteria for frontotemporal lobar degeneration (FTLD) and defined three major subtypes: frontotemporal dementia (FTD), semantic dementia (SD), and progressive non-fluent aphasia (PNFA) [1]. Over the ensuing ten years of scientific progress, these research diagnoses have remained a rational underpinning for characterizing patient cohorts with unique but overlapping genetic and pathological profiles.

Frontally predominant FTD, also known as behavioral variant FTD (bvFTD) begins with atrophy of the orbitofrontal, anterior cingulate, and anterior insular cortex and quickly involves the basal ganglia [2]. Clinically, bvFTD is characterized by a cluster of behavioral symptoms in association with executive dysfunction. Typical behaviors include disinhibition, apathy, social withdrawal, loss of empathy or sympathy for others, sweet cravings, diminished insight, mental rigidity, perseverations, stereotypic behaviors, and repetitive motor behaviors [1,3]. When delusions occur, they are often bizarre, and grandiose but rarely persecutory [4].

SD, also known as temporal variant FTD (tvFTD), begins with asymmetric atrophy of the anterior temporal lobes and anterior insulae [2] with later involvement of the orbitofrontal cortex and basal ganglia [5]. Clinically, patients with more significant left temporal atrophy present with progressive loss of semantic knowledge. Speech remains fluent but becomes empty and jargon-laden with supraordinate word substitutions (such as “food” for “carrots”) and surface dyslexia. These patients have difficulty reading irregular words due to the inability to move from orthograph to meaning so that “yacht” is read as “yachtuh “or “gnat” is read as “gunat”) [6*]. Multimodality agnosia leads to difficulty with object recognition. Patients with predominately right temporal atrophy may present with prosopagnosia [7] or show profound loss of emotion recognition and diminished empathy [8,9]. Typical behavioral changes in SD include irritability, impulsiveness, bizarre alterations in dress, mental rigidity, and goal-directed compulsive collecting [10,11]. Additionally, SD patients develop behavioral features that overlap considerably with bvFTD.

PNFA is associated with atrophy of the left inferior frontal lobe, anterior insula, and basal ganglia. Patients develop aphasia characterized by shortened phrase length, stuttering, agrammatism, and speech apraxia. Often, executive function and working memory are impaired. Most patients with PNFA ultimately develop a clinical syndrome suggestive of either corticobasal degeneration (CBD) or progressive supranuclear palsy (PSP) [12] that is confirmed at neuropathology. Behaviorally, these patients may be impulsive, apathetic, or depressed, but are generally appropriate and many have exquisitely spared insight [13*]. Both SD and PNFA are primarily language disorders, and both types of patients have been classified as subtypes of primary progressive aphasia (PPA) based upon the prominent language deficits that persist for two years with relatively spared cognition and behavior [14]. Additional motor symptoms such as Parkinsonism or motor neuron disease may accompany any of the FTD syndromes; MND most commonly occurs with bvFTD [15]. Alzheimer’s disease may mimic any of the FTLD syndromes [16*], however, advances in imaging such as positron emission tomography with the amyloid ligand, Pittsburgh-B-compound (PIB-PET), AD is becoming easier to distinguish from FTLD [17].

Symptom management

As of January 2007, 16 open-label and randomized clinical trials had been published for patients with FTLD (for review see Boxer and Boeve [18*]); the largest study enrolled 26 patients [19]. Additional clinical trials and case reports published over the past 18 months are provided in Table 1. In 2008, Dr. Boxer began an 11-site placebo-controlled study on FTD and SD using the NMDA antagonist memantine. This six-month study will likely complete

enrollment 2008 and will explore the effects of this compound on behavior and activities of daily living in these populations.

Behavioral changes

The behavioral symptoms of bvFTD and SD are often quite disturbing for caregivers and may lead to situations that are embarrassing to both caregivers and strangers. Changes in personality, commonly seen with more right-sided pathology [26,27], and in empathy [8,28,29] are difficult to treat pharmacologically, and caregiver education is often crucial to maintaining family cohesiveness. Certain behavioral changes, though, such as disinhibition, inappropriate sexual behavior, dietary changes, repetitive stereotyped behaviors, and obsessive compulsive behavior, often respond to pharmacotherapy. Patients with FTLD show deficiencies in the serotonin and dopamine neurotransmitter systems, which provides rationale for the use of medications that boost these neurotransmitters [20]. The most well studied and effective treatments are selective serotonin reuptake inhibitors (SSRI), including fluoxetine, fluvoxamine, sertraline and paroxetine. A meta-analysis of SSRI and trazodone effects on behavioral symptoms in bvFTD, revealed a mean improvement in the Neuropsychiatric Inventory (NPI) [30], a measure of behavioral impairments [20]. In our practice, SSRIs (particularly ones with low anticholinergic properties such as citalopram and escitalopram) are used as first-line agents for the management of behavioral symptoms in bvFTD. The use of trazodone may be limited due to its sedating side effects. Impulsivity, which is common in patients with PSP may respond to treatment with SSRIs.

Given that memantine has a beneficial effect on the neuropsychiatric manifestations of AD [31,32], which may be frontally mediated [31,33], it has been speculated that memantine may also improve behavioral symptoms in FTLD. Additionally, overexcited glutamate receptors, a proposed mechanism for AD, can be hypothesized for FTLD. Over the past year, two studies reported on the use of memantine in FTLD (see table 1): a six-month open-label trial without a placebo-arm studied sixteen patients with either bvFTD or SD, all of whom received therapy [21]; and a case series followed three patients with bvFTD who each received therapy. While the larger open trial showed no improvement in behavior and a decline in cognitive function after six months, the case series demonstrated improved NPI score in all three patients after three months of treatment. Certainly, larger prospective, randomized, placebo-controlled clinical trials are needed, however, in our practice memantine is well tolerated in patients with FTLD and we offer this medication as a second-line agent for behavioral symptoms.

Atypical antipsychotic agents may be considered to treat delusions, severe agitation or aggression [22*], however, atypical antipsychotics should be used sparingly in patients with FTLD because of their sensitivity to side effects including somnolence, weight gain, extrapyramidal symptoms, and exacerbation of apathy.

Apathy

Apathy, characterized by paucity of spontaneous ideation and motivation, localizes to the medial frontal lobe [5,34], a region that is atrophied in all FTLD clinical syndromes, particularly bvFTD [5]. In general, apathy is recalcitrant to pharmacotherapyand can be a welcome relief for the caregivers in the severely disinhibited patient. In some cases, though we have tried bupropion. Bupropion has additional indirect dopaminergic agonist properties [35] and could be considered in a patient with Parkinsonism who is suspected of having low dopamine levels.

Dietary Changes

Dietary changes in bvFTD are characterized by cravings for sweets and decreased satiety, which often leads to weight gain. Later in the disease, hyperorality and oral exploratory

behaviors may arise. Food cravings may be considered a component of disinhibition and has a shared anatomy (the right orbitofrontal-insular-striatal region [36]. In SD, dietary preferences may become more fastidious and even lead to weight loss, although later binge eating may occur. Dietary changes often respond in a limited degree to treatment with SSRIs [37]. Caregivers should be counseled to monitor for dysphagia and gorging behaviors, which are less responsive to pharmacologic management.

Cognitive impairments

To date, no medications have been found to stabilize or improve cognitive dysfunction in any of the FTLD syndromes. Given the success of acetylcholinesterase inhibitorsin Alzheimer's disease, these medications have been tried in patients with FTLD; however, no studies have demonstrated a cholinergic deficit in any of the FTLD syndromes. Similarly, donepezil was actually found to worsen behavioral symptoms in patients with bvFTD [38], and for these reasons we have discouraged their use in FTLD. Conversely, in patients suspected of having frontal variant AD (e.g., those with positive PIB-PET imaging), a trial of acetycholinesterase inhibitors is warranted. In patients with PNFA, speech therapy may offer modest benefit, particularly early in the course of disease.

Depression

Quite often symptoms of apathy are misperceived as depression. While depression is rare in bvFTD, it is more common in patients SD and PNFA [13*]. Often patients with bvFTD are euthymic or even euphoric. While no studies are available on antidepressant efficacy in PNFA, we generally treat depression with either an SSRI, or bupropion when additional Parkinsonism is present.

Sleep

Sleep disturbances occur more commonly in SD than bvFTD [5]. Once more conservative measures have been tried, trazodone should be considered for insomnia. Trazodone may have dual benefits because it was also shown to be effective for the behavioral symptoms of bvFTD in a randomized placebo-controlled trial [19]. Parasomnias such as REM sleep behavior disorder or periodic limb movements of sleep are rare in FTLD syndromes and should raise the suspicion for alpha-synuclein disorders such as dementia with Lewy bodies, Parkinson's disease dementia or multi-system atrophy. As with the evaluation of any patient with dementia, patients with FTLD should be asked about symptoms of obstructive sleep apnea (OSA) such as snoring, apneic spells and daytime sleepiness, a syndrome that may emerge due to the weight-gain associated with FTD. Patients who are obese, as commonly occurs in bvFTD, are at risk for develop OSA and treatment of such a condition may dramatically improve their cognitive function. If suspected, a formal sleep study and continuous positive airway pressure trial should be obtained.

Motor

Motor impairments, including atypical parkinsonism or weakness from motor neuron involvement, are commonly observed with more advanced disease [39], When parkinsonism occurs early in the coarse of the disease, as happens in patients with PNFA, a trial of dopamine agonist therapy should be considered. Generally, axial instability and dysphagia are recalcitrant to such treatment, but patients may experience more fluidity of movements. Lowering of blood pressure, worsening of psychotic symptoms, and constipation are potential side effects. In patients on high-dose dopamine therapy, prophylaxis against constipation with use of a stool softener should be provided. Given the gait instability that often accompanies PSP and CBD, early intervention with a physical and occupational therapist including a home safety evaluation is important. While we encourage exercise in all dementia patients, those with Parkinsonism

may especially benefit from cardiovascular and weight-bearing exercise as a protective measure against further motor decline. Because all of the FTLD syndromes are associated with early-involvement of the basal ganglia or motor neurons, any patient with FTLD should be evaluated thoroughly for signs of motor neuron disease, and when appropriate, referred to a neuromuscular specialist. Patients with FTD-MND are often started on riluzole, which is generally well tolerated and has low drug-drug interactions with antidepressants and memantine.

Incontinence

Incontinence tends to occur earlier in FTLD-spectrum patients than in AD as the medial frontal cortex is an early target of the FTLD-related disorders, particularly bvFTD and CBD. Additionally, in PSP involvement of pyramidal tracts and Onuf's nucleus can lead to incontinence of bowel and bladder [40]. In such cases management may include intermittent catheterization or use of diapers. If suspected, these patients should be referred to a urologist for urodynamic testing. FTLD-spectrum patients, particularly those with predominantly pyramidal involvement, may respond to peripherally acting anticholinergic medications, although these medications may exacerbate confusion and exacerbate problems with lower-motor neurons. Darifenacin may have less cognitive side effects than oxybutynin or tolterodine.

Recent advances

Considerable progress has occurred in elucidating the genetic and neuropathological causes of FTLD and potential molecular approaches to FTLD are beginning to emerge. Approximately 10% of FTLD cases are autosomal dominant in inheritance although up to 40% show a strong family history of FTLD or related neuropsychiatric conditions [41]. In recent years, three major genes have been linked to familial FTLD: microtubule associated protein tau (MAPT) [42–45] progranulin [46,47] and transactive response (TAR) DNA-binding protein-43 (TDP-43) [48]. Tau mutations appear to cause a toxic gain of function with abnormal aggregations of 4R tau leading to selective degeneration of neurons. In contrast, progranulin mutations, appear to cause a haploinsufficiency syndrome with decreased expression of progranulin triggering a neurodegenerative condition.

Tau and progranulin are located within 1.7 megabases on chromosome 17; however beyond their close physical proximity and role as risk factors for FTLD, the mechanism for neurodegeneration associated with each gene appears to be different. The pathological inclusions in the central nervous system associated with MAPT mutations are hyperphosphorylated insoluble aggregates of tau (FTLD-tauopathy) [42–45], whereas those associated with progranulin and TDP-43 mutations are tau-negative, ubiquitinated inclusions containing TDP-43 (FTLD-U/TDP-43) [46–48]. Only a small number of FTLD-U cases show ubiquitinated inclusions lacking TDP-43 [49,50*]. The recent discovery that TDP-43 genetic mutations themselves are sufficient to cause neurodegeneration within the FTLD-U/TDP-43 spectrum of disease [51**] supported a pathogenic role for this protein.

Both familial and sporadic FTLD can be pathologically subdivided into FTLD-tauopathy and FTLD-U/TDP-43 types [52], and the clinical presentation may suggest which pathology is more likely. While the pathological correlate for bvFTD is evenly split between FTLD-tauopathy and FTLD-U/TDP-43 [53], most patients with SD have FTLDU/TDP-43 pathology in neurons and glia [54], PNFA (and CBD/PSP) is nearly always FTLD-tauopathy [54] with H1/H1 tau haplotype [55], and FTD-MND is associated with FTLD-U/TDP-43 [48,53,54].

Future Directions

Potential therapies for FTLD and related tauopathies are in various stages of investigation ranging from preclinical evaluation to phase III clinical trials. In a recent meeting of the Working Group on FTD Drug Discovery several of these strategies were discussed (for review see Trojanowski et al. [56**]). Table 2 provides a list of candidate drug targets.

FTLD-tauopathy

Of the pathological proteins involved in FTLD, tau has received the most attention given the availability of powerful animal models and likely mechanistic overlap with other tauopathies, including Alzheimer's disease. Tau is primarily expressed in neuronal axons where it promotes microtubule assembly and stabilization and is involved in signaling transduction [57]. Tau mutations result in alterations of tau splicing, cleavage, and phosphorylation, any of which may alter tau function and contribute to deposition in neurons and/or glia [57]. Both toxic gain of function and loss of normal function have been proposed in tau pathogenesis, and a combination of mechanisms is likely (for comprehensive review, see Ballatore et al. [82*]). Therapeutic strategies under investigation include inhibiting tau kinases [58*–62], inhibiting/reversing tau aggregation [63], blocking tau cleavage [69], reducing tau expression [66–68], immunosuppression [70], altering chaperone systems [71], interference with splicing machinery [72], and stabilizing microtubules [74–76*]. Clinical trials for many of these compounds are already underway for Alzheimer's disease where tau pathology is always expected. Given the heterogeneity of pathology in patients with FTLD, analogous trials for FTLD should focus on patients with known tau mutations or clinical presentations usually associated with tau pathology (PNFA, CBD, and PSP).

FTLD-U/TDP-43

In less than two years since the discovery of progranulin mutations linked to FTLD-U, 57 heterozygous mutations have been identified, accounting for 5 to 10% of FTLD (AD and FTD Mutation Database; www.molgen.ua.ac.be/FTDMutations) (for review see Gijselinck et al. [83*]). Progranulin is a protein growth factor expressed in a variety of body tissues [77]; in the CNS, progranulin is expressed in neurons, particularly neocortical and hippocampal pyramidal neurons, and in activated microglia [46,84]. Progranulin mediates inflammatory response, cell growth, and cell cycle progression; when overexpressed, progranulin has been implicated in tumorogensis [85]. While full-length progranulin is anti-inflammatory, the proteolytic fragments (granulins) derived from progranulin by elastase-mediated cleavage, are proinflammatory [85]. Neurotrophic properties of progranulin have been demonstrated in neuronal cultures [78*] suggesting a role for this protein in neuronal survival. Most progranulin mutations are predicted to introduce a premature termination codon that leads to nonsense-mediated mRNA decay [83*]; this functionally null allele effectively reduces progranulin expression by 50%. Possible mechanisms whereby progranulin deficiency leads to neurodegeneration include long-term depletion of neurotrophic support and defective response to initial neuronal injury. Interestingly, the clinical phenotypes of patients with progranulin mutations are heterogeneous with some presenting in their 30s and others unaffected into their 80s [83*,86]. Given the haploinsufficiency mechanism, progranulin is a particularly appealing gene for drug targeting because boosting its expression may be beneficial. Ribosomal read-through compounds hold promise because they may circumvent nonsense-mediated mRNA decay and result in more expression of functional protein. One such compound, PTC124, which is orally bioavailable, is already approaching phase II and III clinical trials for other genetic deficiency syndromes including Duchenne muscular dystrophy and cystic fibrosis [79,80]. The Consortium for Frontotemporal Research (CFR), based at The University of California San Francisco, is envisioning clinical trials with read-through compounds for FTLD patients with progranulin mutations (Herz J, personal communication). The challenge will be determining

how much progranulin expression levels need to be raised to have a significant clinical effect while avoiding potential adverse effects such as tumorogensis. The development of worm and mouse models will allow high throughput screening of compounds and genes that modulate progranulin expression (Farese RV and Kao AW, personal communication).

TDP-43 is an evolutionarily conserved nuclear protein that can bind to DNA and RNA, repress transcription, and initiate exon skipping [81,87]. Its pathology is characterized by hyperphosphorylation, ubiquitination, and nucleus-to-cytoplasm translocation [48] and pathogenesis may involve both loss of normal function in the nucleus and toxic gain of function in the cytoplasm. Missense mutations are found in the ribonucleoprotein interacting domain of the TARDBP gene, suggesting a dysregulation of mRNA splicing [88*]. Mutations in either progranulin or TDP-43 are associated with TDP-43 pathology, and a cellular pathway linking the two proteins was recently discovered in cultured H4 neuroglioma cells where progranulin prevented caspase-3-mediated cleavage of TDP-43 [89*]. Caspase-cleaved TDP-43 is also a common pathological finding in AD [90*], implicating progranulin and TDP-43 in other neurodegenerative conditions and possibly broadening the therapeutic potential of progranulin/TDP-43 based therapies.

Two other causative genes for FTLD-U, valosin-containing protein VCP [91] and charged multivesicular body protein 2b (CHMP2B) [92], have been discovered in a much smaller number of families. Although rare, these mutations offer further insights into the pathogenesis of FTLD-U. VCP mutations are associated with a range of clinical phenotypes including inclusion body myopathy, Paget disease of bone and FTD [91]. VCP is a ubiquitously expressed protein involved in multiple cellular processes including endoplasmic reticulum (ER)-stress related protein degradation [93,94]. Loss-of-function mutations in VCP are expected to cause ER stress, oxidative stress, and mitochondria-dependent apoptosis [95*]. Interestingly, patients with VCP mutations who also carry an apolipoprotein E4 (ApoE4) allele are more likely to develop FTD [96], suggesting that apoE4 is a genetic modifier for the clinical presentation of FTLD; thus apoE4 targeted therapy, which is under investigation [97] may benefit patients with FTLD. CHMP2B is involved in endosomal trafficking through the ESCRT (endosomal secretory complex required for trafficking) III complex, which may be involved in degradation of growth factors. Dysfunction of CHMP2B results in the formation of dysmorphic organelles of the late endosomal pathway and autophagosomes [92,98,99].

Therapeutic strategies to target TDP-43, VCP, and CHMP2B pathology will evolve with better understanding of these pathogenic mutations in *Drosophila*, *C. elegans*, and mouse models. These models will also allow for high throughput screening for genes and compounds that modify the mutant phenotypes (Farese BV, Gao F-B, and Shu H, personal communication). As with tau-based therapies, clinical trials assessing the efficacy of progranulin, TDP-43, VCP, and/or CHMP2B based therapies should focus on patients with known genetic mutations or clinical presentations usually associated with FTLD-U/TDP-43 pathology (SD and FTD-MND).

Conclusion

The past decade has witnessed an explosion of research in FTLD spanning bench to bedside. Large-scale, placebo-controlled clinical trials are underway to determine the efficacy of currently available treatments while optimizing measures of clinical progression. A host of strategies targeting the underlying pathology in FTLD are under investigation, and tau-based therapies are already entering phase III clinical trials for MCI and AD. The prospects for disease-modifying treatments for FTLD have never seemed closer.

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Abbreviations

apoE4, apolipoprotein E4
bvFTD, behavioral variant frontotemporal dementia
CBD, corticobasal degeneration
CFR, Consortium for Frontotemporal Dementia Research
CHMP2B, charged multivesicular body protein 2b
FTD, frontotemporal dementia
FTD-MND, frontotemporal dementia with motor neuron disease
FTLD, frontotemporal lobar degeneration
MAPT, microtubule associated protein tau
NPI, neuropsychiatric inventory
OSA, obstructive sleep apnea
PIB-PET, Pittsburgh-B-compound (PIB-PET);
PNFA, progressive non-fluent aphasia
PPA, primary progressive aphasia
PSP, progressive supranuclear palsy
SD, semantic dementia
TDP-43, transactive response (TAR) DNA-binding protein-43
tvFTD, temporal variant frontotemporal dementia

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Table 1

Summary table of clinical trials and case reports published the past 18 months (for review of studies prior to January 2007, see Boxer and Boeve [18*] and Huey et al. [20]).

References	Subjects	Medication	Study Type	Duration	Main Findings	Limitations
Diehl-Schmid et al. [21]	16 (bvFTD and tvFTD)	Memantine 20mg/day	All participants given open-label treatment	6 months	No improvement in behavior; worsening of cognitive function	Small sample size, no control group
Kertesz et al. [22*]	36 (bvfTD and PPA)	Galantamine 16–24 mg/day	All participants given open-label treatment, followed by 8-week, double-lind,placebo-controlled, randomized withdrawal	18 weeks	No improvement in bvFTD, trend of efficacy in PPA	Possible admixture of AD patients in PPA group
Cruz et al. [23]	1 (bvFTD)	Topiramate 100mg b.i.d.	Case report	6 months	Reduction of alcohol abuse but not other compulsive behaviors	Case report, alcoholism uncommon in FTD
Anneser et al. [24]	1 (FTD-MND)	Sertraline 50 mg b.i.d.	Case report	n/a	Successful treatment of inappropriate sexual behavior	Case report
Swanberg et al. [25]	3 (bvFTD)	Memantine 10 mg b.i.d.	Case series, all patients given treatment for 3 months	3 months	All 3 patients had improved NPI score, specifically apathy, agitation, and anxiety	Sample size

Table 2

Summary of potential therapies for the major FTLD pathological proteins.

Protein	Biological role	Proposed pathological role	Therapeutic target	Candidate drugs	Stage of investigation
MAPT	Microtubule stabilization, signaling transduction, neural development [57*]	Toxic gain of function	Inhibit tau kinases GSK3,CDK-5, MARK [58*,59]	Lithium [60,61], valproic acid [62], other small molecules (reviewed by Churcher [59])	Preclinical for FTLD Early clinical trials for AD [58*]
			Inhibit/reverse tau aggregation [63, 64]	Anthraquinones [65], phenylthiazolyl-hydrazides, Rember™ (TauRx Therapeutics Ltd)	Drug discovery (High-throughput screening of compounds [63]) Phase III clinical trials for AD (TauRx Therapeutics Ltd)
			Reduce tau expression [66, 67]	Several FDA approved compounds identified (see [68]), siRNA	Preclinical
			Block tau cleavage	Calpain inhibitor A-705253 [69]	Preclinical for FTLD Early clinical trials for AD
			Immuno-suppression	FK-506 [70]	Preclinical
			Alter chaperone systems to enhance tau degradation [71]	Hsp90 inhibitor [71]	Preclinical
			Interfere with splicing machinery to normalize 3R and 4R tau ratio [72]	Splicing regulators [73]	Preclinical

Protein	Biological role	Proposed pathological role	Therapeutic target	Candidate drugs	Stage of investigation
		Loss of normal function	Stabilize microtubules	Paclitaxel [74] NAP (NAPVSIPQ) [75,76*]	Preclinical for FTLD NAP in phase II clinical trials for mild cognitive impairment (Allon Therapeutics Inc., Vancouver, BC, Canada)
PRGN	Growth factor mediating neural development, inflammation, [77] and survival [78*]	Loss of function (haplo-insufficiency) [46]	Ribosomal read-through of premature termination codons	PTC124 [79,80]	Preclinical for FTLD Phase II or III for other genetic deficiency syndromes
			Regulate PRGN levels	High throughput screening of compounds and RNAi libraries	Preclinical
			Block proteolytic cleavage	Elastase inhibition	Preclinical
TDP-43	Binds DNA and RNA, represses transcription, and initiates exon skipping [81]	Toxic gain of function or loss of normal function	Immune therapy, block cleavage	High throughput screening of compounds and RNAi libraries	Preclinical

Abbreviations: PRGN=progranulin