

Experimental Disease-Modifying Agents for Frontotemporal Lobar Degeneration

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Abstract: Frontotemporal dementia is a clinically, genetically and pathologically heterogeneous neurodegenerative disorder, enclosing a wide range of different pathological entities, associated with the accumulation of proteins such as tau and TDP-43. Characterized by a high heritability, mutations in three main genes, *MAPT*, *GRN* and *C9orf72*, can drive the neurodegenerative process. The connection between different genes and proteinopathies through specific mechanisms has shed light on the pathophysiology of the disease, leading to the identification of potential pharmacological targets. New experimental strategies are emerging, in both preclinical and clinical settings, which focus on small molecules rather than gene therapy. In this review, we provide an insight into the aberrant mechanisms leading to FTLD-related proteinopathies and discuss recent therapies with the potential to ameliorate neurodegeneration and disease progression.

Keywords: frontotemporal dementia, frontotemporal lobar degeneration, therapy, TDP-43, tau, *C9orf72*, *GRN*, *MAPT*

Introduction

Frontotemporal Dementia (FTD), the second most common cause of early-onset dementia,¹ is a neurodegenerative disorder enclosing a wide range of different neuropathological entities and clinical presentations, sharing a main impact on behavioral, linguistic and executive functions, due to the progressive atrophy of frontal and temporal lobes. According to the latest criteria, three core clinical variants have been recognized, namely the behavioral variant of FTD (bvFTD),² the agrammatic/non-fluent variant of primary progressive aphasia (avPPA/nfvPPA) and the semantic variant of PPA (svPPA).³ The occurrence of associated motor symptoms, as in progressive supranuclear palsy (PSP), corticobasal syndrome (CBS) and motor neuron disease (FTD-MND), enriches the spectrum of FTD-related disorders.⁴

Common to all FTD clinical syndromes is the underlying frontotemporal lobar degeneration (FTLD) which can be classified according to the predominant constituent proteins of cellular inclusions. While until 2006 only FTLD-Tau was well characterized, the following discovery of TAR DNA binding protein 43 (TDP-43) and FET family proteins within tau-negative, ubiquitin-positive inclusions of a vast majority of FTLD cases, led to the introduction, respectively, of FTLD-TDP and FTLD-FET neuropathology.^{5,6}

Along with heterogeneity in both clinical presentations and pathological hallmarks, an increasing literature depicts the complex figure of the genetic determinants of FTD,

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with up to 20–30% of the cases with mutations in progranulin (*GRN*), microtubule-associated protein tau (*MAPT*) and chromosome 9 open reading frame 72 (*C9orf72*) genes.⁷ This heterogeneity,⁸ as well the lack of a clear-cut relationship between clinical phenotypes,⁹ genetic traits and neuropathological features, represent the main obstacle hampering the development of a unifying pathogenetic model and, as consequence, of disease-modifying strategies of intervention.

In this paper, we review the most appealing candidates for pharmacological and non-pharmacological interventions and discuss the current achievements and challenges of novel therapeutic approaches in FTD.

FTLD: Crosstalk Between Genetics, Pathology and Clinical Features

FTLD is affected by a high heterogeneity, limiting the establishment of a one-to-one relationship between genetics, neuropathological and clinical correlates.^{10,11}

FTLD-tau, defined by tau-immunopositive inclusions, accounts for about 40% of all FTLT cases and 20% of those with high heritability, related to mutations in the *MAPT* gene, with more than 60 pathogenic variations reported.^{7,12} According to the predominant species in the inclusions, which differ from each other by the number of 31–32 aminoacidic repeats in the microtubule-binding domain (3-repeat or 4-repeat tau),¹³ the actual molecular classification of FTLT-tau accomplishes four main histological subtypes, including Pick's disease (PiD), cortico-basal degeneration (CBD), progressive supranuclear palsy (PSP), and globular glial tauopathy (GGT). Among FTD syndromes, there is a strong association with FTLT-tau and clinical syndromes of bvFTD and nfvPPA, but especially common in CBS and PSP, while only a few cases of FTD-MND have been reported.^{14,15}

Before the discovery of TDP-43 protein in a large group of ubiquitin-positive, tau-negative FTLT samples, in 2006,¹⁶ FTLT-tau was considered the main FTLT neuropathological type. To date, FTLT-TDP pathology has been recognized as the most common neurobiology, underlying about 50% of all FTLT cases including both sporadic and familial forms.⁶ Despite the common molecular substrate, FTLT-TDP covers a wide range of anatomopathological changes. As a consequence, and in consideration of the important clinicopathological and genetic associations, the reviewed criteria for FTLT distinguish four subtypes, with respect to morphology, abundance/presence of distinct inclusion types and their distribution

across cortical laminar layers.^{17–20} Indeed, unlike FTLT-tau, genetic etiology of TDP-43 proteinopathies is complex, involving mutations in four main genes, demonstrating an autosomal dominant heritability.²¹

Mutations in the *GRN* gene, whose list is enriched with more than 110 pathogenic variants,^{7,12} account for 5–20% of familiar and 1–5% of sporadic FTD patients.^{22,23} In spite of the highly phenotypical heterogeneity, most *GRN* mutation carriers receive a clinical diagnosis of FTD, with bvFTD as a more frequent presentation than the language variant, that is nevertheless more prevalent than in sporadic forms and consistent with nfvPPA, as well as CBS.^{24–26}

The hexanucleotide repeat expansion of GGGGCC in a non-coding region of the *C9orf72* gene is the most common genetic cause of both sporadic and familial cases of FTD, MND and FTD-MND.^{27,28} The expansion carrier status influences the susceptibility of specific neuronal populations, producing a more severe loss of motor neurons.²⁹ Clinical presentation matches with the distribution of TDP-43 pathology, explaining a more widespread involvement of frontal and temporal neocortices in cases with FTD or FTD-MND rather than MND only.^{30,31}

Accounting for up to 4% of familiar FTD,³² mutations in the valosin-containing protein (*VCP*) gene, have been associated with the development of the autosomal dominant inherited inclusion body myopathy associated with Paget's disease of bone and FTD (IBMPFD). Pathologically classified as FTLT-TDP type D,³³ the clinical presentation is dominated by myopathy, found in about 90% of the patients,³⁴ and FTD or ALS phenotype was observed in approximately 30% of the patients carrying *VCP* mutations.³⁵

Finally, mutations in the gene encoding TANK-binding kinase 1 protein (*TBK1*) have been reported as probably the fourth most common genetic cause of FTD overall.³⁶ Few pathological cases have been described that, although confirming a TDP-43 pathology recognized both a subtype A and B pattern.^{37,38} ALS is the predominant clinical syndrome with the majority of cases having either ALS or FTD-ALS syndrome, with a cognitive profile covering bvFTD and PPA (both nfvPPA and svPPA).³⁹

Finally, FLDT-FET accounts for about 5–10% of the cases, and this histopathological subgroup was defined since the identification of the protein fused/translocated in sarcoma (*FUS*) within neural inclusions described in some FTLT patients.⁴⁰ However, the possible coaggregation of proteins belonging to the FET family, including

TATA-box binding protein-associated factor 15 (TAF15), Ewing's sarcoma (EWS) and transportin 1, was reported only in FTLD-FET cases, not associated with *FUS* mutations.⁴¹ Indeed, while *FUS*-related ALS is mostly caused by *FUS* mutations, FTLD-FET tends to be sporadic.⁴² In turn, within FTLD-FET pathology, three subtypes are distinguished, named atypical FTLD-U, neuronal intermediate filament inclusion disease (NIFID) and basophilic inclusion body disease (BIBD). The corresponding clinical spectrum, for each subtype, ranges from early-onset bvFTD for atypical FTLD-U to early-onset FTD with MND and/or extrapyramidal motor symptoms for NIFID; it is more heterogeneous for BIBD, covering FTD/ALS, parkinsonism, chorea, dysarthria and gaze palsy.⁶

Tau Targeting Strategies

Tau protein, encoded by *MAPT* gene on chromosome 17, is a microtubule-associated protein, mainly enriched in the axonal compartment of neurons and primarily involved in the regulation of cytoskeletal turnover, by promoting microtubule polymerization and stabilization.⁴³ The protein exists as six major alternative splicing variants, with the inclusion of exon 10 determining whether the protein contains either three or four microtubule-binding repeat regions. Variants are simply distinguished between three-repeat (3R) and four-repeat (4R) isoforms: their relative amount varies in the course of human brain development and is related to the pathological profile of the different tauopathies, with 3R in Pick's disease, 4R in PSP and FTD while mixed forms in AD and chronic traumatic encephalopathy.⁴⁴ Once synthesized, tau undergoes many post-translational modifications that, besides phosphorylation, include acetylation, glycation, nitration, O-GlcNAcylation, oxidation, polyamination, SUMOylation, and ubiquitination.⁴⁵

With regard to the milestones of tau pathophysiology, the actual therapeutical approaches under investigation are articulated around five main strategies, including 1) modulation of *MAPT* expression, 2) post-translational modification, 3) modulation of protein aggregation and clearance, 4) immune neutralization (active and passive immunization), and 5) microtubule stabilization (see Table 1 and Figure 1).

Modulation of *MAPT* Expression

MAPT mutations, mainly concentrated in exons 9–12 and introns flanking exon 10,^{12,46–48} affect the ability of tau to

interact with microtubules and alter the normal ratio among isoforms, enhancing its propensity to aggregate.⁴⁹

Reduction of Tau in pathogenic mouse models has been shown to ameliorate seizure phenotypes and prevent neurodegeneration,⁵⁰ identifying antisense oligonucleotides (ASOs) as potential therapeutics against Tau. Indeed, encouraged by the results achieved in multiple neurodegenerative diseases, such as spinal muscular atrophy and Duchenne muscular dystrophy,⁵¹ the use of small, single-stranded sequences of DNA in transgenic tauopathy mice have been demonstrated to significantly restore the balance between tau species and to revert the associated neuropathological and clinical phenotypes.^{52,53} Based on the preclinical data of the study by Devos et al, the drug BIIB080 is actually being administered in MCI due to AD patients in a Phase 1/2 randomized clinical trial (RCT) (NCT03186989). Another trial with ASOs (NIO752) is currently planned in PSP (NCT04539041).

Moreover, still aimed at modulating *MAPT* expression, novel experimental approaches have been proposed, relying on RNA-guided mechanisms. Based on RNA reprogramming, spliceosome-mediated RNA trans-splicing technique (SMaRT) has provided an alternative method to correct the impaired alternative splicing caused by *MAPT* pathogenic mutations.⁵⁴ Moreover, the use of natural antisense transcripts (NATs) is recently emerging as a potential, physiological tool to suppress tau protein levels.^{55,56}

Post-Translational Modifications Phosphorylation

Since the hyperphosphorylated tau state makes the protein susceptible to aggregation with the loss of cytoskeletal microtubule-stabilizing properties, leading to neural toxicity,⁵⁷ research has strongly focused on compounds able to prevent this modification. Tau protein carries 85 mapped phosphorylation sites,⁵⁸ which are tightly regulated by a plethora of protein kinases and phosphatases, which represent potential therapeutic targets.

Among this class of proteins, glycogen synthase kinase 3 beta (GSK3 β) exerts a pleiotropic effect on neural homeostasis besides the direct action on tau, including axonal transport and synaptic function, adult neurogenesis, cell survival and neuro-inflammation.⁵⁹ Moreover, neuropathological evidence has validated the pathogenetic role of GSK3 β in tauopathies,⁶⁰ fostering the discovery of several chemical classes of GSK3 β inhibitors, some of them reaching human application. However, despite the results

Table 1 Principal Mechanism of Action and Possible Candidate Drugs for the Treatment of FTLD-Tau

Therapeutic Target	Mechanism of Action	Candidate Drug	References
MAPT gene expression	ASO targeting MAPT RNA	BIIB080	[50]
	Spliceosome-mediated RNA trans-splicing technique (SMaRT)		[54]
	Natural antisense transcripts (NATs)		[55]
PTM modulation			
Phosphorylation	GSK3 β kinase inhibition	Lithium	[61,62]
		Sodium valproate	[63]
		Tideglusib	[65,66]
	Fyn kinase inhibition	Saracatinib	[71]
	BCR-ABL kinase inhibition	Nilotinib	[72]
	p38 MAP kinase inhibition	Neflamapimod	[216]
O-GlcNAcylation	O-GlcNAcase (OGA) inhibition	MK-8719	[76]
		ASN120290	[217]
Acetylation	Tau acetylation inhibitor	Salsalate	[83]
Tau aggregation	Inhibition of tau polymerization	Methylene blue	[91]
Tau aggregate clearance	Active immunization	AADvac I	[96]
		ACI-35.030	
	Passive immunization	BIIB092 (Gosuranemab)	[102,103]
		ABBY-8E12 (Tilavonemab)	[104]
		UCB0107 (Bepranemab)	[108]
Cytoskeletal turnover	Microtubule stabilization	Epothilone-D	[110]
		TPI 287 (Abeotaxane)	[111]
		Davunetide	[116]

Abbreviations: MAPT, microtubule-associated protein tau; ASO, antisense oligonucleotides; PTM, post-translational modification; GSK3 β , glycogen synthase kinase 3 beta; MAP, mitogen-activated protein.

of preclinical studies showing the effect of lithium, a non-competitive, non-specific GSK3 β inhibitor, on the state of tau phosphorylation and aggregation,⁶¹ a Phase 2 RCT demonstrated no improvement of clinical or biological outcomes in AD patients.⁶² Whilst no data are available, due to intolerability, in a phase 1/2 RCT in patients with PSP and CBD (NCT00703677), another RCT (NCT02862210) is currently ongoing to assess the efficacy of lithium for the treatment of neuropsychiatric symptoms in bvFTD. Another non-specific inhibitor of GSK3 β , sodium valproate, demonstrated poor tolerability, with a possible clinical worsening when administered to PSP patients (NCT00385710),⁶³ in conflict with preclinical findings.⁶⁴ In order to ameliorate their safety profile, new

specific GSK3 β inhibitors have been discovered. Among these, tideglusib, a non-ATP-competitive GSK3 β inhibitor, though failing in achieving primary clinical outcomes, has shown to reduce brain atrophy progression in PSP patients in the TAUROS study (NCT01049399).^{65,66}

Besides GSK3 β , a number of kinases have proved to be catalytically active on tau and to be associated with pathological epitopes of the phosphorylated protein, including CDK5, TAOKs, TTBK.^{67–69} In this view, expanding research in oncology, focused on inhibitors of the human kinome, has identified novel therapies that can be repurposed for the treatment of neurodegenerative disorders,⁷⁰ making a wide spectrum of target kinase inhibitors available. Recently, three small molecules,

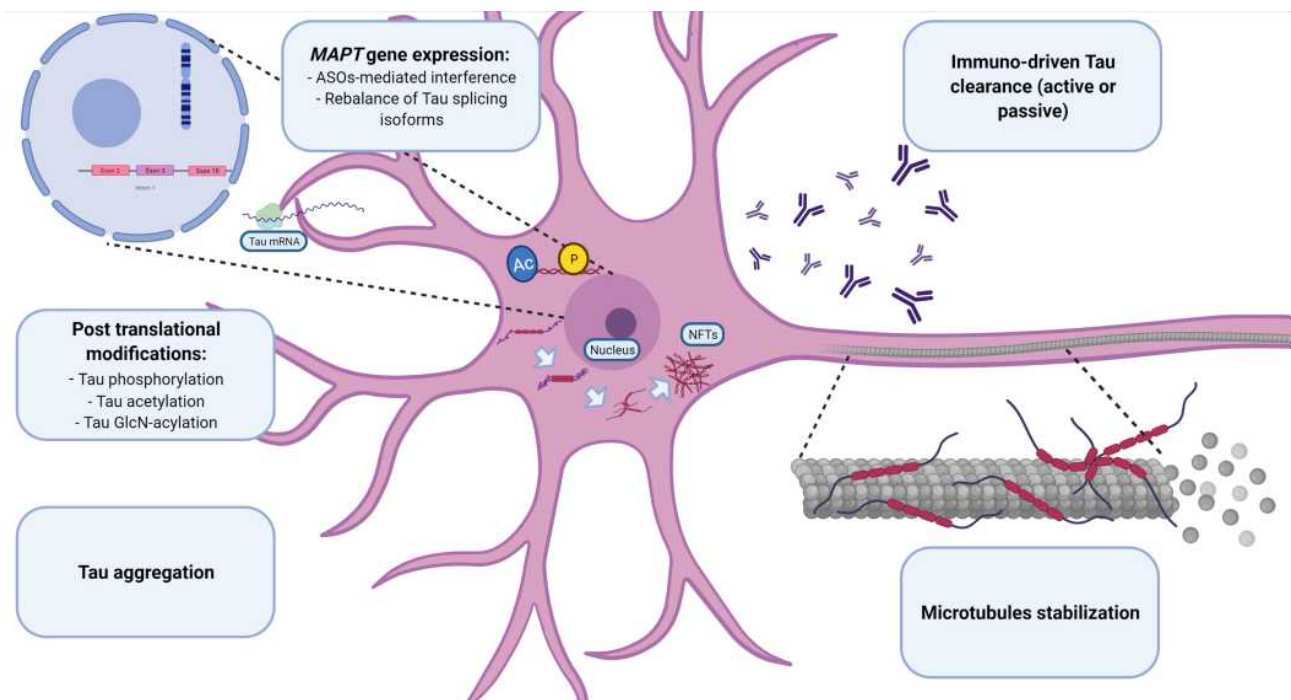


Figure 1 Principal pathogenic steps toward tau-related neurodegeneration. Pathophysiological transformations leading to tau dysfunction. The related potential therapeutic strategies are reported in the boxes. Images created with BioRender.com

Abbreviations: ASOs, antisense oligonucleotides; AC, acetylation; *MAPT*, microtubule-associated protein tau; NFTs, neurofibrillary tangles; P, phosphorylation.

saracatinib (NCT02167256), nilotinib (NCT02947893) and neflamapimod (NCT03402659), designed to inhibit the tau kinases Fyn, BCR-ABL and p38 α , respectively, were assessed in AD patients in phase 2 trials. With the exception of the former, limited by a low availability of CSF samples, nilotinib and neflamapimod provided at least a biological proof of efficacy, with an improvement of neurodegeneration markers.^{71,72}

Tolfenamic acid, which has been shown to lower tau mRNA and protein, as well as the levels of its phosphorylated form and CDK5,^{73,74} is currently being planned for testing in PSP patients (NCT04253132).

Others Post-Translational Modifications

In addition to the intervention of specific kinases, the state of phosphorylation of tau is also regulated by the eventual addition of O-linked N-acetylglucosamine (O-GlcNAc) moieties. Regulated by two enzymes, O-GlcNAc transferase (OGT) inserts O-GlcNAc, while O-GlcNAcase (OGA) removes the moieties on serine and threonine residues, thus creating a competition with the phosphorylation process.⁷⁵ In line with the aim of upregulating the O-GlcNAcylation, two small OGA inhibitors, MK-8719 and ASN120290, shown to reduce tau-related

degeneration hallmarks,^{76,77} have been announced in clinical trials for PSP patients.⁷⁸

Acetylation, another post-translational modification (PTM), is also able to interfere with tau pathogenetic potential, acting on over than 30 lysine residues.⁷⁹ The high acetylation rate found in post-mortem neuropathological samples of tauopathy patients⁸⁰ could promote neurodegeneration by different mechanisms, such as fibrillar aggregation, microtubule detachment and transneuronal spreading.⁸¹ In this regard, salsalate, an anti-inflammatory salicylate, protects against neurodegeneration in FTL Δ -tau mice by the inhibition of p300, an acetyltransferase that targets tau.⁸² An open-label phase 1 study in PSP patients has recently been concluded, reporting non-significant effects on disease progression, that could be due to the low rate of CNS penetrance of salsalate.⁸³

Modulation of Tau Aggregation and Clearance

As described above, PTMs can drive tau aggregation by oligomerization of non-bound hyperphosphorylated tau into pre-tangles, followed by the subsequent formation of filaments such as paired helical filaments or straight filaments, until the assembly of neurofibrillary tangles

(NFTs). In line with the development of a disease-modifying strategy, a direct approach to tau aggregation might be more successful, considering the difficulties in avoiding the disruption of kinases' physiological signaling pathways, together with the heterogeneity of phosphorylation sites on tau, with some promoting and others inhibiting tau aggregation.⁸⁴

Methylene blue (MB) has gained attention for its anti-aggregating properties, achieved by modification of cysteine residues critical for aggregation,⁸⁵ although recent studies have broadened its pharmacodynamic spectrum to proteasome function,⁸⁶ autophagy and oxidative stress.^{87,88} Encouraged by the results of a phase 2 trial showing an improvement in mild to moderate AD,⁸⁹ the same results were not replicated in two subsequent Phase 3 trials in AD and bvFTD patients.^{90,91} The failure of these trials, as recently reported,⁹² could be due to the ability of MB to hinder the synthesis of fibrillar species only, increasing instead neurotoxic tau granule formation.

Immune Neutralization

Parallel to strategies aimed to prevent tau aggregate formation and deposition, the enhancement of clearance systems represents a promising field of research. In this regard, anti-tau immunotherapy approaches turned out as feasible options for clearing toxic species and specific protein epitopes in tauopathies: they can be distinguished in active and passive strategies.⁹³

Active Immunization

Given the devastating *in vivo* results of a first immunization approach against full-length recombinant human tau, the ongoing vaccine development has focused on tau fragments and phosphorylated tau peptides.⁹⁴ Indeed, the first vaccine reaching human experimentation (AADvac1), which consisted of an antigenic peptide hypothesized to trigger misfolding and aggregation,⁹⁵ reduced tau-related pathological alterations with a corresponding behavioral improvement in transgenic rats.⁹⁶ Still confirming its neurobiological efficacy on neurodegeneration markers in the following ADAMANT phase 2 trial (NCT02579252), AADvac1 exhibited only a trend to slow the decline in mild AD patients.^{97–100} The same compound is actually being administered to nfvPPA patients in a phase 1 trial (NCT03174886).

Following this pivotal vaccine, AC Immune developed ACI-35, an alternative liposome-delivered agent, different from the former, instead directed against tau fragments

enriched with phosphorylates residues. ACI-35.030, a second-generation compound redesigned to increase the immune response, is being tested in a phase 1/2 clinical trial in AD patients (NCT04445831), now in recruitment stage.

Passive Immunization

The consolidated experience in the management of monoclonal antibody (Ab)-based therapies, along with the expanding libraries of targetable altered forms of tau protein has made passive immune clearance one of the main areas of intervention in disease-modifying drug research. Although Ab can recognize either the N-terminal, the pro-line-rich or C-terminal regions, published results of clinical trials came only from Ab against the N-terminal region.¹⁰¹ Indeed, BIIB092 (gosuranemab), a humanized monoclonal antibody engaging the extracellular N-terminal tau sequence, reduced CSF-free N-terminal tau in PSP patients in a phase 1 trial.¹⁰² Unfortunately, two following phase 2 trials, PASSPORT (NCT03068468) and TauBasket (NCT03658135), aimed at testing BIIB092 in PSP and in four primary tauopathies (CBS, FTLDTau, nfvPPA and traumatic encephalopathy syndrome), respectively, were prematurely interrupted due to lack of efficacy in the interim analysis.¹⁰³

Similar characteristics were observed for C2N-8E12 (ABBV-8E12, tilavonemab), an IgG4 antibody recognizing an epitope mapped on an extracellular N-terminal region,¹⁰⁴ which was proven safe in a phase 1 trial (NCT03413319), but was then discontinued for PSP after interim results of a phase 2 study (NCT02985879) showing no beneficial therapeutic effects.¹⁰⁵ The failure of these trials, along with the evidence of a lower extracellular/intracellular tau ratio in non-AD tauopathies, suggests that targeting extracellular N-terminal fragments alone could be futile in this population.¹⁰⁶

Moreover, based on spectroscopy studies showing the prevalence of terminals-lacking tau fragments in CSF,^{107,108} an extracellularly acting Ab directed against a mid-domain region could achieve better results. In this direction, UCB0107 (bepranemab), a monoclonal Ab binding to the mid-region of tau, interferes with transneuronal propagation and tau seeding activity *in vivo* and *in vitro*.^{108,109} A phase 1 trial with an open-label extension (NCT04185415, NCT04658199) to evaluate the safety profile on PSP patients is now ongoing and completion is expected in November 2021.

Microtubule Stabilization

In addition to the neurotoxic gain-of-function, also tau loss-of-function may lead to neurodegeneration, primarily through the detachment from microtubule and consequent microtubule disassembly.⁸⁴ In order to overcome this process, three microtubule-stabilizing agents have been developed.

Epothilone-D (EpoD), a taxol-derived small molecule, reduces axonal dystrophy, increased microtubule density and, more globally, ameliorated tau-pathology in PS19 tau transgenic mice.¹¹⁰ However, although translated to a human phase 1/2 clinical trial (NCT01492374) for AD patients completed in October 2013, results were not published.

More recently, TPI 287 (abeotaxane), another taxol-derived compound with a similar mechanism of action to EpoD, was tested in two phase 1 RCTs in PSP, CBS and AD patients. While being better tolerated in 4R-tauopathies, than in mixed 3R/4R pathology of AD, a motor and a dose-related worsening in exploratory cognitive outcomes was reported.¹¹¹ Finally, davunetide (NAP), a derivative from the endogenous activity-dependent neuroprotective protein (ADNP), whose genetic deficiency is associated with tau pathology,¹¹² was found to improve cognitive function in tau transgenic mice by enhancing tau-microtubule interaction.^{113,114} Firstly approved for a phase 2 trial (NCT00422981) in MCI patients, it produced an improvement in memory and attention-based tasks.¹¹⁵ Unfortunately, a following phase 2/3 RCT (NCT01110720) on PSP patients did not confirm these results,¹¹⁶ possibly explained by a recent in vitro study demonstrating the preferential interaction of davunetide with 3R-tau in comparison with 4R-tau.¹¹⁷

TDP-43 Targeting Strategies

Together with FUS, TDP-43 is a ubiquitous protein belonging to the class of nuclear ribonucleoproteins (hnRNPs), with whom it shares two N-terminal located RNA recognition motifs (RRM1 and RRM2),¹¹⁸ that enable the binding and the regulation of several RNA processing pathways. The C-terminal sequence is a determinant of solubility state, cellular localization and interprotein interactions,¹¹⁹ supported by the clustering of many pathogenic FTD and ALS mutations in the corresponding region of the *TARDBP* gene.^{120,121} Predominantly located within the nucleus, when TDP-43 is shuttled to the cytoplasm the protein carries out various

biological functions, including RNA translation, synaptic plasticity, autophagy and mitochondrial homeostasis.¹²² TDP-43 can drive the formation of stress granules in response to environmental stressors like other hnRNPs undergoing a liquid-liquid phase separation.¹²³ Both the presence of mutations and aberrant post-translational modifications lead to the clearance of nuclear TDP-43, its mislocalization and, finally, to the classical TDP-43 cytoplasmic inclusions.¹²⁴ In a similar way to tau, it relies on a simultaneous loss- and gain-of-function, secondary to the sequestration of TDP-43 and to the toxicity of the aggregates themselves.¹²⁵ Paradoxically, if in vitro models show that a comparable degree of neural degeneration can be achieved in both inclusion-bearing and non-bearing neurons,¹²⁶ it is also possible that aggregates might be protective at the early stages of the disease.¹²⁷ However, two main factors have hindered the development of direct TDP-43-targeted strategies: 1) the ubiquitous expression together with the impairment of different cell type-specific pathways discourages the target of the protein in a generalized manner; and 2) the complexity of its biological properties, mostly unexplored, requires the implementation of a function-based intervention.¹²⁸ As a direct consequence, monogenic forms of FTLTDP have received more attention for research purposes (see [Table 2](#) and [Figure 2](#)).

Targeting TDP-43 Pathophysiology

Still debating whether FTLTDP pathological mechanisms act primarily through gain- or loss-of-function effects, in vivo models show that both upregulation and downregulation of protein levels result in the triggering of a neurodegenerative cascade.¹²⁹ Not surprisingly, TDP-43 levels are under tight control, including self-regulation based on a nonsense-mediated mRNA decay (NMD) mechanism.¹³⁰ Given the role of its imbalance and the importance in maintaining protein levels, harnessing the NMD system might be a conserved, promising mechanism for TARDP-43 regulation, as recently reported.¹³¹

A hallmark of TDP-43 proteinopathies is the presence of aggregates predominantly composed of a protein extensively modified by post-translational mechanisms, not observed in healthy neurons and including ubiquitination, acetylation, SUMOylation, and phosphorylation and cleaved to generate C-terminal fragments (CTFs).¹²⁴ As the most consistent feature of aggregates, also linked to disease-associated mutations,¹³² TDP phosphorylation represents a major area of research in FTLTDP therapy.

Table 2 Principal Mechanism of Action and Possible Candidate Drugs for the Treatment of FTLD-TDP

Therapeutic Target	Mechanism of Action	Candidate Drug	References
PTM modulation			
Phosphorylation	Kinases inhibition (CK-1, CDC7, TTBK-1/2, GSK3 β , CDK-2)		[135,218–220]
Recruitment to SGs	Topoisomerase inhibitor	Mitoxantrone	[221]
	PARPs inhibitors	Veliparib	[222]
	Exportin inhibition		[223]
TDP aggregate clearance	Inhibition of mTOR and enhancing of autophagic pathway	Rapamycin	[224]
	Enhancing lysosomal biogenesis	Trehalose	[225]
Increase PGRN levels	Inhibition of SORT-1-mediated endocytosis	AL001	[147]
	Histone deacetylase inhibitor	Vorinostat	[153]
		FRM-0334	[155]
	Gene therapy	AAV-9 vector	[157]
<i>C9orf72</i> expansion	ASO targeting G ₄ C ₂ containing RNA	BIB078	[160]
	RNA interference		[162]
	RAN translation Inhibition	Metformin	[164]

Abbreviations: CK-1, casein kinase 1; CDC7, cell division cycle 7; TTBK-1/2, tau tubulin kinase 1/2; GSK3 β , glycogen synthase kinase 3 beta; CDK-2, cyclin-dependent kinase 2; SG, stress granules; PARP, poly ADP ribose polymerase; TDP, TAR-DNA binding protein; mTOR, mammalian target of rapamycin; PGRN, progranulin; PTM, post-translational modification; SORT-1, sortilin-1; *C9orf72*, chromosome 9 open reading frame 72; ASO, antisense oligonucleotides.

Whilst this post-translational modification can occur in over 50 potential sites, some of them (especially at the C-terminus, with regard to serine residues at position 409/410)¹³³ are believed to contribute to the aberrant behavior of TDP-43. The first TDP-directed kinase family described,¹³⁴ casein kinase 1 (CK-1), has been recently identified as a potential therapeutic target to be an interesting molecular target. Its inhibition was shown to reduce TDP-43 phosphorylation and to restore its cellular nuclear localization in human-based cell models from FTLD-TDP patients.¹³⁵

The impairment of cellular clearance mechanisms represents a core pathogenetic element in FTLD, as supported by the possible occurrence of mutations in genes encoding critical proteins in the ubiquitin–proteasome system (UPS) and autophagy–lysosome pathway (ALP) mediated degradation, such as *VCP*, *CHMP2B*, *TBK1*, *OPTN*, *p62/SQSTM1* and *UBQLN2*.¹²⁵ Both these processes regulate the clearance of TDP-43, although soluble and aggregated TDP are degraded primarily by UPS and ALP, respectively.¹³⁶ Among modules within the autophagy system, the dysfunction of the endosomal sorting complexes required for transport (ESCRT) machinery results in TDP-43 accumulation and mutations

of *CHMP2B*, a key component of this system, have been identified as causative of familiar FTD.^{137,138} While the disruption of CHMP2B perturbs endo-lysosomal trafficking, vesicle fusion and autophagic degradation, it also promotes TDP-43 hyperphosphorylation and insolubility by the control of the UPS-dependent turnover of CK-1.^{139,140} Given that therapeutics have been identified for CHMP2B this could represent a promising therapeutic axis.¹³⁹

On the contrary, TDP-43 itself plays an active role in the regulation of these mechanisms, modulating the expression of the phagosome machinery.¹⁴¹ Indeed, TDP-43 depletion disrupts the fine control on the mTOR-complex overwhelming the last stages of autophagic discharge and the accumulation of immature autophagic vesicles, ultimately inducing neurotoxicity as pointed out in animal models.¹⁴²

Targeting Progranulin Protein Levels

Progranulin is synthesized in the CNS by different cells, including neurons, astrocytes, microglia, endothelial cells.¹⁴³ It is a secreted protein and biologically active on its own or as a cleavage product (granulins), possibly having opposite effects, with anti-inflammatory properties for the former and pro-inflammatory for the latter.^{144,145}

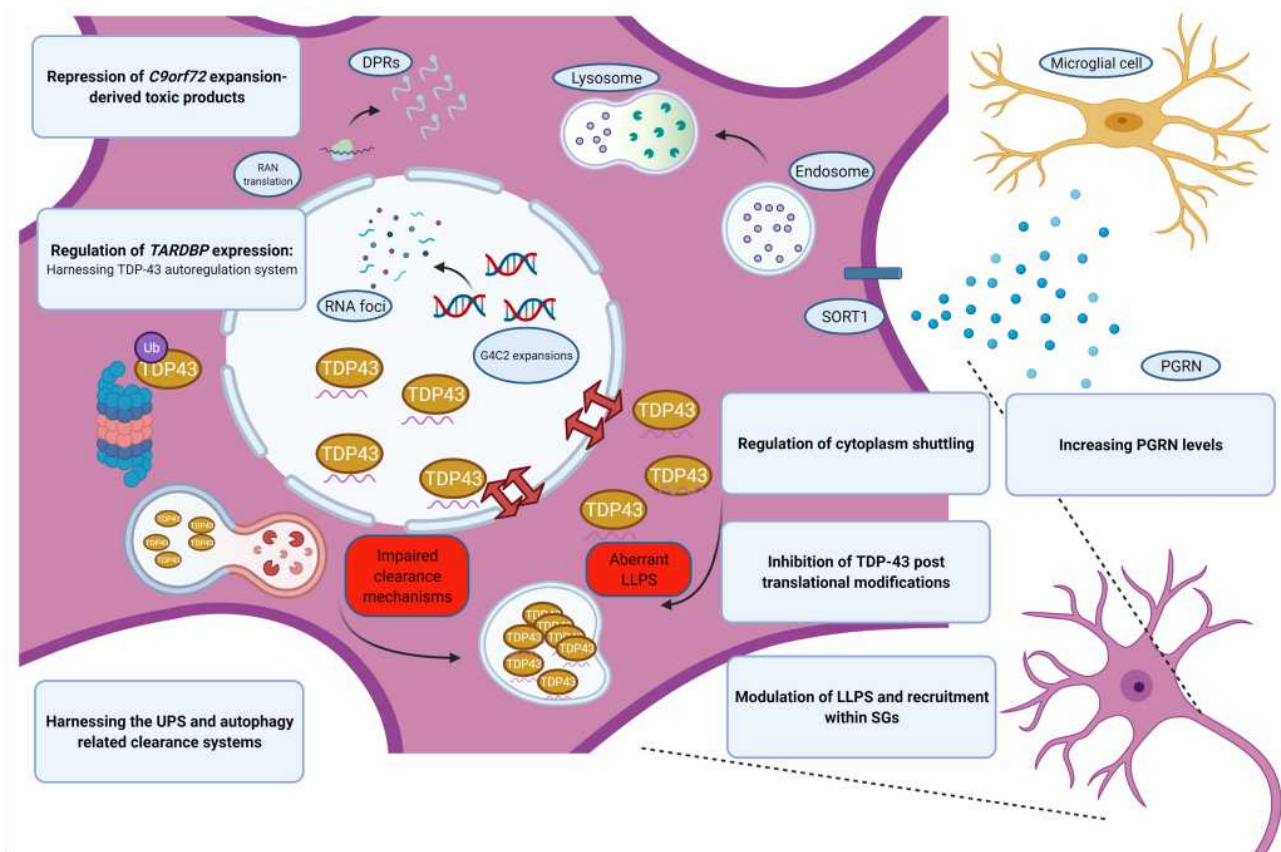


Figure 2 Aberrant TDP-43 biology in FTLD. Pathological model of TDP-43-associated neurodegeneration and the corresponding potential therapeutic approach (in blue boxes). Note the pathways involving *C9orf72* expansions and progranulin. Images created with BioRender.com.

Abbreviations: *C9orf72*, chromosome 9 open reading frame 72; DPRs, dipeptide repeat proteins; LLPS, liquid-liquid phase separation; PGRN, progranulin; RAN translation, repeat-associated non-AUG translation.

Therefore, as well as acting as microglial modulator, progranulin is also involved in neuronal survival, by trophic and neuroprotective functions, synaptogenesis and lysosomal dynamics.¹⁴⁶

Besides the already known high prevalence of *GRN* mutations in the FTD population, since haploinsufficiency of PGRN is the predominant mechanism leading to FTD, the rescue of its deficiency is an attractive objective for drug development. Both in vitro and in vivo models, targeting sortilin-1 (SORT-1) have identified SORT-1 inhibition as a positive regulator of progranulin protein levels. SORT-1, a Vps10 family member, is a PGRN binding protein involved in the extracellular uptake and delivery to the endolysosomal compartment.

Targeting cellular pathways addressing progranulin to lysosomal degradation by inhibition of SORT-1 has demonstrated, in vitro and in vivo models, to influence progranulin brain and serum plasma levels.^{147,148} According to the results in preclinical settings, healthy subjects and *GRN* mutation carriers were enrolled in a phase 1 trial

(NCT03636204) testing anti-human SORT-1 monoclonal IgG1 antibodies (AL001). The study showed a dose-dependent effect of AL001 in increasing progranulin levels to normal ranges.¹⁴⁹ While the study of AL001 in FTD patients carrying *GRN* mutation is ongoing in a phase 2 trial (INFRONT-2, NCT03987295), in July 2020 a phase 3 trial (INFRONT-3, NCT04374136) started enrolling both at risk and symptomatic FTD patients.

A different protein involved in lysosome trafficking, prosaposin, has been identified as a regulator of progranulin levels.¹⁵⁰ AZP2006, a compound thought to prevent tau-phosphorylation and to stabilize prosaposin-progranulin complexes, was approved for a phase 2 trial (NCT04008355) in PSP patients, which is currently ongoing.¹⁵¹

Also aimed at enhancing progranulin levels, the epigenetically active class of histone deacetylase inhibitors has emerged as a possible disease-modifying agent in FTD.¹⁵² The first of this class identified as a possible modulator of progranulin levels, suberanilohydroxamic

acid (vorinostat), was shown to normalize both the mRNA and protein levels in cellular models of *GRN* haploinsufficiency.^{153,154}

Still belonging to the same pharmacological class, but characterized by a better distribution within the CNS,¹⁵⁵ FRM-0334 was assessed in a phase 2 trial (NCT02149160) in 28 individuals with *GRN* mutations. The treatment did not produce significant changes in progranulin concentrations, although this failure might be explained by an insufficient FRM-0334 exposure.¹⁵⁶

Finally, genetic cases of FTD related to *GRN* haploinsufficiency represent an ideal field of application for vector-based gene therapies. Recently, the results of an intraventricular adeno-associated viral (AAV) vector administration in nonhuman primates paved the way for the development of AAV-based gene therapy in genetic FTD.¹⁵⁷ A phase 1/2, multicenter study (PROCLAIM, NCT04408625) is currently ongoing, evaluating the safety and efficacy of intra-cisternal PR006 administration, an AAV-9 vector designed to deliver the *GRN* gene.¹⁵⁸

Targeting the *C9orf72* Expansion

The exact way by which the pathological length *C9orf72* repeat expansions drives neurodegeneration is still debated, but three pathomechanisms are being suggested, including loss of physiological functions and gain of toxicity by RNA foci and DPRs, both derived by repeat-containing RNAs.¹⁵⁹

Directly affecting the production of ribonucleoprotein toxic species, the first in vivo study employing ASOs directed against repeat-enriched RNAs, showed their ability to mitigate RNA foci and DPR burden, with a corresponding improvement of phenotypical signatures.¹⁶⁰ From these encouraging results, a phase 1 trial (NCT03626012, NCT04288856) started enrolling *C9orf72* repeat expansion carrying ALS patients, to assess BIIB078, an ASO specifically designed to reduce only the repeat-containing *C9orf72* transcripts. Other efforts, focused on contrasting repetitions-containing RNAs, engage small molecules that stabilize G4C2 RNA repeats reducing RNA foci and RAN translation.¹⁶¹ Furthermore, some strategies are meant to target aberrantly upregulated components of the transcription machinery, while others work by harnessing RNA interference.^{162,163} Interestingly, the diabetes drug metformin has recently expanded its pharmacodynamic profile as a potential treatment in FTD-ALS. In *C9orf72* transgenic mice, metformin was shown to inhibit the RNA-

dependent protein kinase (PKR) phosphorylation, decreasing RAN translation and downregulating the effects of eukaryotic initiation factor 2 α (eIF2 α) phosphorylation, which is known to impair protein synthesis.¹⁶⁴ Since January 2020 a phase 2 trial (NCT04220021) is ongoing to evaluate metformin safety and efficacy in *C9orf72* ALS-FTD patients.

Therapeutic Approaches Based on Non-Invasive Brain Stimulation

Considering the high clinical and pathological heterogeneity of FTD, exacerbated by the lack of biomarkers accurately predicting in vivo tau or TDP pathology, an alternative approach to pharmacological treatments may be found in non-invasive brain stimulation.¹⁶⁵ Several techniques have been recently developed to enhance cortical plasticity, including repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), or to entrain and modulate cerebral rhythms with transcranial alternate current stimulation (tACS).

Repetitive Transcranial Magnetic Stimulation

rTMS is a method in which externally produced repetitive magnetic pulses lead to depolarization of cortical neurons. rTMS can be applied at various stimulation frequencies or as a patterned train of pulses, and has a modulatory effect on cortical excitability and may induce long-term potentiation (LTP)-like cortical plasticity.¹⁶⁶

There are only few reports describing the efficacy of this technique as a treatment in FTD.

In an open-label study, Antczak et al delivered 10 daily sessions of 10 Hz rTMS over the dorsolateral prefrontal cortex bilaterally in 11 patients with FTD (9 bvFTD, 2 nvPPA), and observed an improvement in cognitive functions and frontal behavioral inventory scores.¹⁶⁷

In another study, Cotelli et al applied a 20 Hz stimulation to both dorsolateral prefrontal cortices (DLPFC) in 10 patients with nvPPA, in a sham-controlled design. They observed an improvement in action-naming possibly due to the modulation of DLPFC pathways and a facilitation effect on lexical retrieval processes.¹⁶⁸

Other small case studies have shown similar positive effects of rTMS or deep rTMS in PPA patients.¹⁶⁹⁻¹⁷¹

Several trials with rTMS are currently underway and awaiting completion in PPAs (NCT04188067,

NCT03580954, NCT03153540, NCT04431401, NCT03406429).

Transcranial Direct and Alternate Current Stimulation

tDCS is a method based on the modulation of cortical excitability by a weak electrical current, which is delivered through scalp electrodes by a portable battery-powered stimulator. Repeated stimulation sessions are thought to generate long-lasting effects on cortical structures, induced by cortical plasticity.¹⁷²

tDCS has shown initial positive effects in a sham-controlled trial in 13 patients with bvFTD. By stimulating frontotemporal cortices bilaterally for 5 days, researchers showed an improvement in neuropsychiatric symptoms and visual reaction times up to 1 month after stimulation.¹⁷³

A recent much larger study, performed in 70 participants, has shown that a 2-week course with left prefrontal cortex stimulation may improve several clinical scores, particularly attention and executive functions, compared to sham stimulation, for up to 6 months.¹⁷⁴ Moreover, tDCS restored intracortical connectivity measures, evaluated with TMS, which have been shown to be impaired early in the disease course.^{175–191} Interestingly researchers found that presymptomatic mutation carriers improved in cognitive tests after tDCS.¹⁷⁵

tDCS has been found to enhance theory of mind, the ability to understand and predict other people's behavior by attributing independent mental states to them, in patients with bvFTD.¹⁹²

Several smaller studies have also shown an improvement in language in patients with PPA and PSP, also combined with individualized speech therapy, compared to sham stimulation.^{193–208}

In a recent meta-analysis, tDCS was shown to be more effective than rTMS in the treatment of PPA.²⁰⁹ Overall, the meta-analysis suggested significant benefits of both methods in PPA patients, with the optimal treatment protocol remaining unknown.

Several trials with tDCS are currently underway and awaiting completion in PPAs (NCT04046991, NCT02606422, NCT03728582, NCT04486586, NCT03887481, NCT04566731, NCT03805659).

Another approach is being used in the GIFTeD trial, which is currently evaluating the effects of alternate current stimulation at gamma frequencies (40 Hz) with tACS in patients with FTD (NCT04425148). So far, reports of

tACS as the clinical disease modifier in FTD have not been published.

Conclusions

The last few years have seen an improvement in the histological comprehension of FTLTD, allowing a more detailed classification among the main underlying neuropathies. Moreover, the strong genetic footprint has enriched the understanding of the disease mechanisms. Together with the results of genome-wide association studies (GWAS),^{210,211} new potential pathogenetic mechanisms have emerged, enhancing the arsenal of possible therapeutic strategies, including new insights from the role of autoimmunity.^{191,212–214}

However, despite this progress, a precise definition of the specific pathogenetic path is still far from reach. Indeed, as depicted in this review, although the biological cascades leading to the specific protein (ie, Tau, TDP-43, FET)-driven neurodegeneration are still to be fully elucidated, they occur along common pathophysiological pathways. These premises have prompted the development of strategies aimed at the recovery of the disrupted proteostatic microenvironment (ie, kinome, UPS, ALP), an alternative approach to the removal of pathological species through selective antibody-based therapies. Indeed, the multitargeted properties of small molecules are emerging as promising in reversing or correcting several pathological pathways involved in neurodegeneration, highlighting the role of a “one drug, many targets” approach.²¹⁵ The persistent failure of therapies based on clearance of deposited pathological species, adopted from the experience in different diseases, such as AD, highlights how future therapies should not only target the epiphenomenon of the pathological cascade but also understand and prevent the lack of physiological functions too. In support of this concept, the best results have been achieved by strategies targeting well-defined pathogenetic pathways (ie, *GRN* regulation), even if based on a more traditional “one drug, one target” paradigm.

In this perspective, given the possible convergence in the same clinical phenotypes, another challenging point in clinical trial settings is the availability of biomarkers able to distinguish between different underlying neuropathologies.

While in these landscape new treatments (ie, TMS and tDCS) are also emerging to reverse the secondary disruption of neuronal functioning, basic mechanistic and diagnostic research still holds the key to success in understanding and effectively treating this disease.

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