33rd Annual Southern California Alzheimer's Disease Research Conference Discoveries and Advances in Frontotemporal Dementia (FTD) Research

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Peter A. Ljubenkov, MD Assistant Professor of Neurology Memory and Aging Center, Department of Neurology UCSF Weill Institute for Neurosciences

UCI MOND Institute for Memory Impairment and Neurological Disorders



Orange County Chapter

Weill Institute for Neurosciences Memory and Aging Center

Disclosures

- Currently PI for trials of AL001 and Fasudil sponsored by Alector and Woolsey respectively
- Sponsor/PI for the Veri-T trial (NCT05184569)
 - supported but NIA grant R01AG073482-01
 - supported the Alzheimer's Association/Gates Part the Cloud Partnership

Introduction to FTD

- Caused by frontal and/or anterior temporal lobe degeneration
 "Frontotemporal lobar degeneration"
- ~3-4 people in every 100k have FTD
- A common cause of dementia in people under 65
 - Similar incidence Alzheimer's disease in this age group
- Often familial
 - Strong family history in ~40% of FTD
 - 3 major sites of risk mutations
 - C9orf72
 - GRN
 - MAPT



Courtesy of Howard Rosen, MD (UCSF)

What is it like to have FTD?

Progressive changes in personality or behavior

- Apathy
- Disinhibition/Loss if decorum
- Loss of empathy for others
- Obsessions/Compulsions
- Dietary changes
- Changes in executive function
- Progressive changes in language primary progressive aphasia (PPA)



Behavioral Variant FTD (bvFTD)¹



Clinical syndromes & FTLD Pathology



Courtesy of Bill Seeley

Amyloid PET Imaging Distinguishes FTLD from Alzheimer's Disease





Rabinovici et al, Neurology, 2007, 2011

Plasma p-tau Distinguished FTLD from Alzheimer's Disease



Amyloid-PET status

- Negative
- Positive
- Unknown

Figures from Thijssen et al, Lancet Neurology, 2021

Neurofilament light chain (NfL): A useful marker of neurodegeneration?

Cerebrospinal Fluid NfL is elevated in FTD relative to controls

Serum NfL is elevated in bvFTD relative to primary psychiatric disease



Ljubenkov et al. Ann Clin Transl Neurol. 2018



Need for biomarkers in FTD research

(Biomarker: laboratory test or imaging tests which tell you something about a disease)

- Diagnosis
 - FTLD Mimics
 - FTLD subtypes
- Screening for presymptomatic risk
- Prognostic Biomarkers
 - Predict progression and onset
- Staging
 - Track progression
- Biomarkers of drug response

Need larger multi-site consortia to prepare for clinical trials

- Identify and enroll patients with rare conditions over large geographic areas
- Collect longitudinal data and biospecimens in hundreds of people
- Allow for broad search and validation candidate biomarkers
- Support the design of FTLD therapeutic trials



- Primary Investigators:
 - Bradley F. Boeve, M.D (Mayo Clinic)
 Adam L. Boxer, MD, PhD (UCSF)
 Howard Rosen, MD (UCSF)
- Started in 2014 as ARTFL and LEFFTDS but renewed as ALLFTD
- Currently 23 sites in USA and Canada
- Collects longitudinal clinical data, imaging, blood, and CSF
- Major emphasis on familial FTLD
 - 3 major risk mutations
 - **Č90RF72**
 - GRN
 - MAPT
 - Enroll > 700 patients FTLD Families ٠
 - Symptomatic ٠
 - Presymptomatic *
- Sporadic FTLD (>700 cases)

Participant distribution





- Founded in collaboration between leadership of ALLFTD and Genetic Frontotemporal dementia Initiative (GENFI)
- Foster sharing of longitudinal data and biospecimens to future foster FTLD clinical trials



- Growing Membership
 - GENFI in Europe and Canada
 - ALLFTD study in US and Canada
 - Dominantly Inherited Non-Alzheimer Dementias (DINAD) study in Australia
 - New Zealand Genetic FTD study (FTDGenZ)
 - Research Dementia Latin America (ReDLat)
 - South East Asia FTD Consortium
 - LEAF-FTD in Korea

Plasma Neurofilament Light for Prediction of Disease Progression in Familial FTLD

ALL FTLD Data (n = 277)

- High plasma NfL predicted clinical change in asymptomatic mutation carriers!
- Also predicated more aggressive disease in people with early and late symptoms

GENFI Validation Data (n = 297)

- Recapitulated ALLFTD findings
- High plasma NfL predicted clinical change in asymptomatic mutation carriers





Temporal order of clinical and biomarker changes in familial frontotemporal dementia



Staffaroni et al. and FPI Investigators. Nature Medicine 2022 (in press)

Temporal order of clinical and biomarker changes in familial frontotemporal dementia



Staffaroni et al. and FPI Investigators. Nature Medicine 2022 (in press)



- Sub-study of ALLFTD (NCT04516499)
- Prospective, longitudinal, observational study to sample NfL more frequently
 - Mobile nurses will collect blood from 335 ALLFTD every 3 months for 3-4 years
 - Focused on asymptomatic carriers GRN, C9orf72, or MAPT mutations
 - Will allow resolution around NfL changes as mutation carriers convert from asymptomatic to symptomatic
 - Validate NfL as a susceptibility/risk biomarker
 - Enable design for prevention trials in familial FTLD





72, 32%

Current Clinical Trials of Disease-Modifying Therapies for FTLD

Disease Modifying FTLD Trials

- Emphasis on precision medicine
 - Targeting specific pathogenic mechanisms for specific pathologic subtypes of FTLD
- There are no reliable biomarkers to distinguish FTLD-Tau vs FTLD-TDP
- Current focus on cohorts highly predictive of specific FTLD subtypes on autopsy
 - Progressive Supranuclear Palsy Richardson syndrome (PSP-RS)
 - Nearly 100% specific for FTLD-Tau (4R) on autopsy
 - Familial FTLD-TDP (C9orf72, GRN)
 - svPPA (80% specific for FTLD-TDP)



Potential Strategies in FTLD-tau





Tau Knockdown via Antisense oligonucleotides (ASO)

- ASO: Oligonucleotides which hybridize to mRNA
 - trigger RNAaseH-mediated degradation
 - Intrathecally injected
- **<u>BIIB080</u>** (IONIS-MAPTRx)
 - Investigated in phase 1 in mild AD (NCT03186989)
 - Reduced CSF tau by nearly 60%
 - Possible candidate for FTLD-tau trials?
- ASOs in FTLD-tau?
 - Ongoing phase 1 trail of <u>NIO752</u> in patients with progressive supranuclear palsy (NCT04539041)

BIIB080 lowers CSF tau in Alzheimer's



Courtesy of Catherine Mummery, University of College London, presented AAIC 2021 (poster 51871)

Targeting Rho-kinase (ROCK) in FTLD-tau

- ROCK 1 & 2
 - Influence tau autophagy and phosphorylation
 - Upregulated in PSP and corticobasal degeneration (CBD) (Gentry et al 2016)
- Fasudil (oral, CNS penetrant, ROCK inhibitor)
 - Reduces total and phosphorylated tau in cultured murine neurons
 - Rescues "rough eye phenotype" in drosophila model of tauopathy (Gentry et al, 2016)
 - ROCKIT-1 (NCT04734379)
 - Phase 2a Open-Label trial of oral Fasudil in Patients with Progressive Supranuclear Palsy-Richardson Syndrome or Corticobasal Syndrome
 - Enrolled 10 patients with PSP and 5 patients with CBS
 - Expect to read out late this year

Additional Ongoing Trials in FTLD-tau

Mechanism	Drugs	Clinical Trial Details	Trial #
Retrotransposon suppression	TPN-101	Ongoing phase 2a in PSP	NCT04993768
Lipid Membrane protection	RT001	Ongoing phase 2 in PSP	NCT04937530
Anti-Tau Vaccine	AADvac1	Ongoing phase 1 in nfvPPA	NCT03174886



Clinical Trials In FTLD-TDP

- Largely focuses on mechanisms specific to familial forms of FTLD
 - Progranulin Gene (GRN) Deficiency
 - C9orf72 Expansion
- Early efforts in clinical syndromes predicative of sporadic FTLD-TDP (svPPA)

Clinical Trials in GRN Haploinsufficiency

- Progranulin (GRN) Gene Mutations
 - Highly penetrant, resulting in FTLD-TDP type A
 - Pathogenic mechanism of haploinsufficiency
 - >50% decrease in extracellular progranulin (PGRN)
 - CSF PGRN is a rational biomarker of drug target engagement

Anti-Sortilin mAB (AL001) boosts CSF Progranulin in GRN Deficiency





(Data not peer reviewed - figures modified from publicly available figures posted online by study sponsor) 24

PGRN CSF concentration

AL001 increases the half-life of PGRN by blocking sortilin

INFRONT-2: Exploratory PD and Clinical Findings

NfL CSF Concentration



²⁵ (Data not peer reviewed - figures modified from publicly available figures posted online by study sponsor)

Current status of AL001 in GRN Haploinsufficiency

INFRONT-3 Currently Ongoing (NCT04374136) :

- A Phase 3 Study to evaluate efficacy and safety of AL001 in patients with GRN mutations
- Enrolls symptomatic patients and asymptomatic carriers at high risk of phenoconversion based on blood biomarkers

Additional Strategies in GRN Deficiency

- Gene Therapy
 - Adenovirus vectors injected intrathecally (sub-occipital)
 - **PBFT02:** AAV1-based therapy in phase 1 trial (NCT04747431)
 - **PR006:** AAV9-based therapy in phase 1 trial (NCT04408625)
- Direct Supplementation of Progranulin
 - **DNL539** currently in early clinical development
 - Progranulin fused with the human transferrin protein
 - Allows for CNS penetration via peripheral infusions

C9orf72 Hexanucleotide Expansion

- Pathogenic C9orf72 expansion is the most common single mutation to cause familial ALS and FTD
- Expanded GGGGCC region
 - ≤11 is normal
 - >30 pathogenic (typically hundreds)
 - Toxic RNA and dipeptides?

DNA sequence



Balendra and Isaacs, Nature Reviews Neurology 2018

Dipeptide Repeat Proteins (DPRs)





Other C9orf72 ASO Programs

Ongoing/future programs:

- Phase 1/2 Trial of WVE-004 in FTD &ALS (NCT04931862)
 - Sponsors have announced positive findings on DPRs

Phase 1 BIIB078 trial of in ALS (NCT03626012)

- Negative trial announced by trial sponsor March 28, 2022
 - Higher dose cohort "trended toward a greater decline"
- Program officially terminated
- Targeted different isoform of C9orf72 RNA than afinersen and WVE-004

Additional Therapeutic Trial Programs in C9orf72 Expansion

- <u>Metformin</u>
 - lowers DPR proteins in preclinical models
 - In phase 2 trial in FTD and ALS (NCT04220021)
- <u>AL001</u>
 - In phase 2 trial investigating impact of PGRN alteration in C9ORF72 FTD (part of INFRONT-2)
- <u>TPN-101</u>
 - LINE1 Reverse Transcriptase inhibitor
 - Blocks dysregulated transposable elements
 - In Phase 2 trial in FTD and ALS (NCT04993755)

Additional Potential Mechanism in TDP-43





The Veri-T Trial (NCT0518456) Veri-T

- A Phase 1 Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial of *Verdiperstat* in Patients with svPPA (semantic variant PPA)
- The first trial to leverage ALLFTD recruitment resources
- The first svPPA clinical trial
 - svPPA is >80% specific for FTLD-TDP on autopsy
 - Seek to establish svPPA as a model cohort for future sporadic FTLD-TDP trials
 - Establish methodology for svPPA trials
 - Opportunity for svPPA blood and CSF biomarker discovery.
- First trial to implement the new ALLFTD app for remote cognitive assessment in FTLD clinical trials
- <u>clinicaltrials.gov/ct2/show/NCT0518456</u> (now enrolling!)



Thank You

Our patients and their families who make all this possible





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