FTD Research and Drug Development Landscape

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The Association for Frontotemporal Degeneration

Opening the gateway to help and a cure

FTD Research and Drug Development Landscape
An Analysis of the Opportunities and Challenges

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Chapter 2 - The Development of Pharmacotherapeutics in FTD – Gaps and Opportunities

Acknowledgments

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Abbreviations

AD	Alzheimer's Disease
ADDF	Alzheimer's Drug Discovery Foundation
ADRC	Alzheimer's Disease Research Center
ADRD	Alzheimer's Disease Related Dementias
AFTD	Association for Frontotemporal Degeneration
ALS	Amyotrophic Lateral Sclerosis
ASO	antisense oligonucleotide
bvFTD	behavioral variant FTD
C9ORF72	chromosome 9 open reading frame 72 gene (or C9)
CBS	corticobasal syndrome
CHMP2B	chromatin modifying 2B
CNS	central nervous system
COMT	carboxyl-O-methyl-transferase
CSF	cerebrospinal fluid
DNA	deoxyribonucleic acid
DTI	diffusion tensor imaging
FDA	Food and Drug Administration
FTD	frontotemporal degeneration
FTLD	frontotemporal lobar degeneration
FTSG	Frontotemporal Degeneration Treatment Study Group
FUS	fused in sarcoma gene
GRN	progranulin gene
GWAS	genome-wide association study
HD	Huntington's disease
HDAC	histone deacetylase
IND	investigational new drug
iPSC	induced pluripotent stem cell
LMTX™	leuco-methylthioninium bis(hydroxymethanesulfonate)
lvPPA	logopenic variant PPA
MAPT	microtubule associated protein tau gene
MBCT	mindfulness behavioral cognitive therapy
MCI	mild cognitive impairment
miRNA	micro ribonucleic acid
MND	motor neuron disease
MRI	magnetic resonance imaging
NACC	National Alzheimer's Coordinating Center
NACC-FTLD	NACC frontotemporal lobar degeneration module
NAPA	National Alzheimer's Project Act
naPPA	nonfluent agrammatic PPA
NIA	National Institute of Aging

NIH	National Institutes of Health
NINDS	National Institute of Neurological Diseases and Stroke
OPTN	optineurin gene
PD	Parkinson's disease
PiB	Pittsburgh compound B
PET	positron emission tomography
PNF1	profilin 1 gene
PPA	primary progressive aphasia
PSP	progressive supranuclear palsy
RFP	request for proposals
RNA	ribonucleic acid
rTMS	repetitive transcranial magnetic stimulation
SAHA	suberoylanilide hydroxamic acid (Vorinostat)
siRNA	small interfering ribonucleic acid
SOD1	superoxide dismutase 1 gene
svPPA	semantic variant PPA
TARDP	transactive response element DNA binding protein gene
TDP-43	transactive response DNA binding protein 43 (or TARDP 43)
UBQLN2	ubiquilin 2 gene
VCP	valosin containing protein
WHO	World Health Organization

For an FTD-relevant glossary of terms:
AFTD Glossary

Executive Summary
FTD Research and Drug Development Landscape

Introduction

Frontotemporal degeneration (FTD) refers to a spectrum of clinical syndromes that demonstrate progressive degenerative changes in behavior, personality, language, cognitive skills and motor function (see Figure E-1). As a group, these disorders typically have brain atrophy in the frontal and/or temporal lobes. FTD is considered a young-onset dementia, occurring between the ages of 45 to 65 and is the most common dementia in those under 60 years of age [7, 16]. FTD is a rare disease (<200,000 in the United States) with an estimated 20,000 – 50,000 persons affected with behavioral variant FTD and primary progressive aphasias in the United States, plus another 10,000 when progressive supranuclear palsy and corticobasal syndrome are considered. Challenges in diagnosis, along with a limited number of population-based surveys make it difficult to provide an exact number [17, 18].

FTD patients display clinical symptoms that can be mistaken for other dementias or psychiatric disorders. The average time from symptom onset to accurate diagnosis is about 3.6 years compared to 2.7 years for Alzheimer's Disease (AD) [19, 20]. The behavioral variant of FTD (bvFTD) occurs in about half of all FTD patients while primary progressive aphasia (PPA), specifically the semantic variant and the nonfluent agrammatic variant are the next most common syndromes and represent about 40% of FTD cases observed. FTD can be associated with parkinsonism (supranuclear palsy and corticobasal syndromes) and the motor neuron disorder amyotrophic lateral sclerosis (ALS).

ALS is included on the FTD spectrum diagrams used in this review in order to reflect new findings that ALS and FTD can each occur in families with the *C9ORF72* gene mutation. When tested, about half of ALS patients demonstrate cognitive loss [21]. Although it may be premature to call ALS an FTD syndrome, categorization of movement disorder versus cognitive disorder in neurological diseases may change as new research unfolds.

Identified Gene Mutations in FTD

About half of all FTD patients are sporadic cases (no gene mutation or other causative agent identified). It is estimated that 40%-50% of FTD patients have familial FTD (but not all with an identified gene mutation) [22-24]. Between 10% and 20% of all FTD patients clearly demonstrate an autosomal dominant mode of inheritance with mutations in the progranulin gene (*GRN*), the microtubule associated protein tau gene (*MAPT*) or the chromosome 9 open reading frame 72 gene (*C9ORF72*) as the main risk genes [25-27]. These gene mutations do not associate with a single FTD syndrome, but may be found throughout the spectrum. However, the *GRN* mutation appears to associate with syndromes displaying asymmetrical brain atrophy patterns, while *C9ORF72* and *MAPT* mutations appear more likely to associate with syndromes displaying symmetrical atrophy patterns [28].

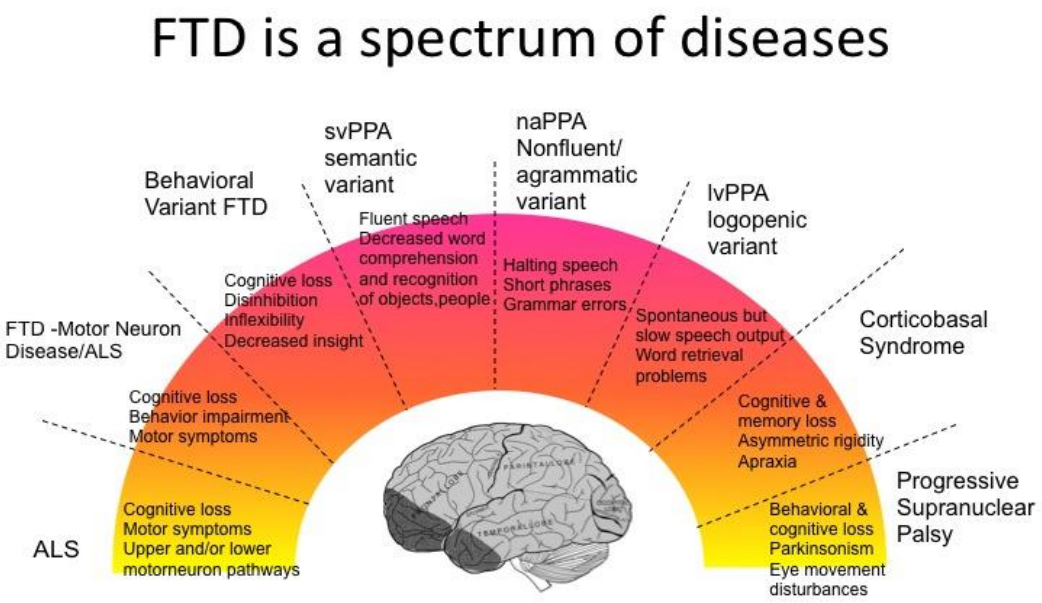

Figure E-1. FTD Disorders Have Significant Clinical and Pathological Overlap. FTD is a spectrum of clinical syndromes that display progressive degeneration of behavioral, cognitive, language and motor function. They include: behavioral variant FTD (bvFTD), the primary progressive aphasia (PPA) variants (semantic, nonfluent agrammatic, logopenic), corticobasal syndrome (CBS), progressive supranuclear palsy (PSP) and the FTD motor neuron variant (FTD-MND) also known as FTD-ALS (amyotrophic lateral sclerosis). ALS is included, as it is now recognized that about half of all patients show cognitive loss (and can share other features of FTD pathology).

GENE	FTD SYNDROME	PATHOLOGY Abnormal Protein Aggregates	LOCATION OF BRAIN ATROPHY
C9ORF72	bvFTD, ALS, FTD-ALS, some sporadic	TDP-43, p62	Symmetrical, frontal more than temporal
GRN	bvFTD, naPPA, CBS	TDP-43	Asymmetrical, frontoparietotemporal
MAPT	bvFTD, PSP, CBS	Tau (3R or 4R)	Symmetrical, anteromedialtemporal and orbitofrontal

Table E-1. Autosomal Dominant Gene Mutations in FTD. *C9ORF72, GRN* and *MAPT* are major autosomal dominant risk mutations for FTD. They can occur in different FTD syndromes and appear to associate with either a symmetrical or asymmetrical pattern of brain atrophy and anatomic location.

Misfolded Proteins – the FTD Proteinopathies

The aggregation of misfolded, dysfunctional proteins in specific brain regions is a common feature across many neurological diseases and acts as a pathologic hallmark of disease. In approximately 50% of FTD patients, the accumulation of mutant transactive response DNA-binding protein 43 (TDP-43) is the defining neuropathology, occurring in sporadic FTD and particularly in *C9ORF72* mutation-identified FTD and ALS. Another 30-40% of FTD patients have tauopathies, displaying a three amino acid repeat (3R) form of tau in bvFTD and PPA; or a four amino acid repeat (4R) which are sometimes found in PSP and CBS at autopsy (Figure E-2).

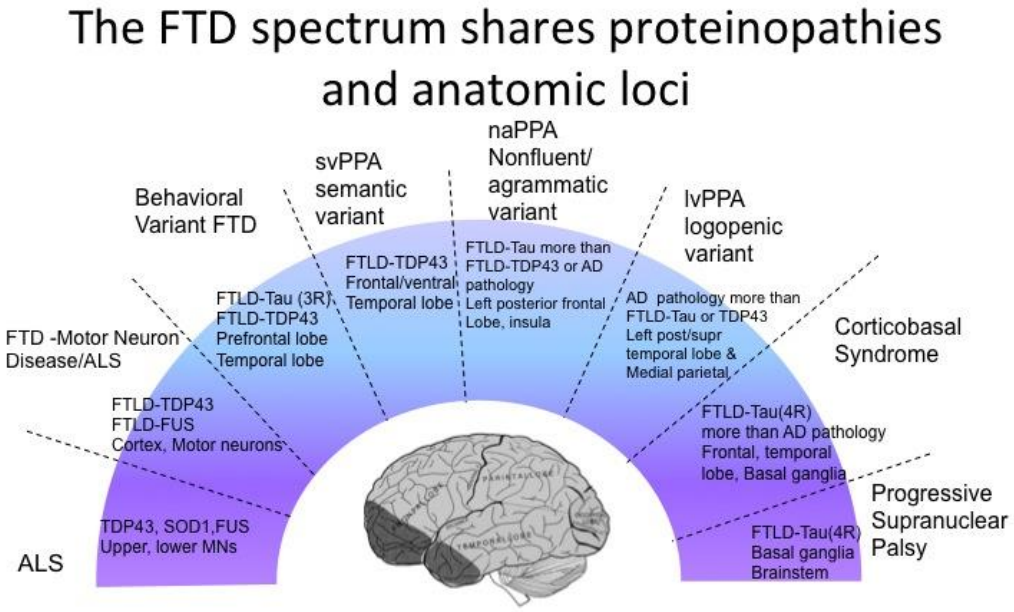

Figure E-2. Tau and TDP43 are the predominant protein aggregates found in neurons in FTD. Brain atrophy in the frontal and/or temporal lobes is a pathologic feature of the FTD disorders. Nerve cells (and in some cases glial cells) contain inclusions of misfolded proteins, mainly tau or TDP-43. Some syndromes feature subcortical degeneration (PSP, CBS, FTD-ALS, ALS), affecting deeper brain regions underlying the cortical layer, while others appear to be essentially cortical (bvFTD, svPPA, naPPA).

Epidemiology and Diagnostic Challenges

The prevalence of FTD in the United States is estimated to be between 4-15 cases per 100,000 [10]. The FTD disorders progress rapidly in comparison to Alzheimer's disease [29, 30]**.** A patient with bvFTD experiences an average delay of 3.6 years from the onset of symptoms and a clinical diagnosis of FTD [19]. The median survival for FTD patients from time of symptom onset is estimated at 6-11 years [10]. This highlights a key unmet need in FTD for reliable, sensitive and objective biomarkers, which would not only serve for diagnosis but also as measures of disease progression and drug efficacy.

Biomarkers and Disease Models- Prerequisites to Drug Development

Two essential requirements for pharmaceutical industry investment in drug development for a particular disease are: a) an understanding of the disease biology pathways (and therefore potential drug targets) and b) biomarkers to assess patient outcomes in clinical trials. A biomarker is an objectively measured indicator that reflects a biological or pathological process and can be used as a diagnostic tool or to gauge the effectiveness of therapeutics in clinical trials. The following tables summarize research, drug development and clinical trial gaps identified in the landscape review proper (see Table E-2a, E-2b, E-2c).

Table E-2a. A Summary Table of Identified FTD Research Tools: Current Options, Unmet Need, Development Initiatives

RESEARCH TOOLS	CURRENT OPTIONS	UNMET NEED	DEVELOPMENT INITIATIVES
DIAGNOSTICS (clinical)	Clinical criteria and neuropsychiatric, cognitive test batteries	FTD-specific molecular diagnostics for ante-mortem use	New study funded to develop and validate clinical rating scale for CBS
PET BIOMARKERS (imaging)	Amyvid, PiB rules out AD on imaging, not available for broad clinical use	Neuroimaging that can diagnose FTD and distinguish FTD subtypes	Multi-modal neuroimaging as correlate with progression; tau PET imaging in development
MR BIOMARKERS (imaging)	Structural MR imaging can detect regional atrophy to diagnose FTD syndrome and contributes to subtyping	Greater specificity for biochemistry of FTD	Potential new imaging sequences Use of multiple time points, modalities
CSF BIOMARKERS (cerebrospinal fluid)	Biochemical (fluid) markers used in research studies	Nothing for broad clinical use, no markers for FTD subtypes	Mass spectrometry for tau, CSF & blood markers in development by academia and biotech partners
ANIMAL MODELS	Dominated by gene mutation, proteinopathy-specific transgenic mice	Appropriate model: mice have not solved drug development for neurology in past 20 years, but industry still views as gold standard	*Drosophila, C.elegans*, zebrafish models to study molecular pathways of FTD

(Table E-2a cont'd.)

RESEARCH TOOLS	CURRENT OPTIONS	UNMET NEED	DEVELOPMENT INITIATIVES
iPSC MODELS (gene identified)	*C9ORF72, GRN, MAPT* human fibroblast and iPSC lines available from academic labs	Standardized gene mutation disease models for FTD	FTD iPSC consortium cell lines available from Coriell Cell Repository 2014, new interest from pharma industry
Cell lines in nongenetic FTD (sporadic)		Sporadic FTD or asymptomatic gene carriers	Some cell lines available
Therapies (technology)	Virus-based and other DNA-integrating technology to reprogram cells	Relatively high variability within cell lines	Non-integrating technology to reprogram cells to reduce variability

Table E-2b. A Summary Table of Identified FTD Therapies, Current Options, Unmet Need and Development Initiatives

THERAPIES	CURRENT OPTIONS	UNMET NEED	DEVELOPMENT INITIATIVES
DRUG PIPELINES repurposed	Repurpose existing drugs FDA-approved for other diseases	No FTD-specific drugs, disease modifying or symptomatic	Testing in preclinical FTD models and Phase I studies
IND investigational new drugs	IND for other neurological diseases, mainly AD	No current FTD-specific, small molecule IND	Possible opportunities with ALS, AD drugs now in pipelines
RNA-based		New RNA-based drug targets	anti-sense oligonucleotides in clinical trial, preclinical studies using microRNA and siRNA to target disease genes
protein aggregate clearance	LMTX™ orphan drug status, clears tau aggregates	Clear tau protein aggregates in FTD	TauRx bvFTD Phase 3 trial, antibody approaches to tau aggregates in development

(Table E-2b cont'd.)

THERAPIES	CURRENT OPTIONS	UNMET NEED	DEVELOPMENT INITIATIVES
CNS DRUG DEVELOPMENT	Pharma industry retreated from sector in last decade: expensive, few successful drugs	Dementias as a growing public health issue and no drugs	Smaller biotechs in rare disease sector see opportunity with RNA drugs
NON-DRUG THERAPIES	Lacking evidence-based medicine general consensus at present	Cognitive therapy, demonstrated short term improvement in AD	Repetitive magnetic stimulation, oxytocin nasal spray currently in research studies
		Speech language therapy	Web-based tool for PPA awarded AFTD pilot grant 2013

Table E-2c. A Summary Table of Identified Gaps in Clinical Trials: Current Options, Unmet Need and Development Initiatives

CLINICAL TRIALS ASPECTS	CURRENT OPTIONS	UNMET NEED	DEVELOPMENT INITIATIVES
trial design	Trials designed for large cohorts, long lifespan	Current design not created for rare diseases, neurological disorders, rapid progression	Increased engagement with NIH and FDA to develop more suitable designs the FDA will approve
patient selection, retainment	Inclusion/exclusion criteria, outcome measures continue to be refined for FTD	Accommodate patients with behavioral issues and/or rapid progression	Developing precise selection and stratification criteria
funding support	2 FTD rare disease consortia U54 grant applications submitted	Limited funding for FTD trials, shrinking NIH budget	Require new public-private sector partnerships

The Economic and Social Burden of Ill Health

Those afflicted with FTD face a greater level of impairment than those suffering from other dementias, and as a result, caregivers most often experience greater psychological burden. Because FTD is a young-onset disease it also places great economic burden on families as an FTD patient is often unable to continue working, and their partner may experience lost

income when required to act as the primary caregiver. It has been estimated that the yearly cost of caregiving for an Alzheimer's dementia patient is about $41,000-$51,000 in the United States [3]. The total monetary cost of Alzheimer's dementia to the United States in 2010 was estimated to be between $157-215 billion. FTD, Alzheimer's disease and the other dementias are quickly becoming a public health crisis with over 35 million people affected globally in 2010. This number is expected to double every 20 years if no therapeutic interventions are developed. This is a public health issue and an economic crisis that we cannot afford.

Chapter 1

A Brief Review of the FTD Clinical and Basic Science Research Literature

INTRODUCTION

Clinical and basic research in frontotemporal degeneration (FTD) has grown quickly over the past decade. In this review of the FTD research landscape, the term "FTD spectrum" will refer to a group of clinical syndromes that share common features of frontal and/or temporal lobar degeneration. Frontotemporal lobar degeneration (FTLD) refers to the neuropathology of the disease. The last two decades show a growing interest in FTD research, reflected in a steady rise in the number of studies published in clinical and basic science journals. Searching PubMed with a simple keyword group search of 'frontotemporal dementia' or 'frontotemporal lobar degeneration' or 'frontotemporal degeneration' for the period January 1994-December 2013 reveals the fundamental growth in peer-reviewed journal publications (Figure 1).

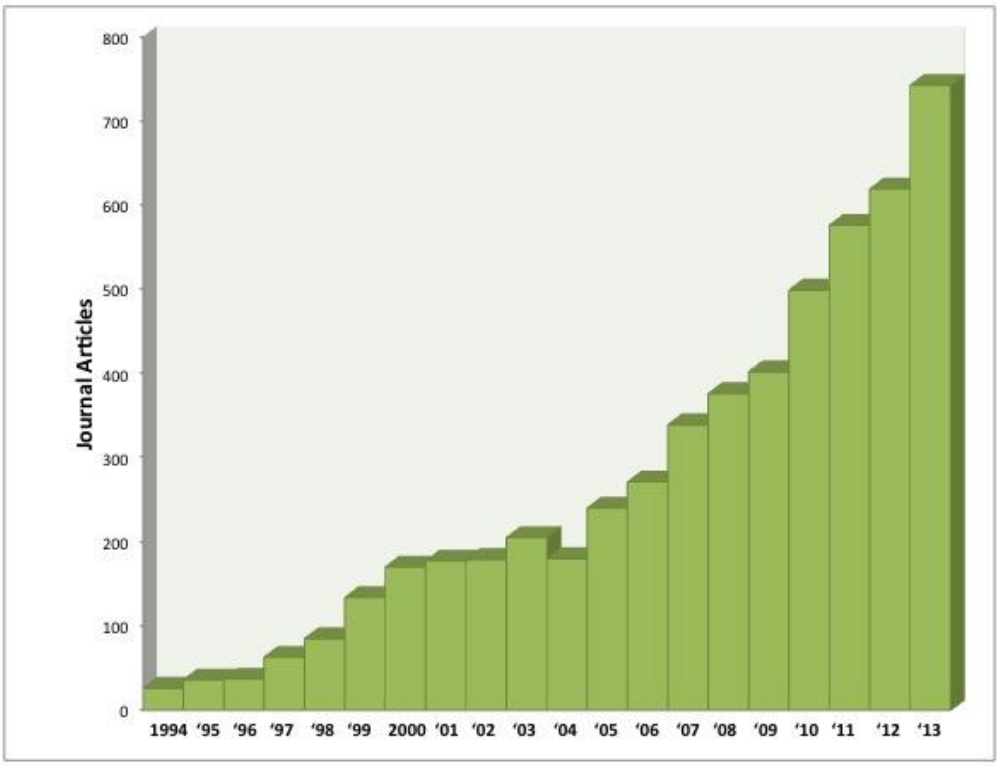

Figure 1. PubMed literature search shows an increasing number of FTD publications over the last two decades. 'Frontotemporal dementia or frontotemporal lobar degeneration or frontotemporal degeneration' was used as a simple group search term, from Jan. 1, 1994- December 31, 2013.

1.1 DIAGNOSIS

1.1.1. The FTD Spectrum

FTD diagnosis, clinical and basic research, patient management and drug development is challenged by the fact that FTD is really a spectrum of syndromes that are highly varied in their presentation of clinical symptoms that include behavioral changes, language impairment, loss of cognitive skills and motor dysfunction. With disease progression, FTD can present a more complex picture as new symptoms arise. For example, some behavioral variant FTD (bvFTD) patients will show early signs of cognitive loss or apathy, and then go on to develop signs of motor neuron disease or aphasia (loss of ability to speak or understand words, read or write). The FTD syndromes all share an insidious onset and clinical symptoms generally appear in the sixth decade of life. FTD is therefore called a young-onset dementia, compared to Alzheimer's Disease (AD) which usually occurs after age 65 and is referred to as a late-onset dementia. The FTD syndromes show progressive and dramatic brain shrinkage, mainly in the frontal and/or temporal cortical lobes of the brain. The FTD disorders have remarkably complex disease pathology; while they share a common neuropathology of abnormal protein aggregation in nerve cells, the type of proteinopathy can vary within one syndrome, for example, TDP-43opathy or tauopathy can occur in bvFTD. And, while PSP and CBS are tauopathies, FTD-ALS is a TDP-43opathy. In addition, FTD gene mutations do not associate with just one clinical syndrome, and some mutations follow an autosomal dominant pattern of inheritance but others do not. See Figure 2a-c for more details.

1.1.2. Consensus on Clinical Presentation

During the past decade, three important milestones were reached – a revised consensus for bvFTD clinical diagnostic criteria [31], a revised diagnostic criteria consensus and terminology for primary progressive aphasia (PPA) variants [32] and a consensus standardization of FTLD histopathology [33-35]. A 'definite' diagnosis of FTD is still based on neuropathology confirmation postmortem. Improved sensitivity and specificity for bvFTD diagnosis in clinical practice is now possible with the expansion of 'possible' and 'probable' FTD criteria. Patients with bvFTD experience progressive deterioration of behavior and cognition. This can appear as socially inappropriate behavior, apathy or even compulsive behaviors. Dietary changes that involve overeating or carbohydrate cravings can occur. The neuropsychological profile of a bvFTD patient includes impairment in executive function, seen as a loss of planning, organizational and judgment skills. There is a relative preservation of memory and visuospatial function in FTD compared to AD [7, 36].

Along with standardized diagnostic criteria, a more logical name definition of the PPA subtypes was proposed in 2011. These are now referred to as semantic variant PPA (svPPA or PPA-S), nonfluent-agrammatic variant (naPPA or PPA-G) and the logopenic variant (lvPPA or PPA-L). However, many researchers still use the 'old' terms semantic dementia and PNFA (nonfluent aphasia). FTD patients diagnosed with PPA must show progressive language impairment as the primary deficit in the first two years. Slow effortful speech with grammar or syntactic errors, sound errors and reduced sentence complexity

distinguish naPPA. Patients with svPPA experience progressive deterioration in naming and with single-word comprehension. Word retrieval is impaired in svPPA patients but they continue to have fluent speech and speak at a normal rate with minimal errors in grammar and syntax. Those with lvPPA display hesitant speech with difficulty in word finding, and sentence repetition but preservation of grammar and motor speech [32, 37, 38].

Similar efforts have been made to clarify the clinico-pathologic diagnostic criteria for progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) (see [39-41]). A clinical rating scale with six categories was created in 2007 for PSP [42]. Last year CurePSP and CBD Solutions announced a partnership to fund a project that will develop a clinical rating scale for CBS (see CurePSP-CBD Solutions press release).

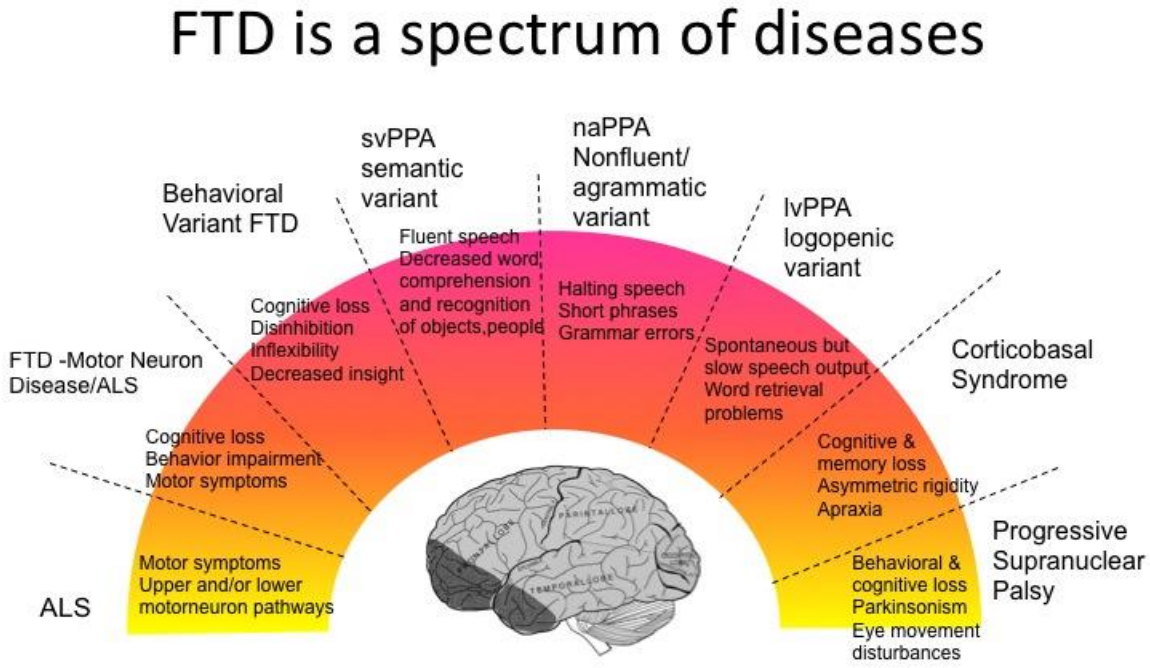

Figure 2a. FTD encompasses a group of neurodegenerative disorders that share significant clinical and pathological overlap. FTD is a spectrum of clinical syndromes that display progressive degeneration of behavioral, cognitive, language and motor function. They include: behavioral variant FTD (bvFTD), the primary progressive aphasia (PPA) variants, corticobasal syndrome (CBS), progressive supranuclear palsy (PSP) and the FTD motor neuron variant (FTD-MND) also abbreviated as FTD-ALS (amyotrophic lateral sclerosis). ALS is included, as it is now recognized that about half show cognitive loss (and can share other features of FTD pathology).

1.1.3. Symptom Overlap in Neurological Disorders

Overlap of clinical symptoms may occur between bvFTD and PPA syndromes with disease progression and the more widespread involvement of frontal and temporal lobes and adjoining regions. PSP and CBS can also display significant pathological and clinical overlap with bvFTD and PPA [41, 43-45]. About 15% of bvFTD patients develop the signs and symptoms of ALS and are referred to as FTD-ALS, known as FTD-MND (motor neuron disease) in Europe. About half of ALS patients also demonstrate cognitive impairment when neuropsychological testing is performed [7, 21].

The Challenge of Obtaining an Accurate Diagnosis in FTD

Misdiagnosis is a major problem for FTD patients and caregivers, and it can contribute to delays in accurate identification of an FTD syndrome. This is due in part to symptoms that appear to reflect aspects of other dementias, such as AD and mild cognitive impairment (MCI) or psychiatric disorders such as schizophrenia, bipolar disorder or depression. A decade-long retrospective survey of patients at a specialty clinic found that patients with bvFTD receive a prior psychiatric misdiagnosis more often (52.2%) than patients with AD (23.1%), svPPA (24.4%) or naPPA (11.8%). BvFTD patients were also more likely than patients with other neurodegenerative diseases to be diagnosed with bipolar disorder or schizophrenia [1].

Although memory loss is considered a distinguishing feature of AD, more papers are appearing in the literature reporting episodic memory loss in FTD [6] [9]. Although revised diagnostic criteria for bvFTD and PPA were implemented in 2011, considerable expertise with FTD and other cognitive disorders is required and it is less likely that the non-specialist can readily distinguish FTD from AD or psychiatric disorders. There is an urgent need for blood- or cerebrospinal fluid-based diagnostic markers to complement neuroimaging along with improved medical education to support the family physician in discriminating FTD and AD from other disorders.

Early Recognition of FTD

Early diagnosis of FTD is challenging given that initial symptom presentation can be highly varied. A patient with bvFTD experiences an average delay of 3.6 years from the onset of symptoms and a clinical diagnosis of FTD [19]. The median survival for FTD patients from time of symptom onset is estimated at 6-11 years [10]. The average survival time after diagnosis was calculated to be between 3 and 4 years [46]. FTD is recognized in the scientific literature as having a more rapid progression than AD [29, 30]. FTD is a young-onset dementia [47] and generally affects patients between 45-65 years of age, the average age of onset being 58 years [28]. Rapid progression of degenerative changes as well as delay in accurate diagnosis can create challenges for FTD drug development: organizing clinical trials becomes difficult from the perspective of identifying eligible patients and retaining them throughout the course of a therapeutic drug trial.

1.1.4. Prevalence and Incidence of FTD

Within the research community, the term FTD is used to include bvFTD and the three PPA variants. The related parkinsonism syndromes, PSP and CBS are considered, by some, as movement disorders. In reviewing the literature, published estimates of FTD incidence and prevalence may therefore reflect bvFTD and PPA only. If the full FTD spectrum is considered, there may be 60,000 cases of FTD in the United States. Prevalence, in epidemiology, is defined as the proportion or number of persons found to have a disease compared to the number studied and is often stated as number of cases per 100,000. Incidence is used to describe the number of new cases of a disease per year and so is an expression of rate rather than an absolute number. Epidemiology studies estimate FTD prevalence between 4 and 15 per 100,000 in the United States and Europe. Incidence of FTD in the United States is estimated at 2.7-4 per 100,000 person-years based on data from the United States and Europe [12]. While both genders may be affected, there appears to be a male dominance in bvFTD and svPPA, while females are predominantly affected in naPPA [36]. Reported regional variances in FTD prevalence may depend on geographic location, the survey method, and the contributing genotype when identified [48] [49-51].

Prevalence - FTD versus AD

FTD is a young onset dementia (before age 65) while AD is considered a late onset dementia (65 years and older). AD is the most common of all dementias and may account for 60-70% of all cases. According to the World Health Organization (WHO) 2012 Dementia report [2] FTD and other young onset dementias account for 2-10% of cases. The young onset dementias are considered as rare conditions. It was the consensus of experts in the WHO Report that a precise estimate of the prevalence of young onset dementias was not possible, since most research reports are based on the number of cases identified through a registry or clinic service and then divided by the latest census count for the region. There are very few population-based surveys for FTD and so the calculated prevalence numbers may be underestimates. In contrast, recent estimates of AD in the United States are based on in-home surveys of a segment of the much larger population-based longitudinal Health and Retirement Study [3].

Among those under 60 years of age, FTD is the most common cause of dementia and is as common as AD in those under 65 years of age. The age of onset for FTD ranges from the twenties to eighties, but 50s are the most common decade [7]. There may be 25,000-50,000 persons in the US with FTD [10-13]. There are about 5 million people with AD over the age of 65 in the United States, and about 200,000 under age 65 with early onset AD according to the Alzheimer's Association (Alz.org facts&figures). This difference in prevalence appears to have influenced drug development initiatives. The US pharmaceutical industry has 82 new medicines in development for AD and none for FTD [14].

1.2 BIOMARKER DEVELOPMENT - MISFOLDED PROTEINS AND GENE MUTATIONS

1.2.1. Proteinopathy - Accumulation of Abnormal Protein in FTD

The aggregation of misfolded, dysfunctional proteins in specific brain regions is a common feature of many neurological diseases and acts as a pathologic hallmark of the disease: for example amyloid and tau in AD, alpha synuclein in Parkinson's disease (PD) [52] and Lewy Body dementia. In approximately 50% of FTD patients, the accumulation of mutant transactive response DNA-binding protein 43 (TDP-43) in nerve cells (and sometimes glial cells) is the defining neuropathology (see Figure 2b) [28] and is also recognized as the most common proteinopathy. Another 30-40% of FTD patients have tauopathies. Their nerve cell inclusions contain either a three amino acid repeat (3R) form of tau, as seen in bvFTD and PPA; or a four amino acid repeat (4R), which can be seen in PSP and CBS. Another 10% of FTD patients have aggregates of fused in sarcoma (FUS) protein [36].

There are four recognized histopathological subtypes of mutant TDP-43 aggregation that can be found in bvFTD, ALS, and FTD-ALS [53]. TDP-43 is the dominant proteinopathy in ALS and FTD-ALS, while a smaller proportion of patients have accumulations of FUS protein. Although there are characteristic associations and affected nerve cell populations with protein aggregates in FTD subtypes, there is not a strict one to one relationship between protein pathology and clinical syndrome (see Figure 2b). Of note, the lvPPA is more likely to demonstrate an AD-like neuropathology than TDP-43 or tau aggregates [15, 54, 55]. In FTD, a single molecular pathology may contribute to more than one clinical phenotype [56, 57] as observed with *GRN* mutation and *C9ORF72* mutation families. Clinical phenotype, or observable characteristics, therefore appears dependent on the regional pattern of neurodegeneration rather than the molecular entity within the damaged cell [58]. A recent literature survey reported that different molecular pathologies (tauopathies, TDP43- and FUS-proteinopathies) display similar spatial patterns of affected neurons in the different layers of cortex [59]. These authors argued that the distribution pattern is consistent with their neurodevelopmental cells of origin and hypothesize that protein pathogenesis occurs along neuroanatomical pathways in neurodegenerative diseases [13].

The proteinopathies of neurological diseases may share a mechanism of initiation and generation of abnormal aggregation and misfolding within neurons that is reminiscent of how prions (the infective molecule of scrapie in sheep, "mad-cow disease" and Creutzfeld-Jacob Disease in humans) accumulate and spread through the brain [60-62]. A deformation of 'templating' can also occur in the FTD proteinopathies [63]. A misfolded mutant protein can act as a 'seed' converting normal proteins to an abnormally folded conformation [64]. Misfolded proteins cannot carry out their normal function in a cell and usually are removed by cellular 'housekeeping' pathways under normal conditions.

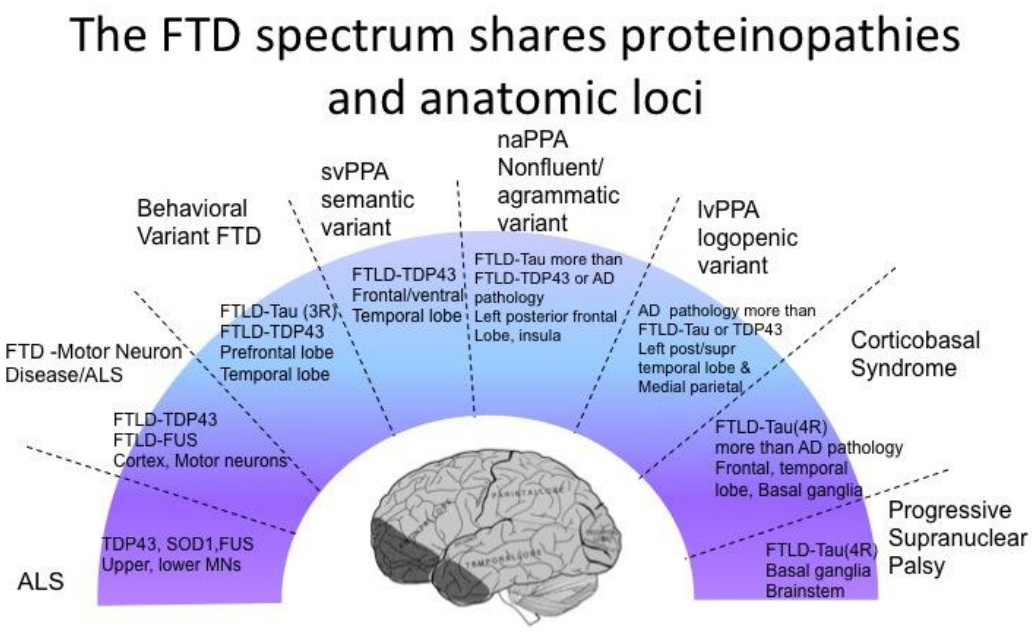

Figure 2b. Tau and TDP43 are the predominant proteinopathies and can be found throughout the FTD spectrum. Brain atrophy in the frontal and/or temporal lobes is a pathologic feature of the FTD disorders. Nerve cells (and in some cases glial cells) contain inclusions of mutant proteins, mainly tau or TDP-43. Some syndromes feature subcortical degeneration (PSP, CBS, FTD-ALS) while others appear seem to have mainly cortical lobe pathology (bvFTD, svPPA, naPPA).

Molecular Nexopathy: Proteinopathies as Drug Targets

A nexus can be defined as a connected series or group. Warren and colleagues [4] have proposed the term "molecular nexopathy" to describe the connection of misfolded proteins in FTD and fundamental characteristics of nerve cell networks. They argue that this pathological nexus is the anatomical disintegration of brain networks in FTD. As we look to the future of FTD research and other neurological diseases, integrating the molecular biology and biochemistry of the disease with various types of high resolution neuroimaging will allow us to better understand how functional brain circuits are disrupted to create the clinically observed features of behavioral, cognitive and motor dysfunction. The diseased or injured brain employs strategies of neural circuit redundancy, neuronal sprouting and network re-organization when under attack, and investigators will likely need to revisit the control processes that created the infrastructure, cell types and their precise grouping and connectivity during nervous system development [8].

The challenge to drug development is to design appropriate therapeutics that can target not just the aggregation and spread of mutant proteins, but to deliver them at the appropriate times of disease onset and progression. The other challenge will be to develop combination therapy drugs that can address the behavioral, cognitive and motor dysfunction that are often present in a single individual with FTD. We will need to understand the anatomical and molecular network connections between frontal, temporal and parietal regions in the normal brain and how FTD can lead to the re-organization and malfunction of such brain networks over time [15].

1.2.2. Gene Mutations – A Window on Clinical Heterogeneity and Geographic Variability

About half of FTD patients are sporadic cases (no gene mutation or other causative agent identified). It is estimated that perhaps 40%-50% of all FTD patients have familial FTD (but not all with an identified gene mutation) [22-24]. Between 10% and 20% of all FTD patients clearly demonstrate an autosomal dominant mode of inheritance with mutations in the progranulin gene (*GRN*), the microtubule associated protein tau gene (*MAPT*) or the chromosome 9 open reading frame 72 gene (*C9ORF72*) as the most common causes [25-27, 65]. Within this autosomal dominant inheritance group the mutation frequencies have been calculated as: *MAPT* – 9 to 21%, *GRN* – 4 to 23%, and *C9ORF72* – 18 to 30% [22, 66] (see Figure 2c). Genetic mutations in four other genes have been documented, but are a rare occurrence in only a few families. These genes are: valosin containing protein (*VCP),* fused in sarcoma *(FUS),* chromatin modifying protein 2B *(CHMP2B)* and transactive repeat DNA binding protein *(TARDBP*).

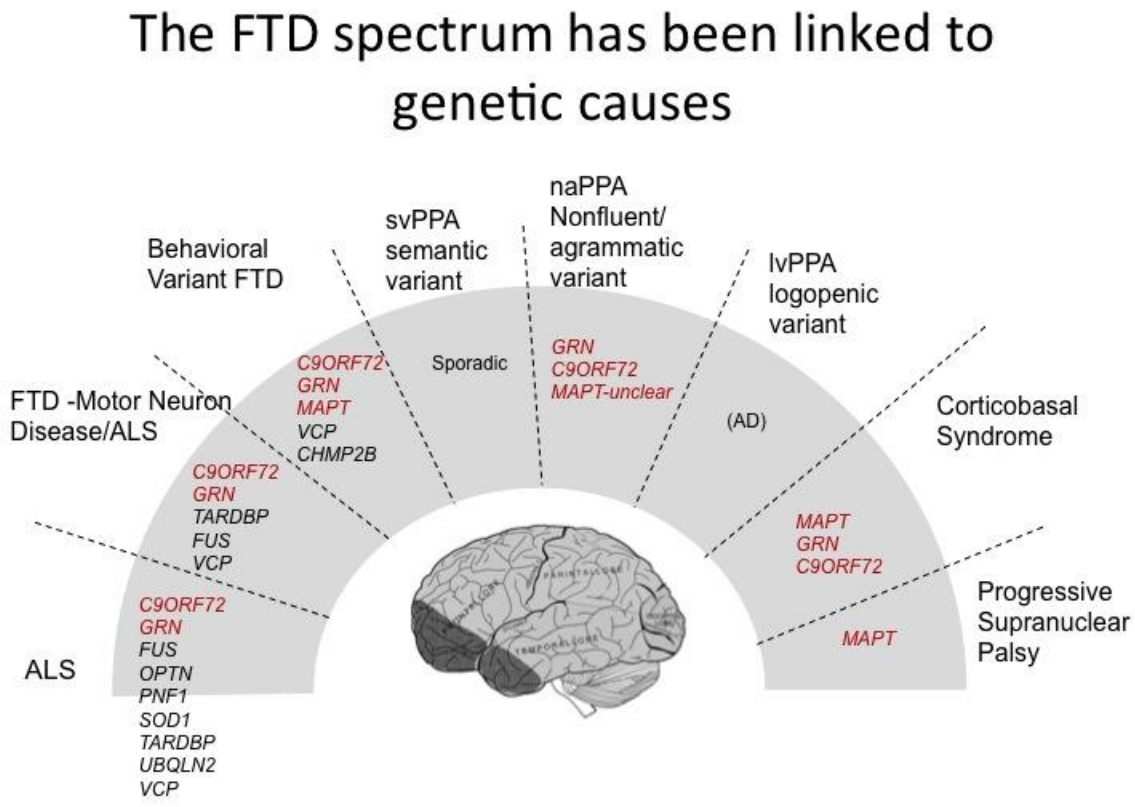

Figure 2c. Approximately half of all FTD cases have a hereditary component. Gene mutations in microtubule associated protein tau (*MAPT*), progranulin (*GRN*) and chromosome 9 open reading frame 72 (*C9ORF72*) are the most common mutations and are not restricted to any one FTD syndrome. Mutations have also been reported in fused in sarcoma (FUS), valosin containing protein (VCP) and chromatin modifying protein 2B (CHMP2B) also referred to as charged multivesicular body protein 2B. *C9* has been identified as the most common gene mutation in familial ALS.

Heritability appears variable across the different FTD clinical syndromes, with FTD-ALS showing the highest degree of autosomal dominance [67] followed by bvFTD [27].

Familial FTD studies in other countries point to a geographic variability associated with the autosomal dominant cases (see Table 1 – expressed as a percentage of all FTD cases) [25, 50, 51]. A recent Finnish study [68] demonstrated a high proportion of *C9ORF72* mutation FTD in their survey of cases (over 26%). Reports from India and Asia reveal that gene mutations representative of North American and European FTD cohorts (a predominantly Caucasian gene pool) are not necessarily representative of other ethnic populations [24, 69-74].

Table 1. Geographic Variation of Autosomal Dominant FTD Compared to All FTD Cases. Values were calculated as percentages of all FTD cases and reflect what appear to be regional differences.

Country	C9ORF72	GRN	MAPT	REFERENCE
USA	7%	5%	4%	[75]
Netherlands	9%	7%	10%	[76]
UK	7%	7%	6%	[77]

In addition to geographic variance observed with FTD gene mutations, other research studies have reported differences in clinical phenotype and neuroimaging in a group of sporadic FTD patients versus *C9ORF72* mutation carriers. *C9* mutation carriers were more likely to display psychotic features on clinical exam compared to sporadic bvFTD patients and demonstrated differences in white matter nerve fiber tract atrophy as revealed by diffusion tensor imaging (DTI) [6]. A Flanders-Belgian study [78] noted distinct clinical presentations in *C9ORF72* carriers compared with *GRN, MAPT* and non-mutation familial and sporadic FTD. A longitudinal study of sporadic and familial FTD in the United States reported that familial FTD patients might have a more rapid cognitive decline and different tauopathies compared to sporadic FTD [79]. As technology develops supporting our ability to diagnosis FTD accurately and earlier, and as we gather data from more countries, these percentage values of sporadic, familial and autosomal dominant FTD may change. And as we are better able to distinguish these groups, our knowledge of FTD natural history will likely expand to better inform clinical trial design.

FTD Gene Mutations: Challenges and Opportunities in Modeling and Drug Development

Research in the last decade has shown that there are currently three autosomal dominant genetic mutations that predominate in FTD: *C9ORF72, MAPT*, and *GRN*. Since the discovery of the candidate gene in 2006, later identified as *C9,* we have learned that it is the most common familial gene mutation found in ALS. Gene mutations play an important role as diagnostic biomarkers when FTD is suspected, and a genetic testing 'decision tree' has been proposed as an aid to clinical diagnostic screening [5]. The *C9ORF72*, *MAPT* and *GRN* mutations may provide an opportunity for the development of disease-modifying drugs tailored for individuals and families with such 'single gene (monogenic) FTD'. For drug development and clinical trial enrollment, the challenge remains that most FTD cases are sporadic or familial with no identified gene mutations.

Gene mutations have allowed scientists to develop animal and cell models of FTD in order to study the biological pathways involved in the disease. Animal models have allowed FTD researchers to learn more about tau and TDP-43 protein pathologies and are currently used to perform pre-clinical testing of experimental drugs aimed at preventing or eliminating protein accumulation in nerve cells. Advances in stem cell biology have led to the creation of induced pluripotent stem cells (iPSCs) obtained from gene mutation-identified FTD and FTD-ALS patients. Nerve cells created from the iPSCs are now being used to study molecular and cellular pathways in FTD and ALS. This technology may be 'game-changing' because for the first time we can use human FTD cells to model disease, screen potential drugs, and explore the molecular pathology of FTD.

1.3 BIOMARKERS

A biomarker, as defined by the NIH Biomarkers Working Group, is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [80]. In other words, it is an objective measurement that can quantify the medical state of a patient, can be observed from outside the patient, and can be determined accurately and reproducibly. Biomarkers therefore, can be used to:

i. Validate drug targets in clinical trials or pre-clinical models,
ii. Reflect the direct interaction of the drug with its target,
iii. Define the consequences of the drug-target interaction relative to pharmacokinetics (drug concentration-time course in body fluids),
iv. Act as correlates of the disease process – initiation, progression, modification, and
v. Select and stratify patients for clinical trials.

When used in a trial, a biomarker can be considered as a surrogate endpoint, and may act as a substitute for clinically meaningful endpoints but it does not necessarily capture how a

patient feels or functions. Biomarkers do not necessarily replace a clinical outcome measure but may have practical value as a measure of drug efficacy. The ultimate goal is to develop measures that capture clear and unambiguous data, whether it is a molecular biomarker or a clinical endpoint. Imaging biomarkers have been used in FTD to examine brain atrophy and may be useful for tracking disease progression (see [81] for review). To act as a surrogate endpoint, a biomarker must have scientific evidence that it consistently and accurately predicts a clinical outcome and so is trusted to stand-in for a clinical endpoint. When used this way, the biomarker can provide interim evidence about the safety and/or efficacy of a treatment while more definitive, clinical data is collected.

1.3.1. Biomarkers in FTD

Diagnostic markers currently in use for FTD include imaging and blood or cerebrospinal fluid studies (see Table 2). They may best serve a diagnostic role when used in a multi-modal approach to achieve as near as possible a 'definite' diagnosis of FTD in the living patient [82]. Of note, a number of these markers are not in broad, clinical use, but may be available only at specialty clinics or as part of a research study. And some of these markers, particularly those using advanced technologies and instrumentation, may not be available in all countries. At present clear guidelines for biomarkers in FTD do not exist, but it has been suggested that criteria developed for AD biomarkers may be useful in developing FTD biomarkers [83] in order to progress in creating disease-modifying therapeutics.

Table 2. Diagnostic Markers in Current Use in FTD

Marker	Types	Purpose
Clinical FTD markers	Behavioral, cognitive, motor symptoms	Can identify FTD syndrome and assist in ruling out non-FTD disorders (not conclusive)
Gene mutations	Autosomal dominant	Can provide a 'definite' FTD diagnosis, distinguish mutation carriers from sporadic, aid in clinical diagnosis
Proteinopathies	Neuropathology	Definitive diagnosis at autopsy based on neurodegeneration and histochemistry of mutant proteins
Cognitive/behavioral	Neuropsychological test profiles	May help distinguish FTD from AD and other disorders
Molecular Imaging	Amyloid imaging with PET	Detects amyloid deposits, distinguishes AD from FTD
Structural Imaging	Quantitative structural imaging	Atrophy patterns aid FTD syndrome identification and can distinguish FTD from AD and other disorders
	Diffusion Tensor Imaging (DTI), white matter	Distinguishes bvFTD patients from controls
Functional Imaging	FDG-PET	Hypometabolism, distinguish FTD from AD, distinguish FTD syndromes
	PET - tau imaging	Benzothiazoliums in development can detect tau inclusions in AD
Biochemical - Blood and CSF proteins	Pathogenic proteins (proteinopathies), neurofilament proteins, inflammatory proteins Not available for general use, and require better detection methods	Distinguish FTD syndromes, tauopathy vs TDP-43, at risk FTD gene mutations *GRN, MAPT, C9ORF72*

Diagnosis: Challenge and Opportunity for Biomarker Development
FTD presents a diagnostic challenge with clinical symptoms that can be mistaken for other neurological disorders. Abnormal protein aggregation in nerve cells is a common feature in neurodegenerative diseases, but the FTD disorders do not have just one protein pathology. The majority of FTD cases accumulate tau or TDP-43 protein in nerve cells, and so define the disease neuropathology. TDP-43 and tau protein inclusions also occur in other diseases like ALS and AD. Biomarkers that can detect the earliest pathological changes in the FTD proteinopathies, or that can predict pathological change are important for diagnosis, but they must also discriminate FTD from other diseases. Blood-based or CSF-based biomarkers are also needed for clinical trials to identify appropriate patients, and provide a measure of disease progression and drug efficacy.

Challenges in diagnosis that arise from heterogeneous clinical symptoms point to the need for accelerated research and development efforts in the FTD biomarker sector. A significant challenge shared with other neurodegenerative diseases is that of early diagnosis, before clinical symptoms appear. This is a challenge that must be solved if disease-modifying therapies are to be successful. By the time clinical symptoms appear in neurodegenerative diseases, it is estimated that only about 20% of the nerve cells in the affected region remain. As our understanding of FTD increases, it may be possible to develop biomarkers that are distinct from protein pathology and that may detect earlier indicators of the disease process or initiation. New data from DNA and RNA modulation in FTD, and the role of DNA/RNA binding proteins like TDP-43 may lead the way. Along with the need for novel biomarkers are longitudinal studies of FTD natural history that will supply critical data on disease progression such as the NIH trial "Natural history and biomarkers of ALS and FTD caused by the *C9ORF72* gene mutation" (see ongoing study at Clinicaltrials.gov).

1.3.2. Outcome Measures – Biomarkers versus clinical endpoints

Biomarkers are a quantifiable measure of a biologic process, but they do not necessarily correspond to the patient's clinical state or experience. Clinical endpoints are variables that capture how a patient feels, functions or survives. Ideally a clinical endpoint should provide unambiguous data as to whether an intervention was effective or not, and whether it is safe or unsafe. One study attempted to help define and initiate guidelines for a prospective FTD trial, recruiting bvFTD and PPA patients (using Neary criteria) and determining what would be the most suitable instruments for outcome measures [84]. The chosen measures were: a global assessment of change, an FTD-specific clinical dementia rating, behavioral scales (the Frontal Behavioral Inventory (FBI) and the Neuropsychiatric Inventory (NPI)), and a cognitive battery of tests that could be completed in less than one hour. Outcome measures are still a matter of debate in FTD trial design, and as we continue to learn more details from multi-modal studies that reveal differences in clinical symptoms, focal atrophy, mutant proteins and gene mutations between familial and sporadic FTD, this will likely inform the development of suitable outcome measures and biomarkers for drug

development and trial design. A list of current FTD biomarkers known to be in development has been summarized in Table 3.

Table 3. FTD Biomarkers in Development

Developer	Biomarker	Proposed Use
Emory University	CSF-based	Distinguish FTD subtypes
U Penn Perelman Medical School	Multi-modal neuroimaging (MRI+DTI)	88% diagnostic accuracy to detect FTD versus AD
	Neuropsychological test battery for memory, word generation and conceptual flexibility	85.7% correct diagnosis of bvFTD and 83.3% correct diagnosis of MCI
Quanterix	Single molecule array technology (SIMOA)	Ultrasensitive assay for circulating tau
Mayo Medical Clinics and A&G Pharmaceuticals	Circulating progranulin test for FTD	Confirm *GRN* mutation in suspected bvFTD patients

1.3.3. Patient Registries for FTD

There is a growing interest in patient registries, particularly in rare diseases. Registries can be viewed from various perspectives: as a means to support clinical trial enrollment, to encourage the pharmaceutical industry to engage in drug development for rare diseases, and to track patient data in longitudinal and cross-sectional studies, or as a public health tool for observing defined populations and even as a means to examine the risk-to-benefit profile of drugs used in neurology patient management [85]. Some patient-powered registries have been highly successful, such as that of the Hereditary Disease Foundation, co-founded by Nancy Wexler and DuchenneConnect, initiated by Pat Furlong, the founder of Parent Project Muscular Dystrophy [86]. However, as with any database, the quality of the data collected and the purpose of the data collection can determine the methodologies and analytical tools employed as well as inherent biases associated with these parameters [87]. Medical societies are also investigating the creation and need for clinical data registries to provide feedback on quality health care delivery and measure performance [88]. A survey or outcome measure of the extent that patient registries are used by the drug development industry would be informative, particularly what type of registry is regarded as useful and whether a patient registry is considered a requirement for drug development in rare diseases. The PPA Connection hosts an international registry for FTD aphasia patients (see International PPA Connection) but at present, a comprehensive FTD disorders registry is lacking.

1.4 RESEARCH MODELS OF HUMAN DISEASES

1.4.1. Animal and Cell Models of FTD

Models of human disease, whether a mouse, rat, fruit fly, nematode or cultured cell, allow us to ask questions and get answers about the underlying biology of disease. They also

serve as a means to screen drugs in pre-clinical studies for the development of disease-modifying therapeutics. Models of FTD have been created based on identified gene mutations. Currently there are no models that recapitulate sporadic FTD, and no known environmental stimulus, toxin exposure or other event that can be used to create a non-genetic mutant model such as those available in other diseases like PD or multiple sclerosis. The mutation-based models have provided remarkable insights on the pathogenesis of FTD proteinopathies and are used to screen potential therapeutics that can be assessed for efficacy via pathology, molecular, biochemical or behavioral assays. However, as with other diseases, no model fully captures the pathology, behavior and biochemical signature of a human FTD.

Transgenic mice. There are several transgenic mouse models that recreate different tauopathies, as well as models of TDP-43 proteinopathy, particularly the more recent *GRN* mouse models [88-90]. There is a long publication history of tauopathy models for AD and FTD [91], with new models focusing on tau, TDP-43, progranulin, FUS, VCP and CHMP2B [92]. Transgenic mice are valuable research tools and have an established use as drug screening, target validation and proof of concept models in the drug development process. Since mice have a short lifespan (about 2 years) they are also useful to study disease progression. Although rodents have not evolved the complex cortical structures characteristic of the human brain, they can still serve as useful behavioral models in FTD in that some large scale networks, such as the salience network of the human brain [93], has a mouse counterpart. Mice also provide useful models of social behavior that can be used to study FTD-relevant questions.

Drosophila. *Drosophila melanogaster* (the common fruit fly) models have proven an excellent route to study the toxicity of FTD (and other) proteinopathies [94]. Flies transfected with human wild type and mutant tau proteins conveniently show degenerative changes in their retinas, as well as having locomotory dysfunction and shortened lifespans. The fruit fly has also proven to be a practical model for high throughput screening with the advantage of short life cycles, a sequenced genome and many fly models of human neurological disorders; *Drosophila* may help speed up FTD drug screening and target validation.

Caenorhabditis elegans *(C.elegans)* is a nematode (round worm) with a simple nervous system and a sequenced genome and is a proven powerhouse in neuroscience research, often providing the leading edge in understanding the molecular biology of neuronal degeneration [95]. *C. elegans* mutants have been used to model tauopathies and, like Drosophila, are also being considered by the biotech and pharmaceutical industry as a screening tool in drug discovery in AD drug development [96].

Zebrafish (*Danio rerio*) are a relative newcomer to neurological diseases modeling but they have been used extensively for studying developmental pathways and gene mutations that can be observed visually in a transparent embryo raised in multi-well plates, which allows for high throughput screening. Zebrafish have been used to model tauopathies as well as TDP-43 proteinopathies [97].

Cell monolayer cultures Neuronal or glial cell cultures can be useful as an inexpensive model to tease out and study cell-specific biochemical pathways and early discovery proof of concept and drug screening studies. However, these cells are often obtained from rodent brain, which may not recapitulate all aspects of human brain cells. Commercially available human neuronal and glial cell lines are also popular, but are in essence tumor cells, such as the PC12 cell line which has been used extensively in Parkinson's disease research.

1.4.2. Induced Pluripotent Stem Cells (iPSCs) from FTD and FTD-ALS Patients

Modeling of neurological diseases has taken a great leap forward with advances in cell culture technology. New technology has contributed to the development of adult human tissue cells that can be converted to a stem cell-like state with the capacity to differentiate into any kind of cell (pluripotency). Fibroblast cells, conveniently obtained from skin biopsies, are reprogrammed to become iPSCs. Nerve cells and glial cells can then be induced to develop from these adult stem cells. FTD gene mutation-specific iPSC lines effectively provide a "disease in a dish" model that allows us to study cell pathways representative of those in specific nerve cell types [98]. These iPSC-derived neuronal lines have already shown us that RNA metabolism is altered in the *C9ORF72* gene mutation carriers and creates toxic RNA that leads to nerve cell death [99]. The National Institutes of Health (NIH/NINDS) has created disease-specific iPSC consortia to facilitate research in FTD, ALS, PD and HD. These cells have the potential to be valuable disease models as well as a drug-screening tool that might answer questions about new drug efficacy in humans, at a pre-clinical test level. The latest advance in stem cell biology and human disease was reported in January 2014 - iPSCs were created from frozen, biobanked AD, ALS, PD and HD brains [100].

1.4.3. The Biology of FTD

Our understanding of the biological mechanisms that contribute to FTD has grown considerably in the last decade. New investigators drawn to the FTD field, advances in research tools and a growing awareness of commonalities in the neurodegenerative mechanisms across diseases are current drivers of research progress. The recent discoveries of shared TDP-43 and FUS proteinopathies in FTD and ALS, and the contributions of large numbers of *C9ORF72* gene hexanucleotide repeat expansions to disease pathology are important breakthroughs that illustrate convergence in pathogenic mechanisms in neurodegenerative diseases. FTD and ALS may be members of a disease spectrum (or process) with shared clinical, pathological and mechanistic disease features. Both dysfunctional protein homeostasis and RNA metabolism play a role in neurodegeneration in FTD and ALS [101, 102]. Interest in the role of RNA in neurological diseases has grown quickly. Micro RNAs, are small, non-coding RNAs that modulate different messenger RNAs that contain complementary target sequences. Dysregulation of microRNA is now implicated in neurodegenerative diseases and, in particular FTD with progranulin, TDP-43 and now tau pathology [103]. MicroRNAs are fast becoming a new drug discovery target.

These new discoveries offer the potential for defining new drug targets for FTD and ALS. Addressing these targets may prove beneficial for drug development in other proteinopathies particularly if they share mechanistic pathways in protein misfolding, aggregation and progression through neural networks [52, 104]. Autophagy is also implicated in neurodegenerative disease pathology and may be dysfunctional (or overburdened) as these cell homeostasis mechanisms attempt to remove the toxic aggregates and dysfunctional organelles of neurodegeneration. Compounds that interact with autophagic pathways may therefore prove useful in FTD drug discovery [105].

FTD clinical and basic science research is in a robust growth phase and can provide new opportunities for collaborative research and academic-industry partnerships.
The number of high quality FTD research publications has increased steadily every year for the last two decades. FTD researchers, many of them members of the AFTD Medical Advisory Council, are at the leading edge of research trends in:

1. Biomarker development for dementias that support definitive diagnosis and can distinguish FTD from other dementias
2. Contributing to and leading knowledge creation of the biology of mutant proteins, seeding of protein aggregates in nerve cells to understand disease progression
3. Aggregation of mutant proteins in nerve cells in FTD and other neurodegenerative diseases
4. Gene mutation discovery in FTD and other neurological diseases
5. Creating iPSC-derived lines that represent the major 'at risk' FTD gene mutations and discovering new RNA-dependent toxic pathways relevant to FTD and other neurological diseases
6. Building a better stem cell with the latest in molecular biology tools that will lead to more robust iPSC-derived nerve cells and glial cells to study FTD and ALS disease pathways
7. Creating new research tools that are more sensitive in detection of FTD biomarkers
8. Leading the way in advanced neuroimaging to understand large neural circuits that underlie complex behaviors
9. Actively contributing data and tissue into publicly-supported central repositories that are available to all scientists in order to advance FTD research and
10. Leading global efforts in clinical trial development and patient engagement

A new study in transgenic Drosophila and mice and Alzheimer's disease argues that tau-induced neurodegeneration occurs via heterochromatin loss and that genetic rescue of this loss reduced neurodegeneration [106]. This may have relevance to FTD tauopathy. Another advance in FTD and other neurological disorders is a growing awareness of the role that systemic- and neuro-inflammation may play in the disease process and the potential contribution of microglia in modulating the inflammatory status of the brain [107, 108]. The *GRN* mutation is of particular interest in FTD as a means to understand the

relationship between this particular mutation and neuroinflammatory pathways. Research in inflammation pathway regulation could potentially lead to new biomarker development or drug discovery targets [109-111]. Microglia (and neuroglia in general) may have a role to play in neuronal atrophy and disease progression. Glia behave as support cells and can guide neurons to their appropriate destinations in the brain during early development, provide nerve growth factors to developing and damaged nerve cells and modulate the inflammatory status of the brain [112].

GAPS in FTD Research and Development

1. Disease-modifying and symptomatic therapies for FTD
2. Molecular diagnostics for FTD that support accurate diagnosis and can distinguish FTD subtypes
3. A true understanding of the prevalence and incidence of FTD that incorporates geographic and ethnic diversity
4. Biomarkers that can identify early stage (or presymptomatic) FTD and biomarkers that can act as surrogate outcome measures and objectively measure drug efficacy and disease progression
5. Consensus on FTD models that can replicate disease pathology, robust human cell-based models that are reproducible and can support fundamental biology research as well as facilitate pre-clinical drug development efforts
6. Patient engagement in clinical trial development and registry efforts
7. Clinical trial design that is appropriate for a rare disease like FTD with limited number of patients available, symptoms that can impact informed consent, rapid disease progression, consensus on outcome measures
8. Developing international collaboration for clinical trials and agreements for open data sharing among investigators and other stakeholders to advance FTD research

1.4.4. NAPA – The National Alzheimer's Project Act (NAPA) and ADRD – Alzheimer's Disease-Related Dementias

NAPA was initiated in 2011 and set goals for research, care and services for AD and related dementias. The primary research goal was "to prevent and effectively treat Alzheimer's by 2025". A full range of pharmacological and non-pharmacological interventions are to be considered in achieving this ambitious goal along with finding ways to translate research findings into proven interactions and then into clinical practice. In May 2013 the ADRD Workshop was organized by NINDS in collaboration with the Alliance for Aging Research, ACT-AD, the Alzheimer's Association, AFTD, and US Against Alzheimer's. Key recommendations for research priorities were presented by leading clinicians and neuroscientists to address FTD, Lewy Body, vascular and mixed dementias.

NINDS Council discussed and approved the ADRD Conference 2013 Report in September of 2013 with these additional comments in a letter to the NAPA Council:

a) "Biomarker and mechanistic discoveries for synucleinopathy, tauopathy, TDP-43opathy, etc., are critically important for FTD and Lewy Body Disease, as they are necessary to inform the design of cohort studies and clinical trials.
b) For FTD, efforts designed to increase understanding of the mechanisms underlying TDP-43opathy, FUS and C9ORF72-related neurodegeneration are as important as efforts to increase understanding of mechanisms underlying tauopathy. "

ADRD Conference Recommendations for FTD Research

Basic Science – Pathogenesis and Toxicity

1. Clarify the mechanism of tau pathogenesis and associated neurodegeneration.
2. Develop better FTD in vivo and cell-based model systems.
3. Determine the molecular basis for C9ORF72 expansion and GRN-related neurodegeneration.
4. Determine the mechanisms of TDP-43 and FUS pathogenesis and toxicity

Clinical Science – FTD Clinical Discovery, Tools and Cohorts

1. Expand efforts to genotype patients with FTD and identify new genes.
2. Develop FTD biomarkers for diagnosis and disease progression.
3. Create an international FTD clinical trial network.
4. Understand phenotypic heterogeneity and natural history.

Chapter 2

The Development of Pharmacotherapeutics in FTD: Gaps and Opportunities

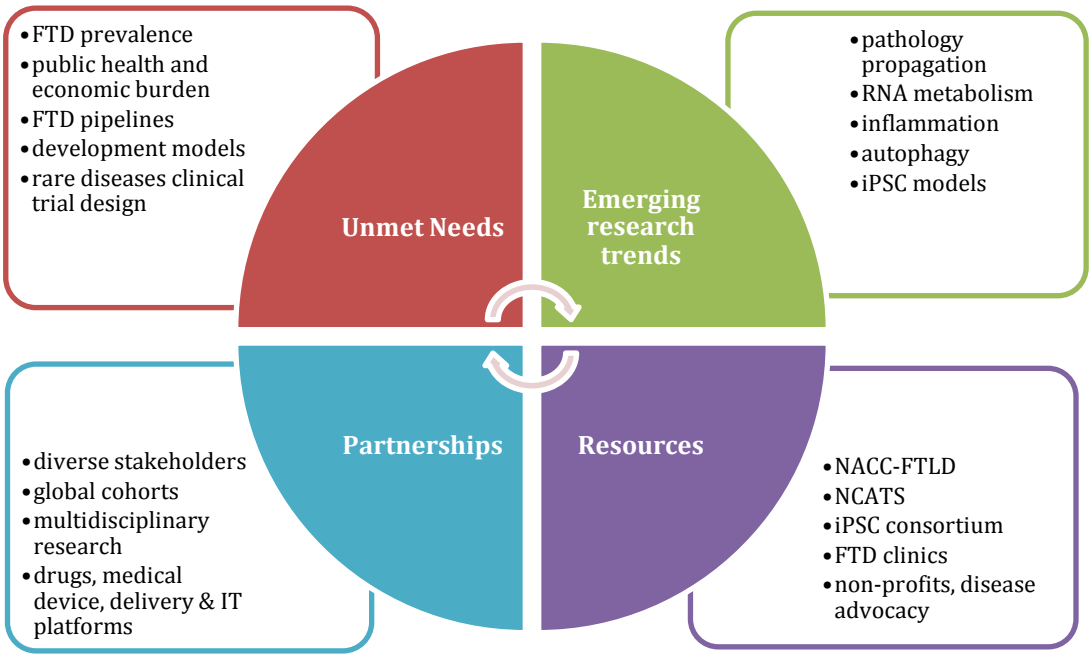

Figure 3. A Simple Schematic of Four Drivers of FTD Drug Development

2.1 UNMET NEEDS

Currently, there are no FDA-approved medications for FTD and prescribing physicians are limited to medications developed for other diseases, relying on data from small case studies and professional judgment [113] [114]. A recent review of existing pipelines that make up the global markets for treatments of dementia and movement disorders [115] does not recognize the FTD disorders of bvFTD or PPA; instead they are considered synonymous with Pick's Disease. CBS and PSP are recognized as separate indications in this market report and listed under movement disorders. Chapter 2 of the FTD research landscape review will attempt to provide a critical analysis and identify gaps and opportunities that exist in FTD therapeutic development.

2.1.1. FTD Prevalence and Incidence – Dementias as a Public Health Issue

Determining the prevalence and incidence of FTD is a challenge. Most epidemiological studies only include bvFTD and PPA in their estimate, and with a qualifier that the numbers

provided may be underestimates given the difficulty of obtaining an accurate diagnosis and likely under-reporting of the disease. Most estimates are obtained from specialty clinic patient records and not as a survey of the general population. One study of FTD prevalence in a geographically defined population, determined from case records of 3 hospitals in Cambridge, U.K., reported a prevalence of 81 per 100,000 in the 45-65 years age range [16]. In contrast, a review of 15 published surveys reported an average FTD prevalence of 17.6 per 100,000 [116]. A community study of two London boroughs by Harvey and colleagues (see [117]for review) reported 98 young-onset dementia cases per 100,000. This variation in FTD prevalence values highlights the need for standardization of survey taking, the need for population-based, longitudinal studies that may more accurately estimate FTD prevalence, and the need for diagnostic markers to unequivocally identify FTD.

The World Health Organization (WHO), in cooperation with Alzheimer's Disease International, released their global consensus report, "Dementia – A Public Health Priority" in 2012 [2]. The global estimate of people with dementia (primarily of the AD type) was given as 35.6 million in 2010. AD was considered to represent between 60-70% of all dementias. The number of dementia cases worldwide is expected to nearly double every 20 years, rising to 65.7 million by 2030 and 115.4 million in 2050. The report noted difficulties in obtaining accurate estimates of young onset dementia, such as FTD, since very few population-based surveys have been carried out. The calculations are based on the number of cases known to health service providers divided by the total local population numbers determined by a census. When examining the limited number of population-based estimates of young onset dementias the WHO consensus group argued that there may be an underestimate of the true prevalence of young onset dementia derived from registry studies by a factor of 2.5 to 4 fold. Therefore, the report admits that the global estimates for all dementias given in the 2012 report may be underestimated.

2.1.2. Social and Economic Burden of Dementia-Related Disorders

Important to our understanding of the challenges and opportunities in FTD research and drug development is the fact that FTD is a young-onset dementia [47] and generally affects patients between the ages of 45-65. This means that FTD strikes middle-aged adults who may be in the prime income-generating phase of their careers. FTD creates a level of functional impairment which can not only leave the patient unable to continue working but also significantly compromise their ability to carry out activities of daily living [118].

A younger age of onset can also have significant impact on receiving the appropriate diagnosis. As noted in Chapter 1, a much higher percentage of bvFTD patients (52.2% at one specialty clinic) are likely to receive a psychiatric disorder diagnosis than an AD patient (23.1%). One retrospective study found that 28.2% of all neurodegenerative disease patients receive a prior psychiatric diagnosis, depression being the most common. Interestingly, cognitive, behavioral and emotional characteristics were found <u>not</u> to distinguish patients who did or did not receive a prior psychiatric diagnosis. But younger age, higher education and family history of psychiatric illness <u>did</u> increase the rate of prior psychiatric diagnosis [1].

A subsample of the Health and Retirement Study population in the United States was reviewed, using the ADAMS diagnosis method to ascertain the presence of dementia and the associated costs [3]. The study estimated that 14.7% of the United States population over 70 years of age had dementia. The yearly cost per person attributable to dementia was either $51,290 (valuation as replacement cost) or $41,689 (valuation as foregone wages). The authors estimated that these individual costs suggest that the total monetary burden on the US economy in 2010 was between $157 and $215 billion, and Medicare paid approximately $11 billion of this cost. A similar study has not been done for FTD. The estimated costs could potentially be higher for FTD because it strikes middle-aged adults in their prime earning years and, in many cases, caregivers may have reduced or lost wages in order to provide part-time or full-time in-home care. Recent publications also report that the level of impairment in the FTD disorders is much greater and has a more profound impact on the patient. This results in greater caregiver burden than what is observed for AD and other neurological diseases [119-121].

2.1.3. Lack of FTD-specific Therapeutics

There are currently no FDA-approved medications for FTD spectrum disorders, although some drugs approved for other neurological or psychiatric disorders have been tested in small case sample studies to address symptomatic issues. From the BCC report on Global Markets for Treatments for Syndromes of Dementia and Movement Disorders [115] some medications are currently used in the FTD sector to provide symptomatic therapeutic options (see Table 4). These medications include anti-depressants, acetyl cholinesterase inhibitors, serotonin re-uptake inhibitors and anti-anxiety medications. More comprehensive listings of symptomatic therapies for FTD can be found in review articles generated by clinicians in the FTD sector (see [81, 114] [113, 122, 123]). Unsurprisingly, many of these medications were developed to treat the disorders that often constitute the initial clinical misdiagnosis of bvFTD, such as AD, bipolar disorder, schizophrenia and depression.

2.1.4. Drug Development for Neurological Disorders

Traditionally, pharmaceutical companies, academic institutions and NIH have been the key stakeholders in drug development in the United States. However, these organizations tend to run independently and there is not a mechanism or pathway in place that creates a nexus of those doing the creative early discovery work (often in academia), the funders of discovery research (public sector granting agencies), and those experienced in, and with the financial assets, to develop and commercialize therapeutics (biotech and pharmaceutical companies). Therapeutics generally fall into three categories – investigational new drugs (INDs), repurposed, FDA-approved drugs and molecules derived from natural compounds or so-called nutraceuticals. In the following schematic (Figure 4), the bottom tier reflects the four usual sources of compounds that enter drug development. The second tier indicates the categories of these compounds. Investigational new drugs will follow the longest development path and must face proof of concept and other validation studies before evaluation in patients with a specific diagnosis or condition. FDA-approved

Table 4. A summary table of medications for bvFTD that make up the current global treatments market in dementia*

Drug Category	Drug/Therapy	Primary Indication
SSRI - serotonin re-uptake inhibitor	fluvoxamine, sertraline, citalopram, escitalopram, paroxetine	major depression
benzodiazepine	lorazepam, clonazepam, alprazolam, diazepam	anti-anxiety, bipolar disorder
acetylcholinesterase inhibitor	galantamine, donepezil, rivastigmine, tacrine	memory loss - AD
NMDA receptor antagonist	memantime	memory loss - AD
Histamine 2 receptor antagonist	cimetidine	inhibit stomach acid - GERD
local anesthetic	lidocaine	ventricular tachycardia
COMT inhibitor	tolcapone	increase dopamine -PD
anti-oxidant	alpha-tocopherol	oxidative stress- AD

*Abstracted from BCC Global Market Report Therapeutics for Dementia and Movement Disorders

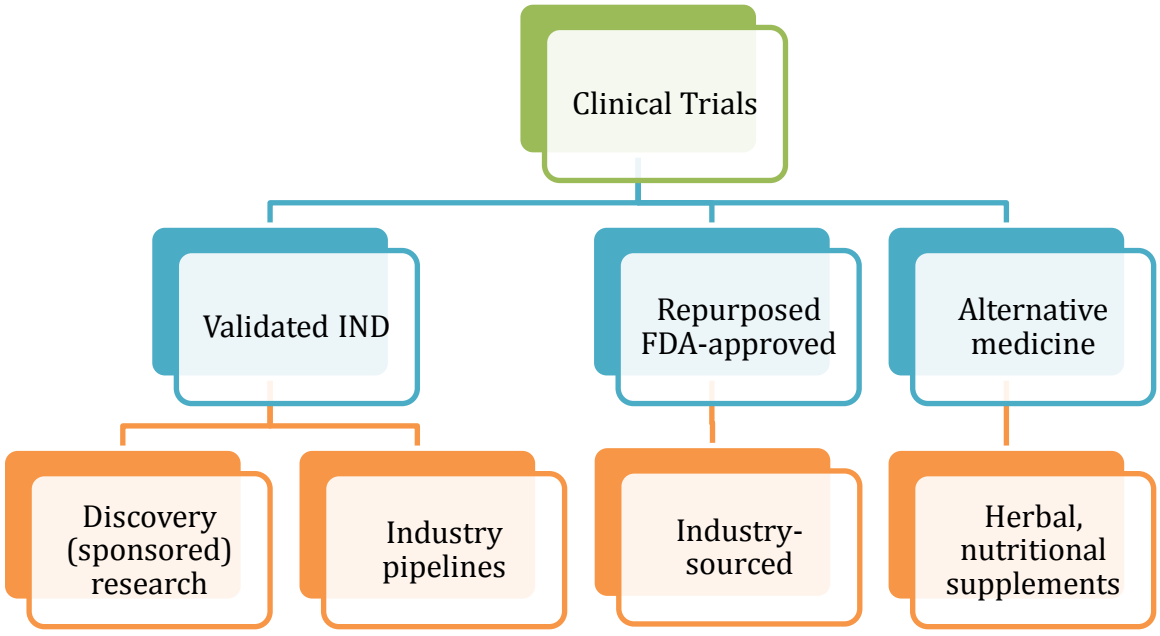

Figure 4. Different sources of molecule-based therapeutics traditionally used in clinical trials.

repurposed drugs have already passed safety trials in humans and the pharmacodynamics are known. Although repurposed drugs can be a 'short cut,' appropriate dosing and safety needs to be evaluated in a new patient disease population; this is a much faster path than an IND. Non-pharmaceutical molecules at present are not FDA-regulated as medications but there are specific FDA guidelines for dietary supplements (see FDA supplements). Dietary supplements are sometimes referred to as nutraceuticals. Although nutraceutical has no definition in United States law, in Canada it is legally defined as "a product isolated or purified from foods that is generally sold in medicinal forms not usually associated with food. A nutraceutical is demonstrated to have a physiological benefit or provide protection against chronic disease."

A working paper produced by the Research Triangle Institute [124] for the New York Academy of Sciences examined economic opportunities that might accelerate the development of Alzheimer's drugs. This analysis is also highly relevant to drug development for FTD. The estimated cost of developing a successful, disease-modifying drug for AD (including the cost of failures) was estimated to be $5.7 billion in the current environment. From their economics-based analysis, it was posited that the main barriers to development opportunities were:

a) A lack of surrogate biomarkers,
b) Demonstrating a treatment effect requires long trials with large cohorts,
c) Identifying appropriate patient populations for trials,
d) Obtaining a significant treatment effect might require a combination of drugs and this would make it difficult for any company to independently develop a single treatment

The following measures were proposed to enhance AD drug development:

i) Invest in biomarkers and cognitive assessment tools
ii) Streamline trial enrollment with advanced registries that would have patients characterized by standard demographics, genetic, biologic, cognitive and environmental information
iii) Establish clinical trial platforms to investigate biomarker and drug combinations
iv) Keep the preclinical pipeline full of novel therapeutic approaches and targets
v) Realize the economies of scope between research and drug development by creating comprehensive AD research centers integrated with existing resources

The RTI-NY Academy of Sciences analysis served to highlight a number of gaps in FTD drug development listed in the box below. Some of these gaps may also be considered more generally as drug development gaps for rare diseases.

FTD Drug Development – Room for Innovation

'Smarter' clinical trial design and drug development for FTD is needed. Existing FDA-approved clinical trial design based on large populations with more uniform disease symptoms are impractical for FTD. FTD could be a disease where innovation can flourish since it shares proteinopathies with other diseases like AD and ALS. There may be development opportunities through the *C9ORF72* gene mutation, which can produce both a movement disorder (ALS) and a cognitive disorder (FTD). Industry may find it rewarding to seek drug targets common to more than one disease, e.g., sharing a causal gene mutation, and provide two disease arms for clinical trial testing.

1. Existing models of traditional drug discovery, development and commercialization pathways are inadequate to meet the growing demand of dementia-related disorders
2. Current clinical trial design (created for non-CNS diseases with greater clinical symptom homogeneity and larger patient cohorts) does not adequately serve drug development in the dementia/neurological diseases or rare disease sectors
3. Patients with neurological disorders have more varied clinical presentations and we lack adequate standardized biomarkers or diagnostic methods to select the appropriate patients for drugs that address different symptoms and/or disorders
4. There are limited (or no) tools to diagnose pre-symptomatic or early stage patients and stratify patients for trials
5. We need innovative trial designs for these patient populations, and the traditional drug development and commercialization route will not address the rapidly growing unmet medical need and public health dilemma created by the growing number of dementia cases.

2.1.5. Dementia Drug Development – A Growth Market

FTD drug development shares many of the concerns noted in the AD drug development analysis, however FTD has not gained the level of awareness that AD has, either with the lay public or within the pharmaceutical industry. A review published by PhRMA, the Pharmaceutical Manufacturers of America entitled "Medicines in Development. Neurological Disorders 2013" [125] reported that almost 450 drugs are in development for disorders of the brain, spinal cord and nerves: 82 for AD, 8 for ALS, 27 for PD. FTD is conspicuous by its omission from this survey. A 2010 review of the market sector for neurodegenerative disease drugs forecast that the global market is likely to exceed $43.4 billion by 2015 (Global Industry Analysts, Inc.) - "Neurodegenerative Drugs: A Global Strategic Business Report-2010" [126]. This market, particularly for AD and PD, is being driven primarily by the global rise in an aging population and the high level of unmet medical need in almost all major segments of this market.

A more comprehensive review was carried out by BCC Research entitled "Global Markets for Treatments for Syndromes of Dementia and Movement Disorders" [115]. These

markets are estimated on the basis of currently available approved medications, drugs in development and their likely approval year, the on-patent or off-patent status of a medication, generic competition, and the global patient demand over the interval surveyed. The global market for CBS is expected to demonstrate the highest compound average growth rate of 13.7% over 2012-2017, PSP and Pick's disease (defined as bvFTD and PPA in this market report) are expected to grow by 11.4%, and AD drug sales are forecasted to grow by 8.6%. AD drug sales accounted for 46.3% of the market share in 2011, while Pick's disease accounted for 4.0%. It should be stressed that these are projected estimates based in part on compounds that were in the development pipeline when this review was initiated. Some of these, such as davunetide, for FTD tauopathy, and many of the monoclonal antibody therapies for AD did not advance beyond Phase II or Phase III and so projected estimates of market size and shares would need to be revised. However, there is still considerable growth potential in this market because of aging population demographics in developed countries.

2.1.6. Existing Pipelines and Incentives

The FDA has created incentives with tax breaks for orphan (rare disease) drug development and fast-tracking for programs where there is unmet clinical need. Some companies are investing in developing drugs for cognitive disorders, though not with FTD as the targeted primary indication or market sector (see Table 5). A rare disease patient population in the United States is defined as less than 200,000 (<6.37 in 10,000, based on a population of 314 million). Worldwide orphan drug sales are forecast to reach $127 billion by 2018, with the orphan drug market making up 15.9% of all prescriptions (excluding generics) by 2018, according to the Orphan Drug Report 2013 by EvaluatePharma [127].

2.1.7. Innovative Drug Development Models and Novel Clinical Trial Design

An NIH-sponsored workshop, Commonalities across Neurodegenerative Diseases (2012) [128] touched upon a key issue in translational and early discovery research. As a group participants felt that we may learn more and speed progress by exploring disease overlap through cellular regulatory pathways, proteinopathies, gene mutations, and functional networks as well as studying what distinguishes one disease from another. Most neurodegenerative diseases share the common feature of neuronal (and sometimes glial) cell aggregates of misfolded, hyper-phosphorylated proteins. This argues for general errors in protein quality control as a disease mechanism, which may include chaperone-mediated autophagy as well as macro-autophagic pathways that remove old (or dysfunctional) cellular organelles like mitochondria.

Effective and practical clinical trial design in FTD syndromes will require innovative approaches to address rapid disease progression and patient deterioration, small cohort sizes and the possibility of global, multi-site trials to provide meaningful data [84, 129, 130]. A familial FTD conference hosted by the Bluefield Project in San Francisco, November 2013 and supported by the FTD Treatment Study Group (FTSG), the Tau

Table 5. Drug development pipelines that may have value in FTD

Company	Drug/Therapy	Purpose
Bristol Myers Squibb	epithilone D/BMS241027 (early development)	microtubule stabilizer for AD and other tauopathies
Glaxo Smith Kline	5HT6 antagonist –Phase II	dementia
Roche	RG1882, GABA receptor modulator – Phase I	cognitive disorders
ISIS Pharmaceuticals	ASOs – early development	tauopathy
Regulus Therapeutics	anti-microRNA ASO	FTD tauopathy
iPierian	IPN007- tau antibody	block secreted tau propagation
TauRx	LMTX (methylene blue analog) – Phase III bvFTD	prevents protein aggregation and disaggregates mutant tau and possibly TDP-43
ALS Biopharma	inducers of HSP70 - early development	autophagy pathway
Lundbeck	5HT6 antagonist – Phase III	AD and other cognitive disorders
Genervon	new molecular entity, GM604- a multi-target, master regulator drug, Phase I	for ALS, which can overlap with FTD clinical syndromes

Consortium and AFTD gathered clinicians from more than 20 countries to present and discuss gene mutation-identified cases and explore collaborative possibilities to aid in clinical trial design and population. This is a first step toward a global, collaborative network to populate FTD clinical trials of gene-mutation-identified patients.

2.1.8. Patient-Reported Outcomes in Clinical Trials

The NIH and FDA actively encourage patient participation in clinical trial design and post-study feedback as one route to improve trial design by considering the patient experience and not just measures of drug efficacy. Currently the FDA provides industry guidance for the inclusion of patient reporting of adverse events (post-study) to support appropriate labeling of pharmaceuticals (see FDA industry guidance) The PROSPER Consortium (Patient- Reported Outcomes Safety Event Reporting) was initiated to better include the patient perspective in outcome reporting and is comprised of industry, regulatory, private sector, academic and patient stakeholders [131]. The consortium noted discrepancies that

can occur between healthcare professional reporting in studies and patient reporting on adverse events:

i) Clinicians may miss patient symptom-related adverse events that the patient does report
ii) Clinicians often miss pre-treatment symptoms that the patient reports and these symptoms may be incorrectly attributed to the drug
iii) Poor communication between patient and the clinician can lead to limited reporting of important safety issues

The PROSPER Consortium noted the challenges that arise in capturing patient-reported outcomes and created a set of instruments for gathering this data. The consortium also recognized the value of acquiring appropriate datasets prior to and in addition to post-study surveys or adverse events. These issues will also be of concern to FTD trial development.

2.2 EMERGING RESEARCH TRENDS

A relatively recent review of global research funding for FTD [132] covering the decade 1998-2008 indicated that 74% of all funding went to basic science research and that very few programs advanced into preclinical and drug development studies. In 2013, RAND Corporation, Europe published a 20 year retrospective of schizophrenia research [133] in an attempt to understand the role of research in the shallow landscape of schizophrenia drug development. Surprisingly, they found that clinical research had a greater payback on health, social and economic benefits than basic research over a 20 year period, when it is generally assumed that basic science research leads the way. The study also found that those individuals, who were able to bridge the gap between the spheres of research, care and policies had greater impact on health care for schizophrenia and were frequently key drivers of change. Although this retrospective survey had limitations, the role of 'research champions' who are aware of the interplay between research, care and policy is an important finding. Such multi-faceted individuals are often the driving force in successful biotechnology companies that take innovative research discoveries and turn them into products that advance healthcare. They will be essential in fostering FTD drug development and diverse stakeholder partnerships.

2.2.1. FTD Proteinopathies Driving Drug Development

Advances in key research sectors in the last decade have expanded our knowledge of FTD and deepened our understanding of the molecular pathways involved. There is active, early development of small molecules/biologics focused on clearing tau aggregates in pre-clinical models of FTD, as well as a multi-site trial, phase III trial to clear tau in bvFTD. TDP-43 proteinopathy is also beginning to attract early stage drug development interest, possibly due to the relatively new understanding that TDP-43 is the predominant proteinopathy in ALS, as well as FTD. Various transgenic mouse models of ALS and/or FTD TDP-43 proteinopathy are in development. Genetic screening has expanded our knowledge of the *GRN* gene mutation and the revelation that bvFTD pathology can be the result of

progranulin haploinsufficiency (low levels of circulating progranulin protein) and potential for new drug targets.

2.2.2. FTD Genetics Creating New FTD Models and iPSC-derived Research Tools

A large number of different FTD gene mutation models are available, which are based on the incorporation of specific gene mutations into various species to create transgenic mice, mutant *Drosophila*, *C. elegans* nematodes, zebrafish or novel yeast mutants. While no particular mutation captures both pathological and behavioral aspects of any particular FTD syndrome they provide different routes to explore the pathophysiology and molecular pathways related to different mutants [81, 91, 92, 134]. Stem cell technology has developed rapidly over the past decade with induced pluripotent stem cell (iPSC) lines derived from gene mutation-identified FTD patients now available. These new tools may become a means by which to examine the cell biology and neural toxicity mechanisms in familial FTD. Neuronal (and glial) lines derived from these iPSC patients also have the potential to be used as drug screening tools. These cells have already given us a new perspective on neurodegenerative diseases, demonstrating that RNA toxicity may contribute to cell death in FTD and is almost certainly a driver of disease in FTD-ALS [99, 102, 135].

2.2.3. High Resolution Brain Imaging as a Tool to Reveal Neural Circuitry

Neuroimaging in the resting and task-challenged human brain will continue to develop our understanding of the specific neural circuits associated with clinical phenotypes. Neuroimaging technologies have advanced considerably over the past decade; and while high-resolution structural imaging has evolved as a tool to diagnose and assess FTD neuronal atrophy, it is no longer the only technique available. However, some of these new imaging technologies are only available at specialty clinics or research centers and are not broadly available as diagnostic tools. A recent development is diffusion tensor imaging of white matter fiber tracts with a resolution that can confirm loss of tracts (and so imply changes or loss in neural circuitry). It is clear from the current literature that FTD and other neurodegenerative diseases affect large-scale brain networks. As technology evolves so does our understanding of the human brain 'connectome' in health and disease [93, 136, 137] [138]. Advances in high resolution and functional imaging may help uncover differences in the neuronal atrophy patterns associated with cognitive behaviors in sporadic FTD and those in gene mutation-identified FTD [6, 139]. A network diffusion model algorithm based on MRI tractography data predicted differential atrophy patterns that could distinguish FTD from AD. The authors argue for the potential of this modeling tool to predict future atrophy patterns using baseline MRI morphometric findings [140]. More work is required to determine the predictive and/or diagnostic value of this model in characterizing the disruption of functional networks in neurodegenerative disease, but this could be a route to early stage biomarkers for FTD [141].

2.2.4. Proteomics, Protein Aggregate Diseases and a Prion-like 'Infectivity' of the Nervous System – Commonalities across Neurological Diseases

Work with in vitro and in vivo models have shown that the abnormal protein aggregation common to most neurodegenerative disorders may spread from cell to cell within the brain. Highly novel from the Marc Diamond laboratory, Washington University and Judith

Steen laboratory, Harvard University demonstrate that certain mutant protein oligomers are more 'toxic' or more 'infective,' may be more likely to aggregate than others and that such mutant proteins have a distinct molecular signature in mass spectrometry [64, 142, 143]. Mass spectrometry provides a sensitive means for identifying biomarkers in CSF and its use has already been attempted for AD [144-146]. The challenge of the FTD spectrum is heterogeneity - no identified protein abnormality segregates with a specific syndrome. But heterogeneity may also become a development opportunity as tauopathies and TDP-43 proteinopathies are shared across neurological disorders and may serve as a means to decrease the risk of targeted drug development if more than one group of patients may benefit from a single drug. The prion-like spread of mutant proteins, as well as what appears to be a common seeding and aggregate formation within neurons may be another route to targeting drugs to disrupt cellular homeostasis mechanisms [52] [147][148]. New therapeutics in development are anti-tau antibodies, which have demonstrated promise in animal models [149].

2.2.5. The Role of Autophagy, Inflammation and RNA Metabolism in FTD Neurodegeneration

Our understanding of the contribution of altered protein homeostasis in neurological disease is growing and flows naturally from research studies devoted to mutant protein and RNA toxicity in FTD. Recent studies in *C9ORF72* iPSC lines reveal that toxic RNA aggregates can also contribute to neuronal degeneration in human ALS stem cell derived neurons [99, 150]. We have discovered that impaired autophagic mechanisms (cellular housekeeping) can impact normal protein folding and disrupt the chaperone mechanisms used to dispose of misfolded proteins [151]. The role of glial cells, particularly microglia and their contribution to neuroinflammation in the brain [152] and in *GRN* mutation-identified FTD patients [111, 153] is a relatively new area of exploration in FTD biology. Molecules like rapamycin, an immunosuppressant drug that may delay the onset of neurodegeneration may be a source of future therapeutics development [154].

2.3 RESOURCES

Common data banks now play a more prominent role in FTD research as well as in other neurological diseases. Government supported initiatives through the National Institutes of Health (NIH), the National Institute on Aging (NIA) and the National Institute of Neurological Disorders and Stroke (NINDS) have led to the creation of shared resources as well as program initiatives that are collaborative in focus and supportive of translation research, in an effort to advance therapeutic development in neurological diseases.

2.3.1. Publicly Supported Initiatives

NIH Blueprint for Neuroscience Research. Blueprint is a cooperative effort among 15 Institutes, Centers and Offices at NIH that support neuroscience research. Under this umbrella group is The Human Brain and Spinal Cord Resource Center, a repository that provides samples from various neurological diseases, including tissue from FTD clinical syndromes. Of potential use in future FTD research and drug development is the Human

Connectome Project. The Connectome project will use state of the art neuroimaging technology to map and collect data on the structural and functional connectivity of the human brain. An NIH press release in 2013 revealed that $40 million was awarded to this project with the hope that it will reveal neural circuitry in the normal brain and thus provide a basis for studying the abnormal circuitry in neurologic and psychiatric disorders.

NACC-FTLD module. The National Alzheimer's Coordinating Center (NACC) was established in 1999 through a joint initiative of NIA and NINDS to support collaborative research efforts among the 29 government-funded Alzheimer's Disease Centers (ADCs). The NACC provides a relational database of clinical and neuropathological research that is freely available. The NACC-FTLD module was initiated in 2010 by the FTLD Working Group, consisting of FTD clinicians and researchers from the ADCs, led by David Knopman, Mayo Clinic. A set of FTD-specific Common Data Elements were developed which allow for data streamlining and the opportunity to share and compare data across numerous studies and sites. The NACC-FTLD database currently holds de-identified, common data elements, described 246 cases and is intended to serve as a resource across the FTD disorders spectrum.

iPSC Consortia – Coriell Cell Repository. A NINDS-supported resource was created in 2010 to create a stem cell line repository for familial PD, ALS and Huntington's Disease (HD). The adult-derived stem cells are stored at the Coriell Cell Repository and are freely available to all qualified researchers [155]. An FTD iPSC consortium has since been added to the group, led by Yadong Huang [156] and Fen-Biao Gao [157]. There are a limited number of lines at present, but this will expand markedly in 2014 with new lines being deposited from these laboratories. In addition, new cell lines are becoming available from FTD *C9ORF72* mutation families (Jeff Rothstein laboratory) and will include FTD-ALS cell lines [99, 158].

NCATS RNA Interference Initiative. The National Center for Advancing Translational Sciences (NCATS) entered into a partnership in December 2013 with Life Technologies of Carlsbad, CA to provide public access to Life Technologies Silencer Select siRNA library. These small interfering RNA molecules are able to selectively silence genes, and the ability to do this may provide a way to identify new genes and molecules that are linked to specific diseases. Experts from the NIH RNAi Initiative (through NCATS Pre-Clinical Innovation) will conduct screens for NIH investigators and new data will be uploaded to NIH's database PubChem. It is hoped that by making the siRNA sequences available this will enable novel strategies to elucidate fundamental biological mechanisms and aid drug discovery.

Brain Banks. There are a number of brain banks which house FTD postmortem tissue, however, there is no central repository, and no FTD spectrum–dedicated repository. Below is a brief selection obtained from web-linked resources of biorepositories found on the webpages for American Biobanks and NCATS (see Biobank Directory).
i) Eloise Troxel Memorial Brain Bank – Mayo Clinic, Jacksonville, FL (PSP, CBS, MSA)
ii) University of Pennsylvania –Center for Neurodegenerative Disease Research brain bank
iii) Columbia University - New York Brain Bank
iv) University of Miami - Brain Endowment Bank

v) University of California, San Francisco – Neurodegenerative Disease Brain Bank
vi) Northwestern ADC Brain Bank for PPA and bvFTD

The ENIGMA Consortium. Enhanced Neuroimaging Genetics Through Meta-Analysis (ENIGMA) is a large scale, publicly available imaging database [159] and is the collaborative result of 70 institutions worldwide (including ADNI – the AD Neuroimaging Initiative). Three major working groups in the consortium address problems in neuroscience, genetics and medicine, while additional working groups investigate psychiatric disorders.

ADRD workshop. The Alzheimer's Disease and Related Dementias (ADRD) workshop was held in May, 2013 as part of the US government's National Alzheimer's Project Act (NAPA) initiative. The workshop collected core recommendations from various groups of top dementia researchers and included a group entitled Frontotemporal Dementia and AD-related tauopathies. The recommendations were collected with the intent of identifying and creating a short-list of the highest priorities to guide research initiatives and lead to the development of therapeutics that could decrease the burden of the ADRD illnesses. At present it is not clear whether there will be federal funding for some, all or any of these recommendations in the near future.

2.3.2. Non-profits, Disease Advocacy and For-Profit Private Sector Organizations Currently Lead the Way in FTD Drug Development

While a growing patient base in the FTD spectrum will contribute as a market driver for FTD drug development, a critical, and perhaps the quintessential driver will be well-characterized and validated biomarkers that can be used as diagnostics – essential for clinical disorders that are so frequently misdiagnosed - and biomarkers that can be used to assess efficacy of interventional new drugs in clinical trials. Research funding initiatives by non-profit organizations like AFTD and the Alzheimer's Drug Discovery Foundation (ADDF) have helped promote biomarker-related research in FTD through the AFTD Pilot Grants and the AFTD-ADDF FTD Drug Discovery Grant programs. These two organizations, along with the Bluefield Project, the Tau Consortium, CurePSP and CBD Solutions appear to form the leading edge of FTD research by supporting targeted FTD spectrum research which is innovative and focused on disease biology as well as by supporting pre-clinical and clinical research studies testing new therapeutics which are interventional and intended to slow or stop disease progression.

Over the past decade the pharmaceutical industry was not heavily invested in R&D for FTD syndromes or other neurological diseases. Of late, there are encouraging signs that potentially 'monogenic' FTD syndromes with the *GRN* or *C9ORF72* mutation, or rare *MAPT* variants like A152T (found in PSP) are being looked at with some interest by industry. AFTD has had recent introductory conference calls with neuroscience development teams from the Novartis Institute of Biomedical Research and from Astra Zeneca to learn about areas of common interest.

Gap: Extending the Research Networks of Non-Profit Organizations
Non-profit organizations support research initiatives in FTD and other neurological diseases. Many have medical advisory or scientific advisory panels and connections to the key opinion leaders in the field. While pharmaceutical companies are forced to change their research and development models to provide a better return on investment, scientists and clinicians must also adapt to the new paradigm. The cost of bringing a new drug to market is estimated at $2 billion for non-neurological diseases. This implies a large target market for sales to recoup investment. Although there is incentive provided by the FDA for rare disease-orphan drug development and fast track status to quickly bring therapeutics to market when there is unmet need, this still may not be enough to attract developers to FTD. Currently large pharma companies are cultivating relationships with or acquiring smaller biotechs that have unique drug delivery platforms, or algorithms for 'big data' analysis needed in genetic studies or novel therapeutic approaches such as new anti-RNA based therapies. Many non-profits currently support the leading edge of new research for neurological diseases and may be able to develop new relationships, support novel collaborations and inform and encourage their patient communities to engage in the research and development process.

2.3.3. FTD Therapeutics – Early Development Initiatives

There is active, early development of compounds in preclinical studies focused on clearing mutant tau protein aggregates in models of FTD. There are also innovative Phase I studies using anti-sense oligonucleotides (ASOs) to combat accumulation of hyper-phosphorylated tau proteins. These research studies are the result of a collaborative partnership between investigators supported through the Tau Consortium and ISIS Pharmaceuticals, which created the ASOs for clinical trial use. Tau provides an attractive target with the advantage of identifying familial FTD patients with *MAPT* gene mutations [160].

Although more FTD (and FTD-ALS) patients demonstrate TDP-43 pathology than tau inclusions, drug development for this has been slower than for the tauopathies. This is due to tau being identified much earlier, with more data on tau biology and its contributing role in AD pathology. Potential drivers for therapeutic development for TDP-43 proteinopathies may be the *GRN* mutation bvFTD cases that has potential as a 'monogenic' disease with a drug target that could impact progranulin haploinsufficiency. *GRN* may also lead to developing drugs that affect (neuro)inflammatory pathways [111, 161, 162]. Another driver of TDP-43 drug development in FTD is the potential for ALS-related targets and FTD-ALS, both TDP-43 proteinopathies [21] [163].

Table 6. Non-Profit Organizations Driving FTD Therapeutics Development

Organization	FTD research projects	Therapeutic Targets
AFTD	Pilot Grants	Yearly RFP, innovative clinical and basic science FTD research, $60,000, 1 grant, 2013 funding web-based speech language therapy for PPA
	Postdoctoral fellowship awards	Bi-yearly RFP, postdoc to study in established FTD lab or clinic, $55,000 per year for 2 years, 1 grant, 2013 funding iPSC FTD models
AFTD-ADDF	Translational Research Grants in FTD	Yearly, targeted RFP, open to academics and biotech industry, up to 3 grants, maximum $150,000 to advance FTD drug discovery
Bluefield Project	Consortium for FTD Research (CFR)	Raise progranulin levels (SAHA, an approved HDAC inhibitor) Lower TDP-43 – find inhibitors of Dbr1 enzyme. Understand neuro-inflammatory role of progranulin
Rainwater Charitable Foundation	Tau Consortium	Tau aggregates in PSP
CurePSP	CurePSP Genetics Consortium	Whole genome analysis for PSP and CBS
	Eloise Troxel Brain Bank, Mayo Clinic-Jacksonville	PSP, CBS, MSA brain tissue repository
	Investigator-initiated research	Fund up to $100k per project, GWAS for PSP
CBD Solutions	Funding scientists at Karolinska Institute, University College London	CBS research projects
	Partner with CurePSP	Develop CBS rating scale
	Fund NsGene, AlzeCure, Peter Davies	Anti-tau antibodies & delivery platform to brain of CBD patients

2.4 PARTNERSHIPS

2.4.1. Diverse stakeholders

Drug development for dementias and movement disorders has been a difficult field over the last decade, with few success stories. In fact, the pharmaceutical industry as a group withdrew much of their investment in neurological disorders and instead aggressively pursued 'blockbusters' in cardiovascular disease, diabetes and cancer [164] particularly as the industry as a whole was faced with revenue shortages due to many successful drugs losing patent protection. Traditionally, the pharmaceutical industry partnered with academic centers and selected promising technologies for further development. Unfortunately this process is expensive, can take more than a decade and on average perhaps one drug candidate out of 1000 advances to clinical trial, without guarantee of reaching endpoints in Phase III and receiving FDA approval.

Partnerships to stimulate drug development for FTD may occur in a variety of ways. These partnership platforms rest on pillars that reflect a practical approach in developing working relationships based on the realities of rare disease neurobiology research, clinical management and patient daily quality of life (QOL) issues, available resources and missing pieces, and finally stakeholders who contribute to advances along different paths, but all of whom share a strong commitment to fight the disease. As an example, development of molecular diagnostics is a key step required for advancing drug development and selecting and stratifying patients for clinical trials in FTD. These diagnostics would include tests that could identify inherited risk, selectively diagnose FTD and categorize FTD subtype based on genes, proteins, RNA and cellular pathways. Guidance documents that address clinical validity and utility in creating diagnostics have been published for other drug market sectors and may prove useful in the FTD sector [165].

2.4.2. Non-Profit Organizations, Biotech and Pharmaceutical Industry and FTD Clinical Treatment and Research Centers

As a group, non-profit organizations act to extend our understanding of the biology of rare diseases, and fund important and innovative research that can act as the 'cutting edge' of knowledge in the field. These organizations also raise the level of awareness of FTD among the general public, health professionals, government officials and industrial R&D. Specialty clinics, either through the ADRC or FTD-focused, provide the latest guidance on clinical diagnosis and patient management and function as data repositories and informal registries with longitudinal data collection from their patients. The health professionals in these clinics are often key opinion leaders in their field and participate in medical advisory councils for non-profit organizations and initiate small case clinical trials in order to fill in the gap of neither disease-modifying nor specific symptomatic therapeutics for FTD. AFTD, along with the Tau Consortium, the Bluefield Project, CurePSP and CBD Solutions currently stand as the main non-profit organizations committed to raising awareness, supporting the patient and caregiver community and funding FTD research.

Foundations and patient-advocacy groups have raised awareness of FTD and other rare diseases. Increased awareness can lead to increased expectations as well as more requests by patients to healthcare professionals and foundations to participate in clinical trials, join registries or donate tissue. There are approximately 25 million people in the United States who suffer from rare diseases and it cannot be expected that demands for increased research efforts and drug development can be met by historic methods of partnering for drug development, particularly in light of decreased government research funding [81, 129] [166].

Novel Partnership Opportunities - The FTSG

The Frontotemporal Degeneration Treatment Study Group (FTSG) is an initiative developed over the course of a number of conferences to fill unmet clinical needs in FTD therapies. This organization is a unique collaborative effort of industry members, clinicians and investigators who are committed to developing better clinical trial design for FTD syndromes and pursuing therapeutic options for FTD. This group, which is housed within AFTD, offers a unique partnership opportunity for drug development that, because of the size of the FTD research and clinical community, may be more nimble at taking up and pursuing novel treatment approaches and trial design that may not be possible in the larger AD sector. Because of the treatment gap, industry may see this as an area for more reward and potentially reduced risk given overlap of FTD clinical syndromes, proteinopathies and gene targets and a rapidly growing field. An area of active inquiry and idea exchange is how an entity like the FTSG should function to serve as a collaborative body that supports FTD therapeutics development and to have the greatest impact on the FTD landscape as a whole.

AFTD "sister-organizations" for an FTD Information Network

There are a number of patient-centric organizations and volunteer groups in the FTD space which serve to inform patients, caregivers, the general public and healthcare professionals about resources and advances in FTD research, clinical trial opportunities and FTD medical centers. These organizations may be able to partner in new ways in order to improve awareness of FTD, cooperate in forming a global FTD patient registry, support promising drug discovery research, and find other ways as a group to address the global public health issue of millions of dementia patients that will need disease-modifying therapies.

Diversity of Stakeholders in FTD Drug Development

To be successful, development efforts will require flexibility and diversity among stakeholders and a shared understanding that unsolved, FTD and other dementias are a growing public health issue with significant economic burden on the global economy.

2.4.3. Multidisciplinary Research

The past decade, particularly the years after 2010, has delivered groundbreaking advances in FTD research in the areas including protein misfolding, protein seeding and propagation, new gene mutations (*C9ORF72*), iPSC lines from FTD patients, RNA toxicity in FTD,

advances in neuroimaging and improved clinical diagnostic criteria. What stands out in a review of FTD research is the degree of overlap with other neurological disorders such as AD, PD and ALS. There are fundamental patho-biological mechanisms that are associated with neurodegenerative processes such as:

i. Accumulation of mutant proteins,
ii. The prion-like spread of mutant proteins in the tau and TDP-43 proteinopathies,
iii. A seemingly generic 'seeding' process of mutant proteins that initiates and progresses through templating abnormal folding of resident normal proteins to create tau and TDP-43 aggregates,
iv. Common gene mutations, and
v. Disrupted RNA metabolism and nerve cell degeneration.

This past year saw clinical and basic science conferences that brought together investigators from several countries, often with primary interests in non-FTD disorders, to share data and techniques that advance research in FTD and other neurological diseases (see 8th Brain Research conference, San Diego 2013- RNA Metabolism in Neurological Disease). The advantage of such meetings is that they bring together scientists with varied expertise but intersecting areas of interest that cross research disciplines – a research 'nexus.' These points of intersection serve to advance research because of the unfettered exchange of ideas that are stimulated by a cross-section of researchers and the opportunity to create new collaborative partnerships.

Gaps in FTD Trials – Questions from the FTSG conference, "Establishing Therapeutic Efficacy in Familial FTLD (fFTLD)", November 2013

1. What clinical rating scales will allow investigators to follow disease progression, to follow progression of multiple phenotypes in the same trial and to measure longitudinal progression in 'mild' cases of fFTLD?
2. What are the first symptoms of familial FTLD? Are these symptoms different for different gene mutations?
3. Would defining these early symptoms aid drug development?
4. What targets and approaches are most promising for drug development in fFTLD?
5. How does a pharmacodynamic biomarker determine the further development of therapies?

The FTSG, funded by the Bluefield Project, the NIH, the Tau Consortium and AFTD sponsored a global clinical conference in November, 2013 to address critical issues in building cohorts for FTD clinical trials. This conference demonstrated a willingness to meet, share clinical data on gene mutation-identified patients and enter into a dialogue to identify the difficult issues that face clinical trials in FTD. The FTSG conference also demonstrated that opportunities exist in FTD clinical trial development and design as outlined below.

Opportunities for Global Partnering: Establishing Therapeutic Efficacy in Familial FTD –November 2013 Conference - Take Away Messages

1. Geographic location can contribute to the gene mutation picture of familial FTD,
2. The percentage contribution of specific FTD genes seen in North America is not necessarily the same as that observed for FTD in India or Europe or Asia or South America,
3. We must consider a more global contribution to populate the cohorts of FTD clinical trials to achieve the necessary statistical 'power' in rare disease trial design,
4. We must develop innovative clinical trial designs for FTD (sporadic and familial) that address the issues of rapid progression and features of disinhibition which affect patient retainment in trials and patient compliance throughout the trial,
5. We need FTD biomarkers to facilitate new drug development, inform on disease progression and support better trial design and, most importantly, provide subjective and reliable measures for accurate and early diagnosis, and
6. Randomized control trials with placebo arms and large cohorts developed for other diseases and 'blockbuster' type drugs will not always be possible with FTD and it will require dialogue with key stakeholders (FDA, pharmaceutical companies, clinicians, patients and caregivers) to develop a rational trial design for the constraints imposed by the FTD syndromes.

2.4.4. Solving Complex Problems

Dementia, and FTD in particular, is a difficult and complex problem. Treatment initiatives will require a broader cross-section of interested partners and funding beyond government grants and pharmaceutical industry investment [166]. Although disease-modifying therapeutics for FTD are urgently needed, other initiatives that address the challenges of daily activities of living faced by FTD patients and caregivers are also required.

A challenge can be defined as difficult when it is complex in three ways: i) dynamically - cause and effect are interdependent, ii) socially complex - stakeholders have different perspectives and interests and iii) generatively complex - its future is unfamiliar and undetermined [167]. Complex challenges such as FTD, therefore, will not be successfully addressed by applying the old and familiar best practices but by creating "next practice" solutions [168].

APPENDIX A

Other Opportunities in FTD
Patient Engagement, Education and Non-Pharmaceutical Approaches to Impact Care

A.1 PATIENT ENGAGEMENT

A.1.1. The "ePatient"

In an era where aging population demographics in developed countries such as the United States, Japan and the European Union forecast millions of patients who will develop AD, and by inference FTD as well, there will be a need for healthcare delivery and early disease diagnosis as never before for both young onset and late onset dementias. Because much of this 'boomer' population is tech savvy, they search the web for medical information when symptoms appear or when a diagnosis is received. These "epatients" also search for treatment opportunities, pharmaceutical- or alternative medicine-based, as well as clinical trials. Unfortunately, they may find so-called 'stem cell therapies' or other advertised 'cures' which are often outside of the United States and are expensive, not supported with solid evidence and may do harm [169].

Gap: Patient Engagement

Patient involvement in FTD clinical trials is essential. Options in trial design, record keeping and testing that facilitate patient feedback provide opportunities to better understand natural history, and the potential for developing biomarkers that establish drug efficacy and FTD heterogeneity. Patient feedback is also critical in monitoring the daily impact of trial design on a patient population with rapid disease progression. Some trial designs may be feasible on paper but not possible with the level of impairment experienced by the patient and the demands of multiple visits for data collection. An identified gap is the need for a trial design for FTD patients who show higher levels of disinhibition and apathy early in the disease and may have difficulty with compliance and retainment to trial's end.

Patient and caregiver engagement in the treatment process is essential. Patients and their families should be treated as active, participating members of their healthcare team rather than as a subject or disease victim. A higher level of patient engagement, developed early in the diagnostic and treatment process, can pay high dividends fostering an element of hope, a sense of positive action, contribution and control, all of which have been significant in their absence for FTD families. This should also result in an increased level of trust and a greater likelihood for cooperation and partnership in research initiatives.

A1.2. IT-based Healthcare Initiatives is a Growing Sector Which Can Benefit Patients

There is a growing demand for bioinformatics solutions that can help sort, analyze and organize the large data sets that can be produced from genome wide association studies, multiple scan, high-resolution neuroimaging, high throughput drug screens of tens of thousands of samples in compound libraries or even batteries of neuropsychological testing in patient data repositories. Two recent reports demonstrate the efficacy of novel screening algorithms as diagnostic aids for AD [170, 171].

Patient-centric IT health applications are also being developed which focus on patient and caregiver engagement and feedback and making them active participants in the healthcare process (see Healthnow.net). Other digital solution providers target the health professional and provide improved patient data communications and other services (see Vocera.com). AFTD awarded the 2013 Pilot grant to Emily Rogalski, an assistant professor at Northwestern University for a web-based speech language therapy program for PPA. This project will test the feasibility of a web-based speech therapy program and determine if this clinical tool can provide symptomatic relief and/or slow progression of clinical FTD features.

Patients/caregivers that will contribute online about their experience may be a support and information base on daily life challenges. Many patient or caregiver-only groups have created Facebook pages to talk candidly about their daily activities experience, novel solutions, or their participation in clinical research studies. Other forums such as the BrainTalk Communities (see Braintalk) which have been in existence since 1993, also serve as a means of sharing information between patients and caregivers, as well as between patients and medical professionals who are encouraged to participate in the various brain community pages. These sites have merit in that they provide an open exchange of information and also an opportunity for patients and families to connect with others when geographic location or caregiving demands prohibits their ability to physically participate in support groups.

A.2 EDUCATION

Non-profit and disease advocacy organizations play a significant role in raising awareness and educating the lay public and health professional community about FTD and other dementias. But there may be some opportunities that have been missed and will require new partnerships to obtain buy-in and follow-through. Some CME courses focused on FTD have been presented, as well as opportunities for organizations like AFTD to present at annual medical society meetings that serve to inform healthcare professionals about current issues in FTD. However, other opportunities to educate that might be considered are the creation of new case studies for medical students so that FTD may reach the front lines of medical care through primary physicians. Such case studies may also be of value in schools of pharmacy and nursing.

A.3 NON-PHARMACEUTICAL APPROACHES TO IMPACT CARE

A3.1. Novel Approaches in Cognitive Therapy

Repetitive Transcranial Magnetic Stimulation (rTMS) has shown benefit for semantic dysfunction and short-term cognitive improvement in FTD and AD studies [172-175]. The mechanism(s) of action of rTMS on synaptic function and large-scale neural networks is not yet clear [176]. This could be an emerging treatment modality and an emerging market opportunity in medical devices. There is still much work required to determine the appropriate level of stimulation, stimulus regimen, on task or off task approaches, and duration of benefit per stimulus treatment 'dosage.' But if demonstrated as effective, rTMS could provide a non-invasive, relatively inexpensive route to achieve symptomatic benefit.

There is a growing literature in AD and psychiatric disorders on the use of mindfulness behavior cognitive therapy (MBCT). These are guided meditation techniques that have achieved symptomatic, cognitive/behavioral benefit for patients [177] and reduced burden for caregivers [178-180]. There are a growing number of clinical trials that are exploring new options in cognitive therapy for FTD, including the use of oxytocin nasal spray, which in early phase studies delivered a short-term improvement as gauged by standardized cognitive tests [181]. Some dementia clinics are exploring art therapy and other approaches to obtain symptomatic improvement in patients [182, 183].

A.3.2. Lifestyle modification

Current aging research now reports the advantages of aerobic exercise on cognitive performance in 'healthy' elderly in addition to cardiovascular benefit [184]. There is a growing literature and some longer-term studies to determine the benefits (if any) of physical activity in elderly AD dementia populations [185-188]. A recent Cochrane meta-analysis review of more than 930 patients has determined that exercise programs can provide cognitive improvement and improved daily functioning in the Alzheimer's dementia group [189]. As yet, no exercise-based research studies have been implemented in the young-onset dementia populations of FTD. In addition to aerobic activity, the aging adult population is encouraged to maintain a healthy weight, incorporate more fruits and vegetables into their diet and in some cases supplement with anti-oxidants such as omega-3 fatty acids. There is a shortage of evidence-based literature on the benefits of these lifestyle changes in the FTD or AD population, although more clinical studies are now focused on implementing diet and lifestyle changes in neurological disease populations, as well as examining any potential benefits of nutraceutical-type supplements to the diet [190-195].

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