Executive Summary

The frontotemporal dementias (FTD) are the second leading cause of dementia in persons under the age of 65, representing 5-10% of all dementias. Despite their significant cause of disability and death in this age group, FTD research clearly lags behind that of Alzheimer's disease (AD). Although research during the past 10 years has contributed much to our understanding of the underlying mechanisms of FTD, little progress has been made in the development of effective therapies for the illness.

The landscape analysis reported here was commissioned by the Association for Frontotemporal Dementias (AFTD), in partnership with the Alzheimer’s Drug Discovery Foundation (ADDF), to better understand the current state of relevant worldwide research for FTD. Identifying gaps in funding will allow us to better identify new strategic opportunities for accelerating the discovery and development of drugs for FTD. In addition, FTD and AD share some common disease pathways; therefore, much insight into FTD treatment development can be gained from analyzing and applying progress in AD to FTD.

For this analysis, data were captured from biomedical grants on FTD-related dementias from grantors worldwide from 1998 up through the first half of 2008. This was accomplished by first defining the disease using clinical and biological terms, compiling a list of putative grantors and desired data fields and then querying grantors for the desired information with these search terms. Concomitantly, a classification system was developed and implemented by which research activities could be categorized by stage of biomedical research with an emphasis on translational research.

The final dataset contained 613 program and infrastructure grants relevant to frontotemporal and related dementias research disbursed from 1998 up through the first half of 2008 totaling $432,167,275. The overall rate of response was 64%. Data were received from 19 foundations and public agencies from 7 countries and the EU. Seventeen out of the 27 (63%) Institutes within the National Institutes of Health (NIH) provided funding for FTD research, representing half (53%) of all captured grants. Over the past decade, the NIH has provided the majority of funding (83%, $360 MM), however over time its fiscal commitments in this therapeutic area have diminished (5-fold, 1999-2007; 2008 data incomplete) concurrent with a reversal in the doubling of NIH appropriations. The bulk of FTD funding has been put towards basic disease research (74%; $319 MM) with roughly 10% (~$37 MM) going towards pre-clinical development, clinical evaluation of treatments, or towards developing diagnostic and imaging technologies and reagents.
Key Findings from the Analysis

- FTD overall received little funding over the past decade compared to Alzheimer’s disease (10% of AD), with even fewer funds explicitly for other FTD-related dementias including: semantic dementia, primary progressive aphasia, progressive non-fluent aphasia, corticobasal degeneration and progressive supranuclear palsy, FTDP-17, FTD with motor neuron disease, or FTD with ubiquitinated inclusions (FTD-U/FTLD-U).
- The majority (83%) of all FTD funding over the past decade originated at the NIH, with the NIA and NINDS sourcing the greatest number of funds (70% overall, combined). However, the relative contribution from the NIH has steadily decreased over time (5-fold 1999-2007: 25 grants, $54.6 MM vs. 45 grants, $10.7 MM; 2008 data incomplete). A concomitant increase seen in grant numbers connotes a drop in funds per grant.
- Steadily increasing contributions from foundations, particularly in the area of pre-clinical drug development, have partially offset the decreasing funds from public sources.

Anticipated Findings

- The majority of FTD funding went towards basic disease research, specifically Target Discovery and Target Validation, with little funding towards drug (lead) discovery and subsequent pre-clinical development and clinical evaluation.
- Drug discovery research programs that were funded focused on few targets, with most programs funded during the past few years.
- Research on targets common to FTD and AD received more funding than those specific for FTD.
- Few FTD-specific clinical trials

Unanticipated Findings

- A steady and significant decrease in NIH funding for FTD over the past decade, coinciding with a recent increase in annual grant numbers, suggesting a drop in funds per grant.
- While relatively modest in amount, a steadily increasing proportion of funds from charitable philanthropies was observed.
- Significant increases in funding for Detection, Diagnostics & Imaging were observed over time despite relatively low overall support.
- Over half of all grants identified as FTD-relevant also mention Alzheimer’s disease (58%), suggesting common mechanisms, but also reflecting funding that may be primarily for AD.
- A near absence of FTD-specific patient, palliative, end of life care management or best care practice research was observed.
**Key Recommendations**

Public agencies as well as foundations need to increase research funding in order for significant progress to be made in the development of effective therapies for FTD:

- More funding is needed for drug discovery related to FTD-specific targets, particularly those discovered recently, including TDP-43 and progranulin.
- More funding could be gained by funding programs on targets common to both FTD and Alzheimer’s (e.g., tau); leveraging the large amounts of existing Alzheimer’s funding for clinical trial infrastructure and core resources.
- More funding is needed for biomarkers in order to differentiate FTD patients with tau versus TDP-43 pathology, an imperative diagnostic criteria necessary for successfully designing and stratifying clinical trials.

Advocate government effectively for increased funding for:

- Basic research in FTD neurobiology that will lead to the discovery of novel targets
- Biomarkers
- The creation of FTD cores within the current ADC network thereby further leverage AD resources

Strategic decisions regarding FTD drug discovery research funding should focus on programs that would benefit from modest sums yet have potential for significant impact:

- Develop academic programs including novel, high-risk approaches to FTD not normally seen by NIH study sections.
- Accelerate drug development by investing in novel technologies for early detection and diagnosis e.g., novel PET imaging technologies, biomarker discovery/validation.
- Create bioinformatics resources to accelerate treatment development and evaluation e.g., patient databases and registries, clinical trial networks.
- Provide seed funding for high-risk, novel pilot clinical trials directed to new FTD targets; expand appropriate AD trials to include FTD subjects at reduced costs.
- Invest in the career development of a cadre of young scientists dedicated to FTD drug discovery research through postdoctoral fellowships and assistance for young investigators in establishing their own labs.
- Given the paucity of research on palliative care, end-of-life issues and other important “non-drug” issues specific to FTD-spectrum patients and their caregivers, fund research in these areas.

**Conclusion**

Despite the fact that FTD is a relatively common cause of dementia, it receives a disproportionately small fraction of overall dementia research funding. In particular, little funding has gone towards translating new research on disease targets into drug discovery programs with the potential to create new drugs. Funding has also been limited for understanding important “non-drug” issues, like palliative care, specific to FTD-spectrum patients and their caregivers.
Acknowledgements

This report was jointly commissioned by the Association for Frontotemporal Dementias (AFTD) and the Alzheimer's Drug Discovery Foundation (ADDF). The data complied, analyzed and reported in this landscape was performed by an independent consultant, Christopher Walentas, PhD under the direction and guidance of Howard Fillit, MD, Executive Director and Diana Shineman, PhD, Assistant Director for Scientific Affairs, at ADDF. We also thank Phil Lovett, Helen Comstock, Kent Jamison, Susan Dickinson, Brad Boeve, MD, and the members of the AFTD Medical Advisory Council for their support and contributions to this report.

This analysis would not have been possible without the support and efforts from a sizable number of individuals worldwide (appendices E-G). We would particularly like to recognize the contributions of: Antony Horton, PhD, International Rett Syndrome Foundation; Robert Goldstein, MD, PhD, and Marie Nierras, PhD, Director of Research, Partnerships and Consortia, Juvenile Diabetes Research Foundation; and Kim Hunter-Schaedle, PhD, Children’s Tumor Foundation. Special gratitude is extended to Kyle Brown, Founder/CEO, Research Crossroads, for his guidance and patient assistance in carrying out iterative queries of his resources.
A STRATEGIC ANALYSIS OF INTERNATIONAL RESEARCH FUNDING FOR THE
FRONTOTEMPORAL DEMENTIAS 1998-2008

TABLE OF CONTENTS

1 INTRODUCTION
1.1 Background to the FTD Landscape Analysis 9
1.2 Overview of Frontotemporal and Related Dementias 9
1.3 Background to Drug Discovery & Development 11

2 METHODS
2.1 Overview of Methods 13
2.2 Search Term Development 13
2.3 Data Sources: International Biomedical Research Grantors Research Crossroads 14
2.4 Biomedical Research Activity Classification System 14
2.5 Classification System Development and Data Coding 15
2.6 Data Collection and Processing 16
2.7 Building the FTD Landscape Funding Database 17
2.8 Clinical Trials 18

3 RESULTS
3.1 Overview of Final Dataset 19
3.2 Funding Organizations 19
3.3 Stage of Discovery: Primary Outcome Measure 20
3.4 Diagnosis-Specific Analysis of FTD-Spectrum Dementias 22
3.5 Target Analysis: FTD Drug Targets and Biological Terms 22
3.6 Funding Gap Analysis of FTD by Research Activity 24
3.7 Clinical Trials 24

4 DISCUSSION
4.1 Overview 26
4.2 Key Findings from the Analysis 26
4.3 Comparison to Other Analyses 27
4.4 Key Recommendations 28
4.5 Limitations of Analysis 29

5 CONCLUSION 30
6 BIBLIOGRAPHY 31

APPENDIX A: TABLES 33
APPENDIX B: FIGURES 63
APPENDIX C: BIOMEDICAL RESEARCH ACTIVITY CLASSIFICATION SYSTEM 100
APPENDIX D: ABBREVIATIONS 103
APPENDIX E: RESEARCH FUNDING CONSULTANTS 104
APPENDIX F: AFTD MEDICAL ADVISORY COUNCIL 105
APPENDIX G: LEAD CONTACTS 106
LIST OF TABLES

Table 1. Combined Search Terms
Table 2. Quantification of Methods: Annotated Algorithm for Research Crossroads FTD Data Subset
Table 3. Quantification of Methods: Annotated Algorithm for Research Crossroads FTD-Relevant Alzheimer’s Disease Data Subset
Table 4. Quantification of Methods: Annotated Algorithm for Grants Independently Obtained from Foundations
Table 5. Quantification of Methods: Annotated Algorithm for Merging Data Subsets
Table 6. FTD Targets and Related Biological Terms
Table 7. Invited and Participating Grantors by Type
Table 8. Ongoing Registered Clinical Trials of FTD-Spectrum Dementias by Phase and Recruitment Stage
Table 9. Ongoing Registered Clinical Trials on FTD-Spectrum Dementias: Drugs or Dietary Supplements
Table 10. Ongoing Registered Clinical Trials on FTD-Spectrum Dementias: Other Interventions
Table 11. Terminated Clinical Trials on FTD-Spectrum Dementias
Table 12. Published Clinical Trials on FTD or Primary Progressive Aphasia by Drug Class
Table 13. Published Clinical Trials on Progressive Supranuclear Palsy
Table 14. FTD Grant For-Profit Recipients
Table 15. FTD Grant Non-Profit Recipients, Alphabetical
Table 16. FTD Grant Non-Profit Recipients, Ranked
LIST OF FIGURES

FIGURE 1. GENERALIZED SCHEMATIC OVERVIEW OF THE DRUG DISCOVERY AND DEVELOPMENT PROCESS 64
FIGURE 2. REPRESENTATION OF ATTRITION RATE OF COMPOUNDS THROUGH THE DRUG DEVELOPMENT PROCESS OVER TIME 65
FIGURE 3. SUCCESS RATES BY CLINICAL STAGE OF DEVELOPMENT 66
FIGURE 4. SUCCESS/FAILURE RATES BY CLINICAL STAGE AND THERAPEUTIC AREA 67
FIGURE 5. OVERALL BREAKDOWN OF GRANTS AND FUNDING BY COUNTRY OF ORIGIN: US VS. FOREIGN 68
FIGURE 6. GRANTS AND FUNDING BY GRANTOR TYPE 69
FIGURE 7. DISTRIBUTION OF GRANTS AND FUNDS BY GRANTOR TYPE OVER TIME 70
FIGURE 8. GRANTS AND FUNDS BY PUBLIC AGENCY 71
FIGURE 9. NIH GRANTS AND FUNDING BY INSTITUTE 72
FIGURE 10. GRANTS AND FUNDING BY FOUNDATION 73
FIGURE 11. TOTAL FUNDING BY MAJOR RESEARCH CATEGORY 74
FIGURE 12. OVERALL EXPENDITURE BY MAJOR RESEARCH CATEGORY & GRANTOR TYPE 75
FIGURE 13. ANNUAL GRANTS AND FUNDS BY MAJOR RESEARCH CATEGORY: BASIC & DISEASE RESEARCH AND PRE-CLINICAL TREATMENT DEVELOPMENT 76
FIGURE 14. ANNUAL GRANTS AND EXPENDITURE BY MAJOR RESEARCH CATEGORY: CLINICAL TREATMENT EVALUATION (3.0) & DETECTION, DIAGNOSTICS & IMAGING (4.0) 77
FIGURE 15. ANNUAL GRANTS AND FUNDS BY MAJOR RESEARCH CATEGORY: DISEASE MANAGEMENT 78
FIGURE 16. TOTAL EXPENDITURE BY DETAILED RESEARCH ACTIVITY: BASIC & DISEASE RESEARCH (1.0) 79
FIGURE 17. TOTAL EXPENDITURE BY DETAILED RESEARCH ACTIVITY: PRE-CLINICAL TREATMENT DEVELOPMENT (2.0) 80
FIGURE 18. EXPENDITURE BY DETAILED RESEARCH ACTIVITY: TREATMENT EVALUATION (3.0), DETECTION, DIAGNOSTICS & IMAGING (4.0) & DISEASE MANAGEMENT (6.0) 81
FIGURE 19. GRANTS AND FUNDS BY DEMENTIA & GRANTOR TYPE 82
FIGURE 20. ANNUAL GRANTS AND FUNDING: PICK’S DISEASE & FTD/FTLD 83
FIGURE 21. ANNUAL GRANTS AND FUNDING: CORTICOBASAL DEGENERATION AND FTD WITH MOTOR NEURON DISEASE 84
FIGURE 22. ANNUAL GRANTS AND FUNDING: PRIMARY PROGRESSIVE APHASIA, PROGRESSIVE NONFLUENT APHASIA & PROGRESSIVE SUPRANUCLEAR PALSY 85
FIGURE 23. ANNUAL GRANTS AND FUNDING: SEMANTIC DEMENTIA & FTD WITH PARKINSONISM LINKED TO CHROMOSOME 17 86
FIGURE 24. GRANTS AND FUNDING: FTD/FTLD WITH UBQUITIN INCLUSIONS & ALZHEIMER’S DISEASE 87
FIGURE 25. GRANTS AND FUNDING BY TARGET OVER TIME 88
FIGURE 26. GRANTS AND FUNDING BY GRANTOR TYPE OVER TIME: TAU, UBQUITIN & PROGRANULIN 89
FIGURE 27. GRANTS AND FUNDING BY GRANTOR TYPE OVER TIME: GSK3β, CDK5 & HEAT SHOCK PROTEINS 90
FIGURE 28. GRANTS AND FUNDING BY GRANTOR TYPE OVER TIME: PIN1, VCP & TDP-43 91
FIGURE 29. FUNDING BY DETAILED RESEARCH ACTIVITY: TAU 92
FIGURE 30. FUNDING BY DETAILED RESEARCH ACTIVITY: CDK5, GSK3-BETA & PIN1 93
FIGURE 31. FUNDING BY DETAILED RESEARCH ACTIVITY: UBQUITIN & HEAT SHOCK PROTEINS 94
Figure 32. Funding by Detailed Research Activity: TDP-43, Valosin-Containing Protein & Progranulin

Figure 33. Target Discovery & Validation Expenditure by Individual Grantor

Figure 34. NIH Appropriations, NIA & NINDS Research Budgets and FTD Extramural Funding

Figure 35. Comparison of FTD Research Expenditure
1 INTRODUCTION

1.1 BACKGROUND TO THE FTD LANDSCAPE ANALYSIS

The FTD Landscape Analysis provides an overview of funding towards frontotemporal and related dementias research, and is designed to capture an historical perspective of funding along a continuum of research activities from fundamental scientific research through to the clinical evaluation of treatments using a bespoke biomedical research activity classification system developed for this analysis.

The intent of this analysis is to review research funding provided by public and private agencies internationally, explore the overall pattern of research spending and determine where gaps and opportunities exist to minimize duplication of efforts, and develop future programs that will facilitate drug discovery and the development of treatments for FTD.

Overall, this analysis is intended to be an informational document to facilitate the future needs of the research community with a specific emphasis on translational research. While it was not possible to capture all data from all grantors worldwide, every effort was made to make this analysis as comprehensive as possible.

1.2 OVERVIEW OF FRONTOTEMPORAL AND RELATED DEMENTIAS

Frontotemporal and related dementias represent one of four major dementia groupings that include: Alzheimer’s disease (AD), Parkinson’s disease (PD), including Lewy body disease, and the vascular dementias. The frontotemporal dementias (FTD), the subject of this analysis, encompass a clinical spectrum of progressive neurodegenerative disorders that share pathological features of frontotemporal lobar degeneration (FTLD). FTD is considered to be the second most common form of early-onset dementia after AD, representing 5-10% of all dementias. However, its prevalence jumps to 10-20% in patients with an onset before 65 years.

Most neurodegenerative disorders are characterized by the accumulation of abnormally folded proteins in or around neurons and glia cells of the central nervous system. These protein aggregates are thought to be central to disease pathogenesis and result in the death of these cells. Parkinson’s disease, for example, results from the accumulation of ubiquitinated α-synuclein into Lewy bodies resulting in loss of dopaminergic neurons in the substantia nigra, the area of the brain that controls movement. Alzheimer’s disease is typified by extracellular amyloid plaques (composed of aggregated β-amyloid protein) and intracellular neurofibrillary tangles of aggregated microtubule binding protein tau, resulting in neuronal loss in the cerebral cortex and hippocampus where memories are stored. FTD patients also exhibit these neurofibrillary tangles, however they are present in the frontal and temporal lobes that control executive and higher behavioral functioning. The vast majority of frontotemporal-spectrum dementias, while clinically heterologous, are characterized by
either neurofibrillary tangles of tau or aggregates of a different protein, TAR DNA-binding protein (TDP-43). Since FTD and AD both exhibit neurofibrillary tangles, this analysis was designed to capture all research on tau irrespective of disease. On the other hand, grants focused on targeting other protein aggregates not seen in FTD were not captured including, for example, research on amyloid plaques for AD or on α-synuclein and Lewy bodies as seen in PD.

FTD can be divided into tau-positive and tau-negative for the presence or absence of intracellular neurofibrillary tangles composed of deposits of aggregated microtubule associated protein, tau. Pick’s disease, the historical name for FTD, multiple system tauopathy, and FTD with Parkinsonism linked to chromosome 17 (FTLD-17) comprise the tau-positive FTDs. FTD with ubiquitin-positive and tau- and α-synuclein-negative inclusions (FTD-U), and FTD with motor neuron disease (FTD-MND) represent the tau-negative FTDs. Clinically, the FTD-related dementias also include corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP), as well as the language affecting disorders semantic dementia (SD), primary progressive aphasia (PPA), and progressive nonfluent aphasia (PNA or PNFA). Patients with these clinical diagnoses also usually exhibit tau pathology.

Mutations within the tau gene, MAPT, are thought to cause FTD with Parkinsonism linked to chromosome 17 (FTDP-17); common variations in MAPT are strongly associated with an increased risk for PSP and CBD as well. Tau binds and stabilizes microtubules, an intracellular protein scaffold along which the cell can selectively route materials. In neurons, microtubules conduct the proper delivery of cellular components along the axon and are thus central to normal functioning. The over-phosphorylation of tau under disease states leads to its aggregation and the formation of neurofibrillary tangles. Neurofibrillary tangles are also a pathological hallmark of AD, implicating tau as a principle actor across these neurodegenerative diseases.

Heat shock proteins (hsp’s) represent a family of functionally related proteins that assist in facilitating the proper folding of other cellular proteins by binding to unfolded or misfolded polypeptide sections. These folding chaperones are named for their increased expression as a cellular response to a range of stressors including heat, toxins, UV irradiation, or inflammation. Hsp70 and hsp90, named by their molecular masses in kilodaltons, have been actively studied in the dementia field for their ability to affect the misfolding and subsequent pathogenic aggregation of proteins.

Ubiquitin also plays a central role in protein turnover and acts as a molecular tag for proteins targeted for degradation by the proteosome. This tag is attached to mutated or misfolded polypeptides, as well as on normal proteins at the end of their useful lifetime. The ability of the ubiquitin-proteosome system to detect, target, and remove misfolded proteins involved in the pathology of many neurodegenerative diseases has made it an attractive therapeutic target.

Cyclin-dependent kinase 5 (cdk5) and glycogen synthase kinase 3 beta (GSK3β) have both been implicated in catalyzing the over-phosphorylation of tau at specific motifs (serine- or threonine-proline) promoting its aggregation and neurofibrillary tangle formation. Proline is a structurally
unique amino acid in that it can exist in one of two interchangeable conformations, and thus introduce a “flippable” bend or kink at its position within a protein. When in an “open” conformation, the residue to be phosphorylated is more exposed permitting the kinases easier access. While the change between these conformational states occurs naturally, its rate is very slow, but can be accelerated by enzymes, called geometrical isomerases, that are able to catalyze these alterations in protein shape. The prolyl isomerase, Pin1, catalyzes this cis/trans transition at proline permitting easier access for GSK3β and cdk5 to phosphorylate tau9. Inhibiting the activity of these kinases would block tau over-phosphorylation, and the subsequent formation of neurofibrillary tangle, representing another promising area for the development of treatments for FTD-related dementias.

Recently, a genetic study found mutations in a new candidate gene are strongly associated with FTD and also map to chromosome 17, but in the absence of tau mutations or tau pathology10. This gene is located adjacent to MAPT and codes for a secreted precursor protein, progranulin, which has growth factor-like properties and weak anti-inflammatory activity. Extracellular proteolytic cleavage of progranulin generates a family of granulin peptides (6-25 kDa.) that are strongly pro-inflammatory; however, the exact function of these granulins in brain remains undetermined3, 11.

Two other proteins newly implicated in FTD and related dementias include TAR DNA-binding protein (TDP-43) and valosin-containing protein (VCP). TDP-43 is a nuclear protein involved in transcriptional regulation and was only recently found to be a major protein component of the ubiquitin-positive, tau-negative inclusions characteristic of both sporadic and familial FTD-U, FTD with motor neuron disease (MND), as well as sporadic amyotrophic lateral sclerosis (ALS)11. TDP-43 in these disorders is aggregated, abnormally phosphorylated and ubiquitinated, and defines a unique class of proteinopathies. Valosin-containing protein (VCP) is a member of the AAA-ATPase superfamily of enzymes involved in multiple cellular systems including protein transport and ubiquitin-proteosome-dependent degradation. While rare, mutations in VCP are now known to cause FTD with inclusion body myopathy and Paget’s disease of the bone. However, as seen in FTD and ALS, brains of these patients also contain pathological inclusions of ubiquitinated TDP-43 protein12.

1.3 BACKGROUND TO DRUG DISCOVERY & DEVELOPMENT

The basic stages that comprise the overall process of drug discovery and development will be outlined here, along with some recent estimates to place the complexity, duration, and cost of drug development in its proper context.

Recent studies estimate the average cost of developing a single drug to be $1.3-1.7 billion and that the process takes 10-15 years13, 14. Given the size of this commitment in terms of both capital and time, it is perhaps even more startling to learn that only 2 or 3 out of every 10 marketed medicines, irrespective of therapeutic area, break even in terms of recouping their research and development costs.

Because FTD is a relatively rare disease, drug discovery research for FTD can be expedited through provisions set in place by the Orphan Drug Act. This act was put into place as means to encourage pharmaceutical companies to develop drugs for diseases that have a small market. The government
can offer tax incentives, enhanced patent protection and marketing rights, and financial subsidies for clinical and basic research. These efforts will aid in bringing FTD-targeted drugs to market faster and for less money when compared to other more prevalent diseases.

Briefly, drug discovery and development can be broken down into a progressive series of activities. For the purposes of this overview, these are: target discovery/validation, lead discovery/validation, pre-clinical development and clinical evaluation (fig. 1). As one moves along these stages, an increasingly substantial commitment of funding is required and each stage is associated with a considerable amount of risk. This analysis was explicitly designed to broadly capture a wide spectrum of healthcare research activities as well as those that comprise drug discovery and translational research in greater detail.

Drug discovery was classically serendipitous and many drugs taken even today have no known target or mechanism of action. However, as the understanding of diseases at a molecular level has increased, a more rational, target-driven approach to drug discovery is now possible. A target can be defined as the biological component upon which a potential drug exerts its efficacious activity. Once a target has been validated for its role in pathogenesis, the next goal is to identify lead compounds or biologicals that are able to positively affect disease with a minimum of side effects. Target-based drug discovery has been driven by the genomics revolution of the last decade and has given researchers many thousands of genes, and gene products to target in drug discovery efforts. This can be a complex, and time and resource consuming task. Furthermore, insight into the normal function of a specific gene does not always directly connect the gene, or its product, to a disease process.

It has been estimated that for every 5,000-10,000 compounds that enter the drug development pipeline, only 250 (2.5-5%) will progress to pre-clinical development as “leads”. 5 (0.1-0.5%) will move forward into first-in-man studies (Phase I), of which only a single compound will survive to be an approved drug (0.01%; fig. 2). These numbers represent an average across all therapeutic areas and thus include treatments for which the mechanism of action has been established, reformulations (“me too drugs”), as well as truly novel agents.

Focusing upon the clinical evaluation end of the drug development pipeline, the average overall likelihood of a compound making it from a first-in-man study (Phase I) to FDA approval (new drug application, NDA) has been reported to be 11% (fig. 3). This number varies substantially across therapeutic areas, and CNS (8%), under which FTD and its related dementias were categorized, was the third lowest. This was better than oncology (5%), whereas infectious disease, arthritis/pain (each ~17%), and cardiovascular disease (~20%) enjoyed higher average rates of success (figs. 3-4).
2 METHODS

2.1 OVERVIEW OF METHODS
This landscape analysis was defined by two fundamental decisions: which data to include and how to structure and therefore analyze it. Both were made after consultation with senior directors from biomedical research foundations that have direct experience conducting similar analyses in their own therapeutic areas (appendix E). Their advice was tailored to the AFTD/ADDF’s needs by soliciting input from the AFTD’s medical advisors (AFTD MAC, appendix F), and scientific/executive staff at the ADDF; a list of lead contacts can be found in appendix G.

Briefly, a preliminary set of search terms was compiled and submitted to the AFTD advisors for comments. The finalized set of terms was then used to extend invitations to participate with formal requests for data. Concomitant with these requests, a biomedical research classification system was developed that was to be the primary outcome measure of this analysis. This tool was necessary to quantize the myriad research and development activities from basic scientific and disease research through to the clinical evaluation of treatments. Furthermore, it was structured to capture a wider range of supporting technologies and complementary activities in a manner independent of therapeutic area. For a more detailed description, see section 2.4, Biomedical Research Activity Classification System.

2.2 SEARCH TERM DEVELOPMENT
Initially, two sets of search terms were compiled. One contained clinical terms developed to define the spectrum of frontotemporal and related dementias. The second set was comprised of biological terms, including proteins, genes as well as other validated biomarkers and mechanistic pathway components in an attempt to encompass all known common molecular mechanisms, and thus capture all related research on FTD-spectrum dementias. Prior to the formal solicitation of data from grantors, preliminary queries of the Research Crossroads database with both sets of search terms (clinical and biological) was undertaken. As anticipated, the clinical set of terms returned a sizable number of pertinent hits focused on FTD research, whereas some of the biological terms returned a considerable number of irrelevant grants eg, heat shock proteins, ubiquitin. A final set of combined search terms (table 1) was approved by the ADDF scientific staff, and Bradley F. Boeve, MD, Chairman of the AFTD Medical Advisory Council.

In order to capture and include grants focused on Alzheimer’s, but with programs related or applicable to FTD, Research Crossroads was also queried with “Alzheimer’s” as the sole search term to capture the entire Alzheimer’s dataset. This Alzheimer’s dataset was then culled to contain only those grants with any of the FTD-relevant biological search terms. This dataset was then merged with the results returned from the query with our combined terms (the FTD dataset) and duplicates were removed. This final Research Crossroads dataset should thus contain all grants applicable to
frontotemporal and related dementias (clinical terms) as well as all Alzheimer’s research that addresses known common mechanism between FTD and AD.

2.3 DATA SOURCES:

International Biomedical Research Grantors

Internet searches supplemented consultations with opinion leading researchers and clinicians in the field, and senior directors from a range of medical research grant awarding institutions. Contacts were obtained either through these consultations and searches, or by direct contact with grantors. Formal requests for data were forwarded electronically and included: search terms, time frame (1998-2008) and a list of desired data fields. The fields requested included: principle investigator name, institute, start year, end year or duration, award amount, title and abstract. However, the absolute minimum required fields for the primary outcome measure were: title and/or abstract, dates or start date and duration, and grant amount awarded.

Research Crossroads

This analysis would simply not have been possible without Kyle Brown and Research Crossroads. This database represents a singular resource for biomedical funding by the NIH and constituted the majority of our dataset, as the NIH is by far the largest patron of biomedical research. Research Crossroads merges all data contained within the NIH CRISP (Computer Retrieval of Information on Scientific Projects) database with the respective financials contained within the RePORT (Research Portfolio Online Reporting Tool) database maintained by the NIH Office of Extramural Research. CRISP contains scientific abstracts, but no award amount information. RePORT contains disbursements data, but no scientific abstracts (titles only). Both databases were created and maintained by the NIH, however they are unable to exchange information.

2.4 BIOMEDICAL RESEARCH ACTIVITY CLASSIFICATION SYSTEM

The primary outcome measure for this analysis mapped where funds have been allocated along the continuum from basic disease research through to the clinical evaluation of treatments, including complementary and supporting technologies eg, development and validation of biomarkers, diagnostics, imagining reagents and technologies, as well as a wider range of additional healthcare research disciplines.

In order to structure the overall analysis so that research priorities, preferences and funding patterns by research activity could be discerned, a classification system was developed that combined two tools already in use. The overall structure was taken from the Health Research Classification Scheme used for both the UK Health Research Analysis (2006)\(^1\) and the subsequent analysis of a larger number of UK charities, From Donation to Innovation (2007)\(^1\), both published by the UK Clinical Research Collaboration. These Research Activity Codes were themselves modeled on the Common Scientific Outline developed at the National Cancer Research Institute (UK) in their 2002 strategic analysis of cancer research funding in the UK\(^2\).
Into this broader outline was built a more detailed breakdown of the drug development process developed on behalf of the Institute for the Study of Aging and the Alzheimer’s Research Forum; it was recently utilized in an analysis of the Alzheimer’s Drug Discovery Foundation’s entire research portfolio to chart the investigator-verified progress of its lifetime research portfolio [unpublished data]. A complete breakdown of the 96 composite subcategories and the detailed structure of research activities presented here can be found in appendix C.

2.5 CLASSIFICATION SYSTEM DEVELOPMENT AND DATA CODING

There were two major changes between the initial and final schemes, both of which would affect the outcome of the analysis. The first was the placement of natural history studies. Initially these clinical observational studies were a part of other clinical studies, including treatment evaluation. These epidemiological studies, along with genotype-phenotype assessments, were therefore moved to a more appropriate place at the traditional beginning of our understanding of disease and its presentation. This also had the effect of splitting clinical research and anchoring the clinical evaluation of treatments at the end of the drug development pathway. The second significant change concerned the in vivo validation of targets and how the progress from construction of models to their validation and subsequent usage of cellular and animal models should be codified. Previous iterations had two subcategories: cellular and animal models with no distinction made between construction and usage. This additional layer of granularity warranted inclusion and so category 1.2.5.3, in vivo pre-clinical proof-of-concept, was added to capture the usage of animal models to generate proof-of-concept data. These data are normally crucial for attracting sufficient capital to progress on to lead discovery and pre-clinical development.

Attaching a single research activity code to a grant can be seen in one of two ways. From the point of view of accumulated knowledge, assigning a single activity to any biomedical research grant oversimplifies all of the work that came before. However, from a forward looking perspective, one can assume that to be at any stage, important foundation laying work had to take place beforehand. Therefore, we assigned a biomedical classification code to the single furthest, reasonably attained stated aim of the grant.

Another fundamental decision that was made during the course of this analysis was how to capture disbursements over time. In an effort to justifiably maximize the retention of data, but use it unaltered, it was decided that this analysis would place grants’ funds in their entirety at the first year of support. For instance, if a $10 MM grant ran from 1995-2005, then the annual average of those funds that fell within the timeframe (1998-2008) would be summed and pegged to the first year eg, $7 MM in 1998. This had two immediate effects. First, it negated any complications arising from the manipulation or conversion of date data, an unanticipated technical pitfall that arose during this analysis. Secondly, it permitted more grants to be retained despite missing date fields or whole disbursements. As with the mapping of grants to a single research activity, and placing all funds at a single time point, this significantly reduced the signal-to-noise of subsequent analyses while minimizing exclusions. The selective and judicious easement in accuracy was deemed acceptable in light of the many-fold returns in data retention, final dataset size, and consequent robustness.
2.6 **DATA COLLECTION AND PROCESSING**

All data came from external sources and therefore there can be no warranties to its accuracy or completeness. Data were obtained electronically in a range of file formats, containing a variety of data fields.

The entire dataset can be broken down into 3 constituent subsets: the FTD and Alzheimer's disease data subsets from Research Crossroads, and data from all other sources. The FTD dataset was obtained querying Research Crossroads with the combined search terms (table 1). The Alzheimer's disease subset used “Alzheimer” as a search term. All other data from individual sources was also obtained using the combined search terms, except for the ADDF, AFTD, AHAF, MRC, NHMRC, and the Cure Alzheimer's Fund, where the entire database was either obtained, or as in the case of CIHR data, accessed remotely. These methods are articulated in tables 2-4 and the entire process is summarized in table 5.

The FTD dataset from Research Crossroads was obtained on 26 Aug. 2008 and on 30 Sept. 2008 the Alzheimer's dataset was received. Data acquired by invitation from other sources were accepted on a rolling basis from Aug-Dec. 2008, and represents the third data subset.

Research Crossroads updates weekly from its sources and so 2008 values, while included in this analysis, should be noted as **incomplete**. The FTD dataset contained 35 weeks of data and the Alzheimer's set contained 40 weeks, or on average 67% and 77% of the entire year, and thus both are at least two-thirds complete if one assumes an even distribution of grants over the year.

Data were provided in one of two ways and every effort was made to retain as much useful data as possible. Research Crossroads outputs, and hence the majority of the data, were supplied with rows representing single disbursements with multiple rows representing a multi-disbursement (multi-year) award. All other data were provided as “parent grants” either with or without disbursement details.

Research Crossroads data were obtained as a .csv file and uploaded directly into a spreadsheet. All other data were obtained in a range of file formats and transferred to a master spreadsheet where fields were reconciled manually. Research Crossroads data were structured as entries, where disbursements were provided in individual rows, and investigator name and title were matched to form a complete “parent grant”. Else, data were provided as parent grants with any specific disbursement information, if provided, residing in additional columns.

Disbursements or whole grants without award amounts were excluded as a condition of the primary outcome measure, as were missing both start and end dates (or start date and duration), or title and abstract. These data were presented here as grants for the purpose of maximizing their retention, however no attempt was made to either backfill or interpolate missing fields. Independently obtained grants data, owing to their very inclusion contained total award amount and information regarding their date and duration. However, owing to how CRISP, and thus Research Crossroads, data were structured, grants could be retained despite missing information. A missing abstract in
one disbursement could be reasonably associated with that of another disbursement of the same parent grant. The same however was not assumed for missing award amounts and no attempts were made to interpolate missing disbursements. The remaining disbursements were consolidated into parent grants by matching investigator and grant title and any duplicates not automatically reconciled were done so manually. In both instances, the entirety of the grant was pegged to the initial year of support.

Foreign awards were converted from local currency into U. S. dollars ($ USD) using historical tables of inter-bank rates. Owing to vacillations in value of the dollar over time, an annual average for the year of each disbursement was used (www.oanda.com).

### 2.7 Building the FTD Landscape Funding Database

Briefly, the FTD Research Crossroads data subset, obtained by querying with the combined set of search terms (table 1), initially contained 662 entries ($193 MM). 248 entries were removed for having no award amounts, and the remaining 414 entries were determined to represent 136 unique grants. 8 entries (from 3 grants) were removed that represented formatting duplicates, as were 17 entries (from 6 grants) that fell wholly outside of the timeframe, leaving a final FTD Research Crossroads dataset of 127 grants ($188.2 MM). Table 2 outlines this process.

Similarly, the Research Crossroads Alzheimer's subset initially contained 23,776 entries ($6.1B). 7,414 entries were removed for not having award amounts. The remaining 16,362 entries were queried against the list of biological search terms (table 6) to extract FTD-relevant grants. Duplicates and entries with crucial fields missing were removed, resulting in 345 grants ($428.3 MM) that were retained. 21 additional grants were removed at this stage for falling wholly outside the desired timeframe (1998-2008) leaving 324 FTD-relevant Alzheimer's grants representing $418.5 MM in funds summarized in table 3.

All other data were obtained in a myriad of file formats and were transferred to a master spreadsheet where like fields were manually reconciled. Grants were normalized by per anum disbursement, and converted to U. S. dollars as necessary using an average annual exchange rate. Average annual disbursements that fell outside of the timeframe were removed and consolidated back into parent grants. From an initial ~500 independently acquired grants, 449 ($101.1 MM) were retained as summarized in table 4.

The three data subsets: FTD (127 grants, $188.2 MM), FTD-Alzheimer's (324 grants, $418.3 MM) and grants from other sources (449 grants, $101.1 MM) were merged to form a 900 grant master dataset, representing $707.7 MM in funding (table 5). Duplicates captured within the FTD-specific and FTD-relevant Alzheimer's subsets were removed.

Grants were then individually considered for their overall relevance and most reasonably attained specific stated research aim. Any grant whose research classification category or overall relevance was not obvious was flagged for secondary review. It was noted at this stage that 11 tau-relevant grants were excluded for not containing any of the selected tau-related search terms within their titles or abstracts. They did however contain the term “tangle”, and so it was added as a term at this
stage, and these grants were retained. Additionally, the typographical error, “vasolin”, was found in 3 grants and so it and VCP, which had not made the initial list, were also included. All final classification and exclusion determinations were made with the approval of ADDF research staff.

2.8 CLINICAL TRIALS
Data on registered clinical trials for FTD and related dementias were obtained by querying clinicaltrials.gov with the following search terms on Dec 12, 2008: frontotemporal, pick’s, corticobasal, supranuclear, aphasia and semantic. Out of the 373 hits returned, 31 clinical trials (8 completed, 21 ongoing, 2 terminated) with a total patient population of over 20,000 were found to be of direct relevance to the FTD-spectrum dementias from 1991-2008. No additional trials were found on the WHO clinical trials database and the European clinical trials registry, EudraCT, is not publicly available outside of member states.

Published trials relevant to FTD were compiled by Boeve who has subsequently updated those results to include more recent trial reports.
3 RESULTS

3.1 OVERVIEW OF FINAL DATASET
The final dataset contains 613 grants for research programs relevant to frontotemporal and related dementias awarded between 1998-2008, representing $432,167,275 ($432 MM) in funding from 19 foundations and public institutions from 7 countries and the European Union, as well as 17 of the 27 (63%) Institutes and Centers of the U. S. National Institutes of Health (NIH) (table 7). 89% of all captured funding was US-based (fig. 5) and 83% originated at the NIH (fig. 6).

The overall response rate for participation was 63.6% taking into consideration that data from the NIH, NSF and CORDIS were obtained from Research Crossroads, and that grantors with no relevant data were still included as respondents (table 6). Looking at the distribution of support for FTD research over time, it is clear that the majority of funding is from the NIH. However, its financial contribution has dropped 5-fold from 1999-2007 ($54.6-10.4 MM), despite a sizeable increase in number of awarded grants over this time period (25-45 grants; fig. 7); data for 2008 were incomplete and only covered the first two-thirds of the year, see section 2.5, Data Collection and Processing. This 5-fold decrease in funding was in part offset by steadily increasing, yet modest contributions from non-NIH sources, including philanthropies. Foundations funded $37.8 MM in FTD-related research from 1999-2007 (fig. 7b). Support from other US (non-NIH) and foreign governments has remained low with the exception of two awards in CORDIS for over $2 MM in 2007, and a $2 MM grant from the Health Research Board of Ireland for a genetic association study on ALS-MND and related disorders.

3.2 FUNDING ORGANIZATIONS

Public Funding
Data were obtained from 9 public agencies from the US, UK, Canada, Australia, Ireland, Switzerland and the EU, including the entire research portfolio from the NHMRC and MRC (table 7). Public funding for FTD and related dementia research constituted 90% of all data captured in this analysis (fig. 6b). The NIH was the majority contributor ($359.2 MM; 83% of total funds, 92% of all public funds) with the next largest public grantors being the CIHR (31, $7.9 MM), MRC (12, $7.6 MM), CORDIS (4, $7.0 MM), NHMRC (19, $3.2 MM) and the HRB (3, $2.6 MM); the remainder contributed less than $1 MM each. All non-NIH public funding totaled 75 grants worth $29.9 MM (fig. 8).

Grants from 17 out of the 27 (63%) institutes and centers of the NIH were captured in this analysis totaling 325 grants or $359.2 MM (fig. 9). 68% ($243.7 MM) of these funds originated at the NIA with an additional $57.2 MM from the NINDS, and ~$15 MM each from the NIGMS and NHGRI (fig. 9b); the NHGRI funds were to establish a Center of Excellence for Genome Sciences at the University of Washington (Seattle) dedicated to studying natural genetic variation in patients with progressive supranuclear palsy, amongst other diseases.

Other Public Agency Funding
This mixed grouping of international public grantors consisted of the federal agencies of Australia (NHMRC), Canada (CIHR), Switzerland (SNSF), and the Medical Research Council (UK), National
Institute for Health Research (UK), and Health Research Board (Ireland), but also contained data from the European Union’s Community Research & Development Information Service (CORDIS), and the National Science Foundation (US). Some of this data were obtained through Research Crossroads (CORDIS, NSF), however most were compiled independently.

**Foundations’ Funding**

Data were obtained from 10 foundations from the US, UK and Italy totaling 213 grants (34.7% of total grants) and $43.0 MM (10.0% of total funds), with nearly two-thirds (61.9%) of all non-government funds originating at either the Alzheimer’s Association or Wellcome Trust (**fig. 10**). An additional ~$5 MM (~10%) was from the Alzheimer’s Drug Discovery Foundation (ADDF) and the American Health Assistance Fund (AHAF), their contributions representing 17% and 28% of their entire respective research portfolios [data not shown]. The Cure Alzheimer’s Fund, AFAR and the AFTD funded 8 grants for a combined $483,000.

**3.3 Stage of Discovery: Primary Outcome Measure**

Analyzing the entire dataset by the primary outcome measure, nearly three-quarters (73.9%, $319.3 MM) of the research funding captured was dedicated to **Basic & Disease Research**, the first major category of this scheme (**fig. 11**). Category 1.0 encompasses all research activities that span from studying fundamental biological processes and determining how they normally function (1.1), through to the clinical presentation and pathogenesis of disease, *i.e.*, understanding how these processes can break (1.2.1 & 1.2.2), and on towards achieving a molecular understanding towards developing a therapy (1.2.4 & 1.2.5). Other major categories include **Pre-Clinical Treatment Development** (2.0; 55 grants, $36.7 MM), **Clinical Treatment Evaluation** (3.0; 19 grants, $43.7 MM), **Detection, Diagnostics & Imaging** (4.0; 58 grants, $31.5 MM), and **Disease Management** (6.0; 4 grants, $990 K); no grants were found within **Prevention & Risk Factor Management** (5.0), or **Healthcare Services, Policy & Methodology** (7.0; **figs. 12-15**). A full breakout of the classification scheme employed here, with descriptions of inclusive research activities, is detailed in **appendix C**.

This classification system should not be considered strictly linear. While there is some degree of temporal relationship between the first three major categories of this scheme *i.e.*, the development of treatments normally precedes their evaluation, moving along component subcategories does not necessarily translate into progress in therapeutic development.

Looking at the distribution of grants and funds by major research category over time, funding for **Basic & Disease Research** was steady from 1999-2004, after which a continual decline was observed (**fig. 13a**). This decrease coincides with the drop-off in NIH support seen above (**fig. 7**). The other major categories were relatively under-resourced as evidenced by the diminished scale of both grants and funds (**figs. 13b-15**). Funding within categories 2.0, 3.0 and 4.0 was 7-8 fold lower than **Basic & Disease Research** (1.0).

**Basic & Disease Research (1.0)**

Ten out of the 11 component subcategories within **Basic & Disease Research** were populated with grants (**fig. 16**). Funding within this category clustered in three distinct areas: 133 grants...
($84.9 MM) were directed towards a clinical (1.2.0, 1.2.1) or mechanistic (1.2.2) understanding of disease processes, 279 grants ($151.6 MM) were devoted to target discovery (1.2.4) or target validation (1.2.5), and 9 grants ($47.3 MM) went towards infrastructure in support of research activities within this category, including grants for core facilities and capital equipment. An additional 52 grants ($30.7 MM) were devoted to understanding normal underlying biological processes (1.1.0 & 1.1.1).

**Pre-Clinical Treatment Development (2.0)**

This major category and its component subcategories were developed from a drug discovery tutorial commissioned by the ADDF/ART\(^{19}\). Forty-five percent of the component subcategories within Treatment Development were populated with grants, nearly half as many as that seen in Basic & Disease Research (1.0), not unsurprising with roughly one tenth the number of grants and funds. Looking at funding within this category (fig. 17), the largest portion of grants was devoted to developing assays and conducting primary screens towards discovering drug leads (2.1; 22 grants, $4.3 MM). However, in terms of funds, $5.3 MM went towards 8 programs involved in the pre-clinical development of gene or cell-based therapies (2.5). This was a higher sum than that working towards the corresponding pre-clinical development of small-molecule therapies (2.4; $1.3 MM); 71% of this funding (2.5; $3.8 MM) came from foundations. The NIA contributed an additional $1.6 MM including two follow-on program grants to NYU towards developing vaccine technology to potentiate the clearance of tau. Apart from the spike in grants for Lead Discovery (2.1), there was an additional $20.0 MM investment from the NIA towards infrastructure in support of treatment development activities (2.7; fig. 17, inset).

**Clinical Treatment Evaluation (3.0)**

Overall there were 19 grants, representing $43.7 MM in funds, directed to the clinical evaluation of treatments for FTD and related dementias (fig. 18). 82% of these funds ($35.8 MM) came from the NIA and were devoted towards 6 infrastructure or clinical core development grants (3.4), two to the Mayo Foundation, or one of its clinics, and two to the University of California (Irvine and San Diego). Outside of capital for clinical infrastructure, the most significant investments were an NIA grant for $5 MM to the University of Kentucky to conduct a study of vitamin E and selenium on tangle formation and a NCCAM grant for $1 MM to UCLA to evaluate the effects of omega-3 fatty acids. Foundations and other public (non-NIH) agencies, while contributing 40-fold less funding than the NIH, administered half as many Clinical Evaluation grants totaling $1.1 MM in aggregate funding from the CIHR, NHMRC, ADDF, Alzheimer’s Association, Alzheimer’s Society (UK), and The Wellcome Trust. For additional information regarding activities within this category see, section 3.9, Clinical Trials.

**Detection, Diagnostics & Imaging (4.0)**

Seven percent (7.3%) of all funding (58 grants, $31.5 MM) went towards the development and evaluation of reagents and technologies that enable an earlier or more accurate diagnosis, or imaging of disease state or progression. Over three quarters (77.6%) of these funds were from the NIH, and the NIA alone contributed $9.4 MM towards 14 programs in the discovery/pre-clinical validation stage (4.1) with an additional $7.8 MM towards 8 programs in clinical development (4.2; fig. 18).
These resources have yet to lead to the development of improved diagnostics or validated biomarkers for FTD.

Foundations contributed $2.8 MM in support of 21 different programs (12 discovery/pre-clinical, 8 clinical stage, 1 infrastructure), including 12 grants from the Alzheimer’s Association ($1.5 MM). Other public (non-NIH) grantors contributed an additional $4.2 MM, including a $2.5 MM grant in CORDIS to the Technical University of Denmark to develop a microfluidic device for the early detection and diagnosis of neurodegenerative disorders.

**Disease Management (6.0)**
Activities within this category included palliative (6.1) and end of life care (6.2), as well as decision-making in healthcare management (6.3) and contained 4 grants totaling $990,000. Research in these areas was funded by: Health Research Board ($82.0 K), NHMRC ($357.3 K), NIHR ($436.4 K) and the Alzheimer’s Society, UK ($114.1 K), all of which are foreign (fig. 18).

The major research categories *Primary Prevention and Risk Factor Management* (5.0) and *Healthcare Services, Policy and Methodology* (7.0) were unpopulated with grants in this analysis.

### 3.4 Diagnosis-Specific Analysis of FTD-Spectrum Dementias
Using the clinical terms previously defined to analyze the data, trends across the various clinically-recognized disorders can be discerned (figs. 19-24). For instance, in figures 20a & b, the top chart depicts grants by initial year of funding with a title or abstract that contained *frontotemporal, FTD, or FTLD*. The bottom graph depicts the same for Pick’s disease, where only 4 grants captured here used the historical name for FTD. While it is difficult to draw any conclusions given the small size of this data subset, overall patterns can be seen in both frames. The decrease in funding and increase in grants over time seen in the larger FTD dataset is qualitatively mirrored by the decreasing size of disbursed funds for Pick’s disease.

An analysis of the dataset by clinical term shows only a minority of grants (13%) even mention many of the other FTD-related dementias. Funded research within this spectrum is predominantly focused on general FTD (fig. 19). A search of “Alzheimer’s” within this FTD dataset returned 353 grants representing half (53%) of all captured funding (fig. 24b), reflecting the degree of overlap between these two dementias. The same general pattern of decreasing funding with increasing grant numbers if witnessed in Alzheimer’s disease further underscores a trend seen in overall average grant amounts, with the immediate effect of trying to increasingly do the same amount of work with fewer resources.

### 3.5 Target Analysis: FTD Drug Targets and Biological Terms
Frontotemporal dementia and related neurodegenerative diseases, including Alzheimer’s, share some common disease mechanisms. By analyzing funding using these shared targets, it becomes possible to identify early adopters, grantor preferences for target and/or research activity, and to assess how any of these trends have changed over time. The list of biological search terms relevant to the spectrum of FTD-related dementias is provided in table 6.
The earliest papers linking the microtubule-binding protein, tau, to frontotemporal dementia were published in 1995. This lends confidence that this analysis captures the majority of lifetime funding for research into FTD and tau; the earliest papers linking FTD and ubiquitin also date back to this year. Of the biological targets analyzed in this section, tau and ubiquitin have received the largest amount of funding, a component of which is undoubtedly due to their early and accurate implication in FTD, and the resultant longevity of support (figs. 25a & b). However, despite tau and ubiquitin both being identified at the same time, tau research has benefited from 5-fold more grants and funding over the past decade within the data captured ($228.3 vs. $44.8 MM). While NIH funding on these targets has traditionally represented the vast majority, as seen in the overall analysis of total funding, its support has significantly waned while funds from foundations increased (fig. 26a).

The targets and mechanisms that were analyzed, in order of decreasing support, were (grants, funds): tau (389, $228.3 MM), ubiquitin (68, $44.8 MM), GSK3β (44, $23.6 MM), cdk5 (33, $20.3 MM), heat shock proteins (25, $18.0 MM), Pin1 (11, $8.5 MM), progranulin (9, $4.5 MM), VCP (8, $3.4 MM), and TDP-43 (6, $1.4 MM; figs. 26-28).

Looking at funding over time, there is an obvious correlation between overall support and length of time since a target’s involvement with FTD was discovered, with newer targets, TDP-43 and VCP, receiving a combined 60-fold fewer funds than that identified for tau. This is further illustrated by considering that VCP received roughly twice the funding of TDP-43 ($3.4 vs. $1.4 MM) having been funded for about twice as long. Interestingly, while the NIH took the early lead in funding for VCP in FTD and related research, philanthropic foundations have also been early adopters in funding work on TDP-43, contributing an equal measure of support (fig. 28).

Funding for cdk5, heat shock proteins, GSK3β, and Pin1 more closely resembled that seen for ubiquitin: grants have been consistently, albeit erratically awarded over the past decade. Individual terms have their own unique profiles of funding over time, however owing to the paucity of data for some, only qualitative comparisons should be made.

Heat shock proteins as a potential therapeutic target in FTD research enjoyed early NIH support that has waned over time, and modest yet steady support from philanthropies and foreign governments (fig. 27c). In contrast, research on GSK3β and cdk5 consistently increased until 2004 when overall NIH funding dropped (figs. 26c & 27a). There was also a sizeable foundation contribution to research on these targets in 2005. Funding for progranulin research, while modest overall, has increased in recent years reflecting its validated role in FTD (fig. 28a). Pin1 funding has been sporadic at best (fig. 27c).

In a finer-level analysis, looking at targets by research activity (figs. 29-32), recapitulates that seen in the overall analysis by the primary outcome measure (fig. 7): the majority of grants are directed towards the discovery (1.2.4) and validation (1.2.5) of targets and more funds have been directed towards these and “preceding stages” of research than subsequent pre-clinical and clinical development.
3.6 Funding Gap Analysis of FTD by Research Activity

One of the intentions of the hierarchical structure of the Biomedical Research Activity Classification System was to enable the analysis of research activities on any number of levels. The system’s structure permitted us to perform specific queries of the dataset, but also afforded a higher-level perspective of funding trends.

Pre-Clinical Treatment Development (2.0) programs received an average of one tenth that of Basic & Disease Research (1.0) funding (figs. 12, 16-17) with maxima at target validation (1.2.5, fig. 16). $151.6 MM, or 35% of the entire dataset captured, was devoted to target discovery and validation, and $111.3 MM (73.4%) originated with either the NIA or NINDS; the distribution between the remaining grantors is depicted in figure 33.

While the overall funding by specific target varies, a qualitative pattern can be seen across multiple drug targets. Generally, most support was focused on early stage clinical and laboratory research with maxima at the validation of targets (figs. 29-32).

Since a similar pattern can be discerned in both the overall analysis by research activity, as well as in a finer analysis by target, this reflects a clear bottleneck in progressing past the validation of drug targets into the pre-clinical development of treatments for FTD.

3.7 Clinical Trials

All available details from the 10 currently active interventional clinical trials for FTD-spectrum dementias are given in table 9 where they are arranged in alphabetical order by drug; 2 dietary supplement trials are listed at the bottom. These trials were at a range of stages (table 8), but on the whole evaluated modest numbers of subjects directly limiting the statistical power with which to meet efficacy outcome measures. All interventions were either pharmaceuticals that have FDA approval, or were dietary supplements and therefore are not regulated in the same way as conventional food and drug products. Under the “Dietary Supplement Health and Education Act of 1994” (DSHEA)\textsuperscript{21}, the dietary supplement manufacturer is responsible for ensuring that any supplement is safe before it is marketed. In either instance, there is a considerable amount of safety data available for these agents eg, cognitive enhancers, lithium, valproic acid, pyruvate, creatine, or coenzyme Q, and all trials require approval from their institution’s competent Investigational Review Board (IRB).

Within the interventional/drugs section of this list of mostly symptom-mitigating compounds and dietary supplements is the NINDS-funded phase I/II trial of lithium in subjects with PSP or CBD. This trial, which began in September 2008 and is still at the recruitment stage, is perhaps the most interesting in terms of not only validating a mechanistic-based drug development program, but if proven efficacious, could represent a near-term anti-tangle agent with centuries of safety data\textsuperscript{22}. Lithium is now known to dose-dependently decrease both tau total protein levels and tau phosphorylation by inhibiting GSK3\textbeta; inhibition of cyclin-dependent kinase-5 (cdk5) decreases tau phosphorylation, but not total protein levels\textsuperscript{23}. Although the primary outcome measure is the ability to complete the study period (5-week titration phase followed by 6 months of treatment) on lithium
at a serum concentration of at least 0.4 mEq/L, secondary measures include monitoring levels of tau phosphorylation and brain-derived neurotrophic factor in cerebral spinal fluid. While the small trial (n = 45) is perhaps underpowered to statistically weigh in on clinical improvement, changes in biomarkers can be now be routinely detected with a high degree of precision.

There were also as many other, interventional registered clinical trials as there were conventional interventional studies on FTD patients (table 10). These evaluated a broad range of areas including genetics and risk factors, biomarkers, diagnostics, imaging reagents and technologies, and non-invasive therapies. The results of many of these should also be monitored for their near- to intermediate-term impact on diagnosis and treatment. Clinical trials that have been terminated are listed in table 11.

As not all trials are registered, tables 12-13 display results from Boeve, 2006\textsuperscript{20} of published interventional clinical trials for FTD-spectrum dementias that has been subsequently updated to include published studies from 1996 to the present. There is also a recent rigorous study of clinical trial endpoints and outcome measures representing research into successfully objective clinical trial methods for FTD subjects\textsuperscript{24}.

While a range of different drugs and drug classes have been clinically evaluated in FTD-spectrum patients, all were after initial FDA approval and in general were dementia or comorbid symptom modifiers \textit{eg}, antidepressants, cognitive enhancers, antipsychotics, or some other neuroleptic agent approved for an array of psychiatric indications.
4 DISCUSSION

4.1 OVERVIEW
This analysis was designed to capture, distill, and provide an overview of funding worldwide for research relevant to frontotemporal and related dementias over the past decade. Data were obtained on 613 grants, representing $432,167,275 from 19 foundations and public agencies from 7 countries and the EU, including 17 NIH Institutes disbursed since 1998. Data collected for 2008 were included in this analysis, but it should be noted as incomplete. These grants were coded using a bespoke Biomedical Research Activity Classification System so that activities could be mapped along the drug discovery process, from basic and disease research, through to the clinical evaluation of treatments. Analysis of the dataset resolved a number of patterns in funding, many of which may be obvious to those well versed in FTD-related dementia research. This section will summarize and explain these as well as some of the less obvious patterns that were observed.

4.2 KEY FINDINGS FROM THE ANALYSIS
This analysis of international FTD funding was designed to provide a quantitative and objective assessment of fund allocations pertinent to FTD over the past decade. It revealed that FTD received little funding over the past decade compared to Alzheimer’s disease. Funding for all forms of FTD was only 10% of that for AD. Even fewer funds were allocated for specific FTD-related dementias, including semantic dementia, primary progressive aphasia, progressive non-fluent aphasia, corticobasal degeneration, progressive supranuclear palsy, FTDP-17, FTD with motor neuron disease, or FTD with ubiquitinated inclusions (FTD-U/FTLD-U).

The majority of the funding FTD received over the past decade originated at the NIH (83% of total). The NIA and NINDS were the major contributors from the NIH, contributing 70% of total funds (84% of NIH funds) targeted to FTD. Surprisingly, NIH contributions towards FTD research have steadily declined over time. According to these data, NIH funding decreased five-fold from 1999 to 2007. During this same period there has been a steadily increasing contribution from the philanthropies, particularly in the area of pre-clinical drug development.

Not surprisingly, the majority of FTD funding went towards basic disease research and Target Discovery and Validation, with little funding to drug (lead) discovery and subsequent pre-clinical development and clinical evaluation. The drug discovery research programs that were funded focused on few targets, with most programs funded only during past few years. Research on targets common between FTD and Alzheimer’s disease received more funding than those specific to FTD. In addition, there are very few FTD-specific clinical trials underway. This analysis also indicated that there was a significant increase over time in funding for Detection, Diagnostics & Imaging, even though this area made up a relatively small proportion of overall funding.
Also somewhat unanticipated, the majority of grants identified as FTD-relevant also mention Alzheimer’s disease (57.6%), suggesting common mechanisms, but also reflecting funding that may be primarily for Alzheimer’s disease with additional benefit for FTD. There is also a near absence of FTD-specific patient, palliative or end of life care management research or best practice research; all four grants in this area were of foreign origin.

The considerable amount of preclinical research on Alzheimer’s disease, particularly tau-related work as studied in this report, has resulted in some clinical trials that may have implications for FTD. For example, work originally at the NIH by Ilana Gozes and others was ultimately the basis for the creation of a new public biotechnology company, Allon Therapeutics (TSX: NPC), that is currently in clinical trials with a microtubule-stabilizing agent. In addition, as shown in tables 9-13, several funded clinical trials for FTD resulted from work that originated in research on Alzheimer’s disease, including studies of lithium, valproic acid, memantine, and the cholinesterase inhibitors donepezil and rivastigmine. However, continuing translation of relevant preclinical research is needed to insure that more, novel trials are conducted.

4.3 Comparison to Other Analyses

Our results can be qualitatively compared to NIH funding. For instance, the overall NIH budget has been analyzed by the Association of American Medical Colleges in their response to the reversal in NIH appropriations after the Congressionally-directed doubling of the NIH budget from 1998-2003. From the data captured here, FTD research did not enjoy a doubling of NIH funding during this period, but did recapitulate the drop-off coinciding with the decrease in overall appropriations in 2003 (fig. 34a & c).

Historical top-level budget data for all NIH institutes from 1983-2007 were obtained from the NIH Budget Office. RePORT contains extramural and intramural research financials by institute for 1983-2006. Figure 34b depicts selected budget values for the NIA and NINDS, the two single largest funders of FTD research captured here. The Research Program Grants (RPGs) subtotal contains competing and non-competing grants, Small Business Innovation Research/ Small Business Technology Transfer Research (SBIR/STTR) grants, but does not include internal administrative costs for managing its extramural research portfolio. It also does not include support for Research Centers, individual or institution training, R & D contracts, or “other research”. From these data, it can be estimated that the NIA and NINDS have an annual budget for external research of approximately $1 billion, and have disbursed a combined $13 B from 1998-2006. This is in comparison to the ~$300 MM that was found in this analysis to be attributed to the NIA and NINDS towards FTD research. This sizable discrepancy seems reasonable considering the NIA/NINDS numbers include all areas within their respective remits, and that although explicitly stated FTD research has traditionally received modest support, a substantial amount of research of direct relevance to FTD is still being carried out.

More recently, the NIH has itself conducted an Institute-wide analysis of its complete research portfolio. This analysis was made possible by universally adopting a research, condition and disease category (RCDC) scheme for all research areas and activities. These data reflect steady annual
support for FTD research from 2005-2007 to be ~$31 MM (fig. 35). In 2007, the RCDC system was implemented and changed the “fingerprint”, or list of search terms, used to define and automatically retrieve grants within a particular disease category. Using these numbers, NIH funding for FTD has remained steady from 2004-2008; the slight dip from 2006-2007 would seem to stem from the implementation of this new scheme, and the consequent effect of this Institute-wide readjustment. However, owing to the large discrepancies in, and continuity of, methods employed in the recent NIH analysis and this FTD landscape, only qualitative comparisons should be drawn. The RCDC initiative has been subsequently terminated.

In addition to funding from 17 separate institutes at the NIH, this analysis captured nearly an additional fifth (17%) in funding from foreign governments and foundations from 7 countries and the EU representing almost half (47%) of all captured grants.

While the majority of research funding was directed towards Basic and Disease Research ($319.3 MM, 74%), only a fraction of these funds ($30.7 MM, 7%) were dedicated to underpinning biological research (1.1). By far the largest contribution went toward the validation of known targets through the construction of animal models, more than either target identification or basic research infrastructure. The relatively modest funding for drug development activities that lie subsequent to target validation ie, Treatment Development (2.0), is a simple reflection of the inherent challenges in this type of research, perhaps further underscored by the fact that there are at present only symptom-modifying therapies approved for FTD and related dementias

4.4 Key Recommendations

Based on the analysis presented in this report, it is clear that more research funding is needed for drug discovery related to FTD-specific targets, particularly those that have been discovered recently. Since Alzheimer's disease received significantly more funding than FTD, more FTD drug discovery could be accomplished through programs on targets common to both dementias, leveraging the sizable resources initially targeted for Alzheimer's disease. This includes monies targeted to clinical infrastructure, core resources, organizational networks and common overheads.

The NIH makes up the vast majority of funding towards FTD research. While a relatively small contribution to overall funding, philanthropies can make strategic decisions with a potentially significant impact FTD drug discovery. Philanthropies should focus funding towards programs that would benefit from modest sums and are not already well funded by public funds. For example, academic programs including the development of FTD-specific animal models, identification/validation of biomarkers, and novel, high-risk targets that are not funded by NIH study sections would greatly benefit from philanthropic sources of funding.

It is important to advocate for increased government funding on basic research in FTD neurobiology that will lead to novel target discovery. To expand the FTD research community, it is necessary to invest in the development of a cadre of scientists dedicated to FTD drug discovery research such as a modest investment in postdoctoral research fellowships and by providing assistance for young investigators in establishing their own labs. Providing seed funding for high risk, novel pilot clinical
trials directed to new FTD targets is also important for future FTD treatment development. Drug discovery for FTD could also be catalyzed by funding novel technologies for early detection and diagnosis that can also accelerate drug development, including novel PET imaging technologies and spinal fluid biomarkers. Robust biomarkers that differentiate FTD patients with tau pathology versus TDP-43 pathology would be invaluable for future clinical trial planning. Creating bioinformatic resources such as patient databases and registries can also help organize, coordinate and accelerate this process.

Lastly, given the paucity of research on palliative and end-of-life care, and other important “non-drug” issues specific to FTD-spectrum patients and their caregivers, more funding should be devoted to research in these areas.

4.5 Limitations of Analysis
When analyzing and discussing these data, it is advisable to be mindful of the limitations in the methods employed. The majority of these limitations fall within 1 of 2 categories: limitations in the data themselves or in their structuring and interpretation. All data came from external sources and therefore there can be no warranties to its accuracy or completeness. Grants with critical missing information (award amounts, both start and end dates (or start date and duration), or title and abstract) could not be analyzed and were excluded. There was no attempt made to either backfill or interpolate missing fields. The data analysis was limited by the search terms employed, which were determined by a panel of experts as described in the methods. Each grant received only one biomedical classification code to the single furthest, reasonably attained stated aim of the grant (stage of drug discovery). Another fundamental decision that was made during the course of this analysis was how to capture disbursements over time. It was decided that this analysis would place grants’ funds in their entirety at the first year of support. Therefore, our analysis depicts funding for FTD research awarded per year, rather than disbursed per year.

Lastly, it should be noted that the FTD and Alzheimer’s datasets from Research Crossroads were obtained with 35 and 40 weeks respectively of data from 2008. Excluding 2008 might have risked missing recently funded research, and despite its inclusion in this analysis, its presence must be qualified.
5 Conclusion

Despite the fact that FTD is a relatively common cause of dementia, it receives a disproportionately small fraction of overall dementia research funding. In particular, little funding has gone towards translating new research on disease targets into drug discovery programs with the potential for the creation of new drugs. There has also been limited funding allocated towards understanding important non-drug issues specific to FTD patients and their caregivers. Finally, little funding has been dedicated to pilot clinical trials that could test novel therapeutics for FTD. Nonetheless, drug discovery for FTD has greatly benefitted from the many years of AD research that has focused on elements common to both diseases. As these pre-clinical efforts move into clinical trials for AD, for example programs targeting tau phosphorylation and/or aggregation, clinical trials for FTD can and should also be initiated.
6 BIBLIOGRAPHY

