A Detailed Review of PGRN:

A Pivotal-Stage Clinical Development Program for Frontotemporal Dementia with Broad Additional Opportunities Including Alzheimer's Disease

Forward Looking Statement

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements other than statements of historical facts contained in this presentation are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potentially,” “predict,” “should,” “will” or the negative of these terms or other similar expressions. Forward-looking statements contained in this presentation also include, but are not limited to, statements regarding the beneficial characteristics, safety, efficacy, and therapeutic effects of our product candidates; our plans, timelines and expectations related to our product candidates and our other clinical and pre-clinical programs, including with respect to the availability of data, the initiation of future clinical trials and plans and expectations regarding planned regulatory filings with respect to such programs; expectations regarding the timing and financial benefit of our collaborations; and objectives of management for future operations, as well as statements regarding industry trends.

We, Alector, Inc. (“Alector”), have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, among other things: Alector’s plans relating to its research programs and the development and manufacturing of its product candidates; the ability of Alector’s clinical trials to demonstrate safety and efficacy of its product candidates, and other positive results; the timing and focus of Alector’s clinical trials, and the reporting of data from those trials; Alector's plans relating to commercializing its product candidates, if approved, including the geographic areas of focus and sales strategy; the expected potential benefits of strategic collaborations with third parties and Alector's ability to attract collaborators with development, regulatory and commercialization expertise; Alector’s estimates of the number of patients in the United States, the European Union and world-wide who suffer from the diseases it is targeting and the number of patients that will enroll in its clinical trials; the size of the market opportunity for Alector’s product candidates in each of the diseases it is targeting; Alector’s ability to expand its product candidates into additional indications and patient populations; the success of competing therapies that are or may become available; the beneficial characteristics, safety, efficacy, and therapeutic effects of Alector’s product candidates; the timing or likelihood of regulatory filings and approvals, including Alector’s expectation to seek special designations, such as orphan drug designation, for its product candidates for various diseases; Alector’s ability to obtain and maintain regulatory approval of its product candidates; Alector's plans relating to the further development and manufacturing of its product candidates, including additional indications that it may pursue; existing and future regulations and regulatory developments in the United States and other jurisdictions; Alector’s reliance on third parties to conduct clinical trials of its product candidates, and for the manufacture of its product candidates for preclinical studies and clinical trials; the impact of worldwide economic conditions, including macroeconomic downturns stemming from increased inflation, supply chain and other economic impacts of the coronavirus (COVID-19) pandemic and geopolitical events on our business; and the other risks, uncertainties and assumptions discussed in the public filings we have made and will make with the Securities and Exchange Commission (“SEC”). These risks are not exhaustive. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements.

This presentation also contains results based on data from our clinical trials. These clinical trials are ongoing and this presentation does not speak to, and you should make no assumptions about, any additional data. In addition, the information we have chosen to publicly disclose regarding our product candidates has been selected from a more extensive amount of available information. You or others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise. If the initial data that we report differ from updated, late, final or actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize our product candidates may be harmed, which could harm our business, financial condition, results of operations and prospects.

This presentation discusses certain investigational therapeutic agents which have not yet been approved for marketing by the U.S. Food and Drug Administration. No representation is made as to the safety or effectiveness of our product candidate for the therapeutic use for which it is being studied.

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Today's Agenda

01	**Opening Remarks: Elevating PGRN for the Potential Treatment of Neurodegenerative Disease** *Sara Kenkare-Mitra, Ph.D., President and Head of Research and Development, Alector*	**8:00-8:15 am**
02	**PGRN: A Promising Target for FTD and AD** *Fenghua Hu, Ph.D., Associate Professor, Department of Molecular Biology and Genetics and Weill Institute for Cell and Molecular Biology, Cornell University*	**8:15-8:35 am**
03	**Latozinemab/AL101 Overview and Clinical Development** *Lawrence Carter, Ph.D., Vice President of Clinical Development, Neurology*	**8:35-8:55 am**
04	**Promising Advances in PGRN Therapeutic Development** *Adam Boxer, M.D., Ph.D., Professor, Neurology, UCSF, Weill Institute for Neurosciences*	**8:55-9:15 am**
05	**Closing Remarks and Q&A** *Sara Kenkare-Mitra, Ph.D., President and Head of Research and Development, Alector*	**9:15-9:30 am**

Opening Remarks: Elevating PGRN for the Potential Treatment of Neurodegenerative Disease

Sara KenKare-Mitra, Ph.D.

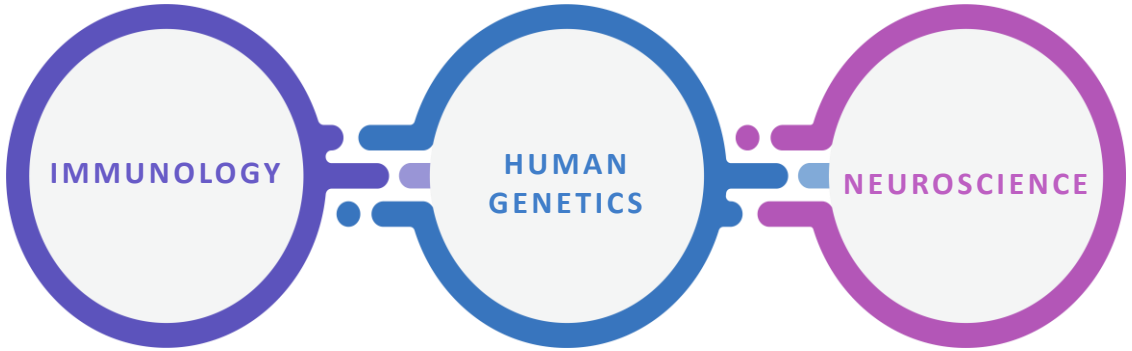
President and Head of Research and Development
Alector

Alector: Pioneering the Potential of Immuno-neurology to Address Neurodegeneration

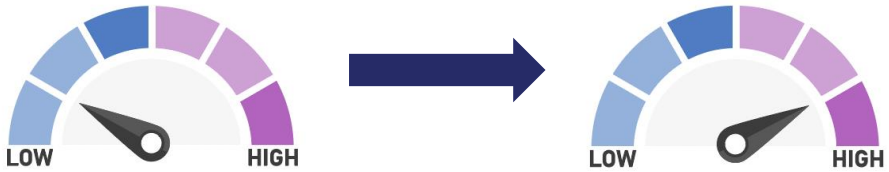
- Pioneering immuno-neurology as a novel therapeutic strategy
- Targeting immune dysfunction as a root cause of neurodegenerative disease
- Ongoing Phase 2 studies in AD (TREM2 & PGRN) and pivotal Phase 3 study in FTD (PGRN)

RESTORING MICROGLIA, THE BRAIN'S IMMUNE SYSTEM

Integrated Insight



Investigational Therapeutic Approach



Dysfunctional and damaging Microglia

Healthy disease fighting Microglia

alector

Frontotemporal Dementia (FTD)

A rapidly progressive form of dementia, with no approved treatment

Tommy Nash Jr., with his daughter, Alyssa Nash. Tommy was diagnosed with FTD at 38 years old.[1]

- **Prevalence:** Most common cause of dementia under age 60

- **Progression:**
  - Rapid progression of memory impairment, other cognitive functions
  - Life expectancy after diagnoses is 7-10 years

- **Diagnosis:**
  - Compulsive behavior, lack of restraint, apathy, anxiety, and aphasia
  - Symptoms typically begin between the ages of 45-64 years old
  - Frequently misdiagnosed as AD, depression, PD, or psychiatric condition

- **Treatment:** No approved treatments to cure or slow progression of FTD

- **Forms:**
  - Sporadic FTD occurs without a clear familial or inherited pattern
  - Genetic FTD occurs due to a single mutation, which typically occurs in one of three genes: *GRN*, *C9orf72* or *MAPT*

1. With permission from Tommy Nash Jr. and Alyssa Nash, May 2023
Greaves et al. *J Neurol.* 2019;266:2075-2086.
Taylor RT, et al. *Pract Neurol.* 2019:72-77.
Kansal K, et al. *Dement Geriatr Cogn Disord.* 2016;41:109-122.
Boeve BF, et al. *Brain.* 2006;129:3103-3114.
UCSF Weill Institute for Neurosciences Memory and Aging Center: Familial FTD

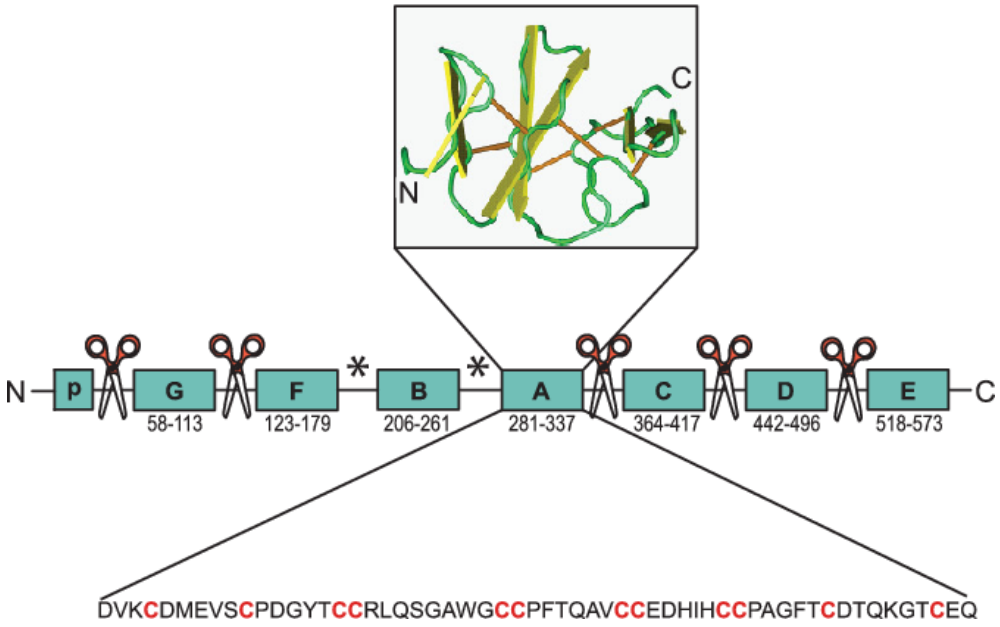
Progranulin (PGRN)

A secreted immune and lysosomal regulator in the brain

PGRN IS IMPLICATED IN SEVERAL PROCESSES NECESSARY FOR NORMAL FUNCTION IN THE IMMUNE SYSTEM AND CNS

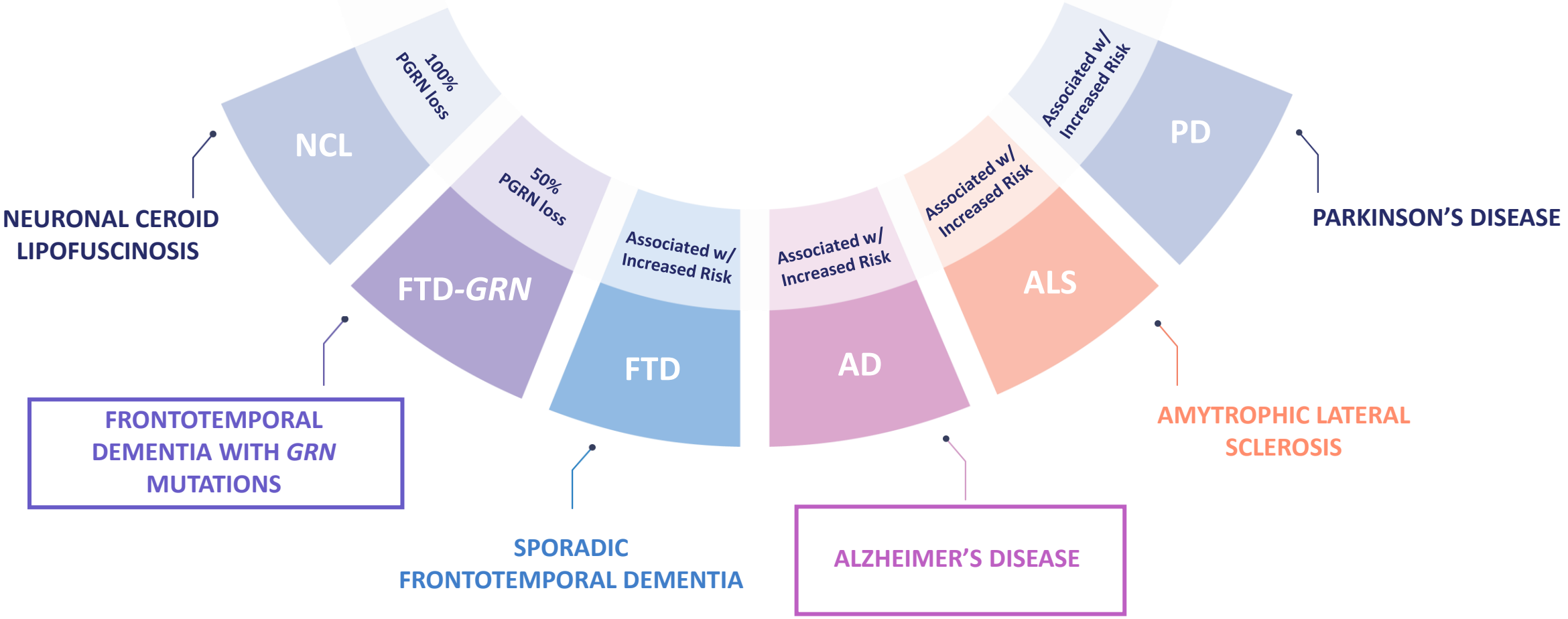
- Encoded by the *GRN* gene
- Secreted 593 aa immune regulatory glycoprotein
- Promotes neuronal survival
- Controls microglial function
- Controls inflammation
- Controls the processing of lysosomal enzymes

THE PGRN PROTEIN IS CLEAVED BY PROTEASES INTO SMALLER PEPTIDES CALLED GRANULINS



Mendsaikhan A., et al., *Acta Neuropathologica Communications* volume 7, Article number: 215 (2019); Nicholson A., et al., *Alz Res Therapy* 4**,** 4 (2012); Cenik B, et al., *Journal of Biological Chemistry* 287(39):32298-306.

GRN Mutations Are Causal or Increase Risk for Multiple Neurodegenerative Diseases

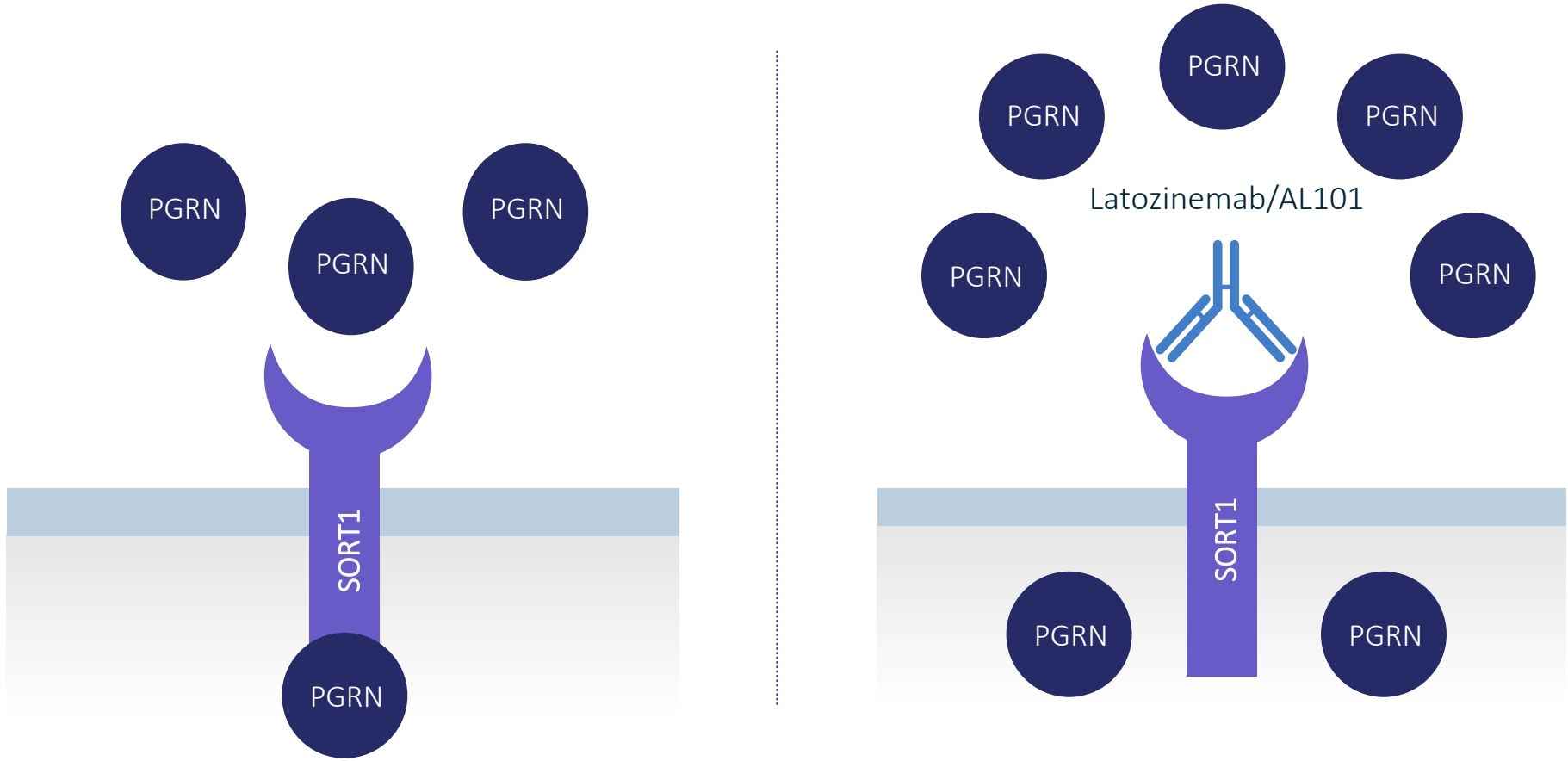


Rhinn H, et al. *Trends Pharmacol Sci.* 2022;43(8):641–652.
Nalls MA, et al. *Brain Commun*. 2021;3(2):fcab095.
Sheng J, et al. *Gene*. 2014;542(2):141–145.
Kumar-Singh S. *J Mol Neurosci*. 2011;45:561–573.
Paushter DH, et al. *Acta Neuropathol.* 2018;136(1):1–17.

Our Approach to Elevating Progranulin: SORT1 Blockade

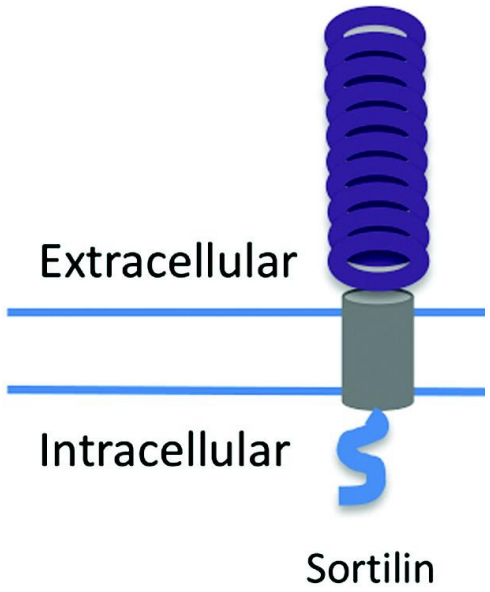
Latozinemab and AL101 Are Human Monoclonal Antibodies That Are Designed to Increase Extracellular Levels of Progranulin

ELEVATES PGRN LEVELS BY BLOCKING SORT1, A DEGRADATION RECEPTOR FOR PGRN

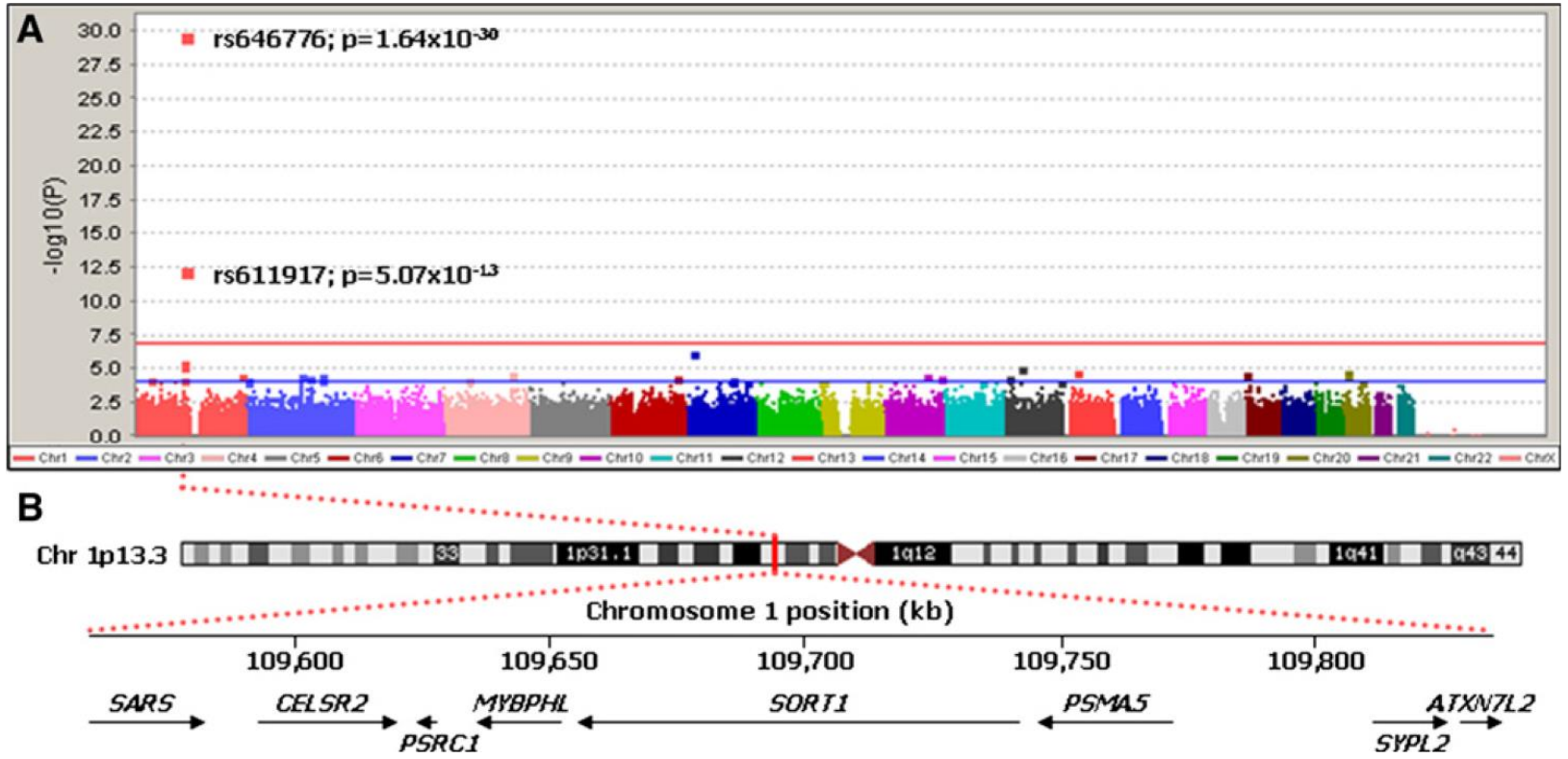


SORT1: a Negative Regulator of PGRN

SORT1 IS A SINGLE TRANSMEMBRANE RECEPTOR[1]



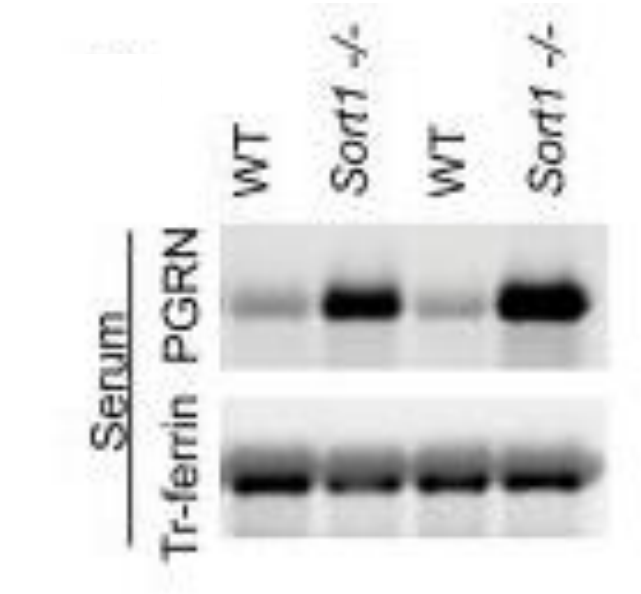
GWAS STUDIES: SORT1 EXPRESSION LEVELS INVERSELY CORRELATE WITH THE LEVELS OF PGRN IN HUMANS[2]



1. Xu SY et al, Sortilin: a new player in dementia and Alzheimer-type neuropathology, Biochemistry and Cell Biology, 96, 491-487. https://doi.org/10.1139/bcb-2018-0023. © Canadian Science Publishing or its licensors
2. Carrasquillo, M, et al., *Am J Hum Genet*. 2010 Dec 10;87(6):890-7.

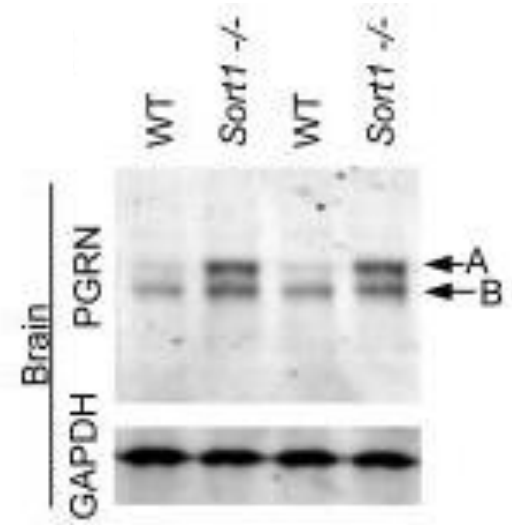
Total Progranulin Appears to be Elevated Following SORT1 Ablation in Mice

SERUM LEVELS OF PGRN WERE INCREASED IN THE *SORT1* −/− MICE



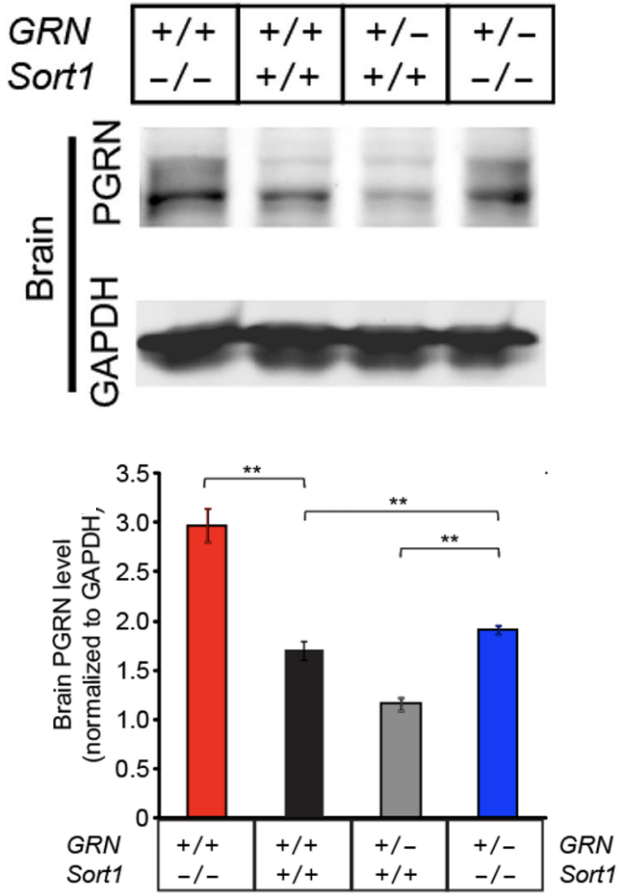
Serum samples from 7-month-old *Sort1*−/− and WT mice were collected, stripped of albumin and IgG and immunoblotted for PGRN and transferrin.

LEVELS OF TOTAL PGRN IN BRAIN EXTRACTS WERE INCREASED IN *SORT1* −/− MICE



Tissue lysate collected from the cerebral cortex of 7-month-old mice was subjected to SDS-PAGE and anti-PGRN immunoblot. Two PGRN bands are increase in the *Sort1*−/− samples.

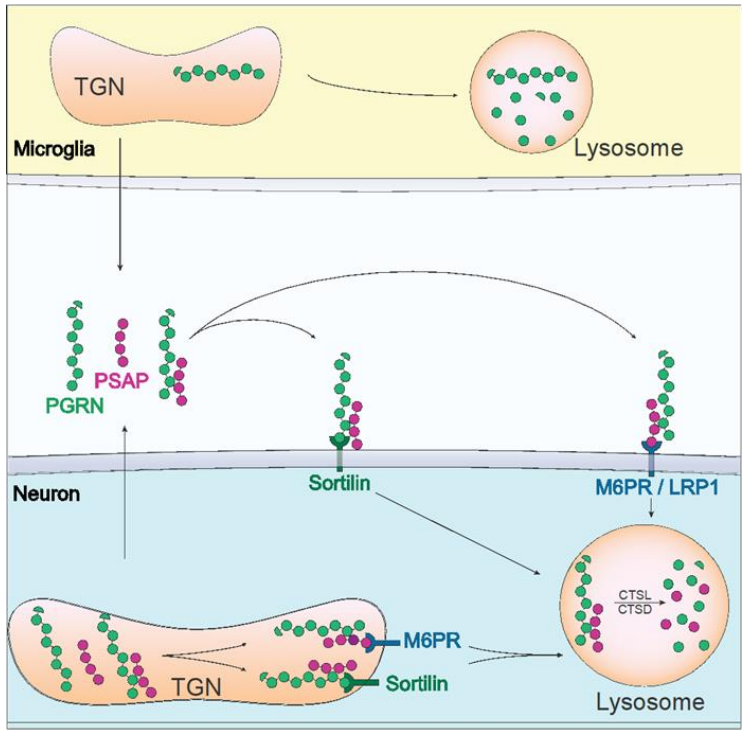
LEVELS OF TOTAL PGRN IN BRAIN EXTRACTS WERE INCREASED IN PGRN+/- SORT1 −/− MICE



Hu F. et al., *Neuron*. 2010 Nov 18;68(4):654-67.

SORT1 is a Redundant Receptor for Sub-cellular Localization and Function of PGRN

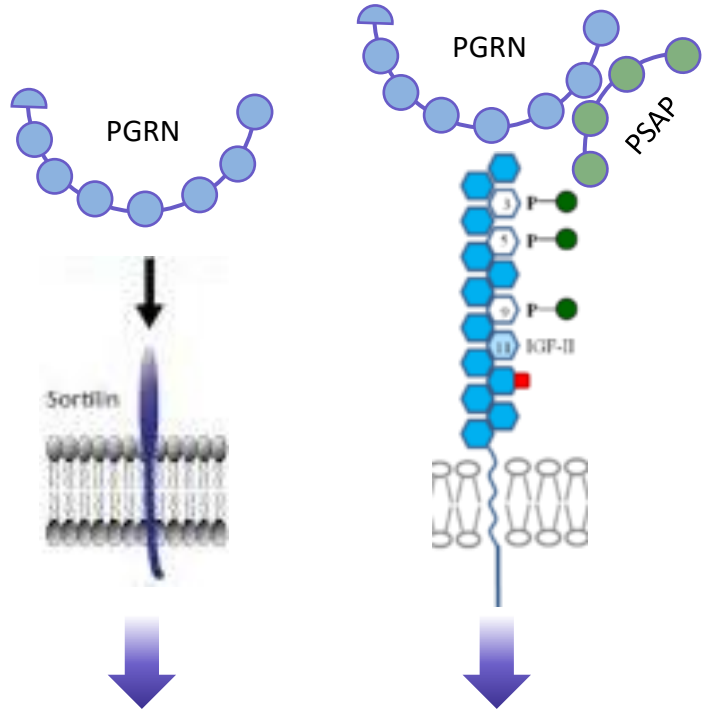
PGRN UTILIZES MULTIPLE RECEPTORS TO TRAFFIC TO THE LYSOSOME (SORT1, PSAP, M6PR/LRP1, ETC)[1]



INTRACELLULAR EFFECTS OF PGRN DO NOT REQUIRE TRANSPORT BY SORT1 TO INTRACELLULAR COMPARTMENT[2,3]

- **PGRN does not require SORT1:**
  - To be trafficked to the lysosomes
  - To be secreted
  - To promote neuronal survival
  - To reverse lysosomal pathology
  - To reverse microglial pathology
- SORT1 ablation does not lead to neurodegeneration in rodents
- SORT1 haploinsufficiency is not associated with FTD in humans

PGRN IS TRANSPORTED AND PROCESSED BY REDUNDANT TRAFFICKING RECEPTORS[2]



Processing and action as chaperone in lysosome

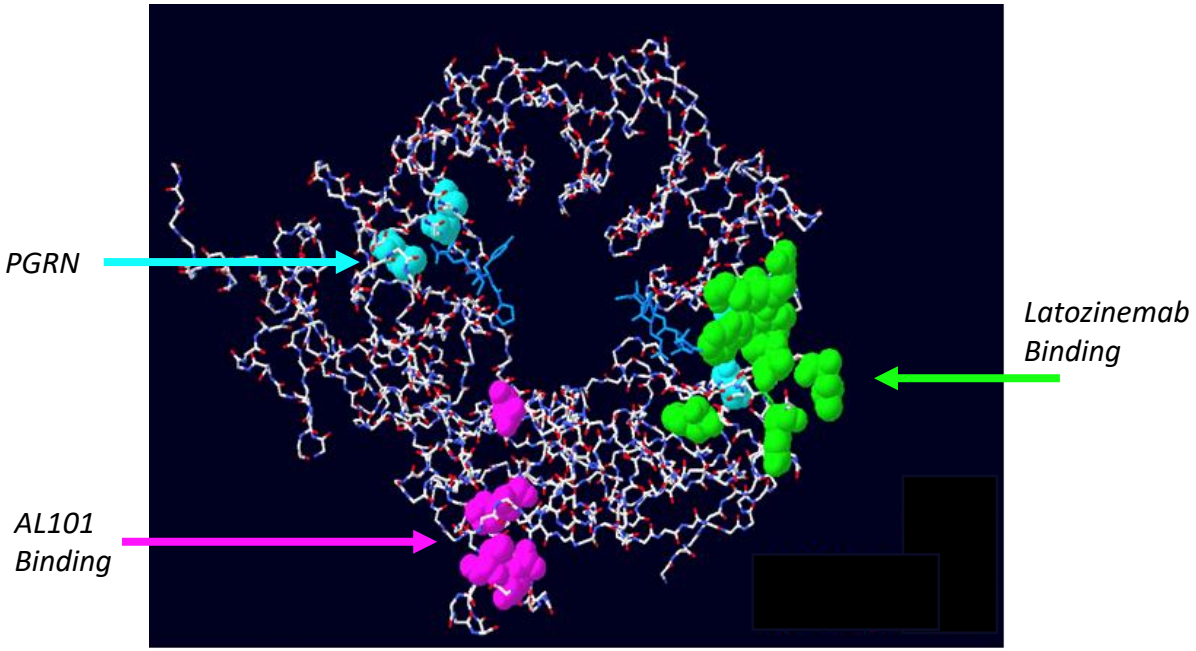
1. Du, H et al., *Brain Communications*, Volume 4, Issue 1, 2022, fcab310.

2. Zhou X, et al., *J Cell Biol* (2015) 210 (6): 991–1002.
3. Hu F, et al., Sortilin-mediated endocytosis determines levels of the frontotemporal dementia protein, progranulin. *Neuron.* 2010 Nov 18;68(4):654-67.

Alector's Two PGRN-Elevating Antibodies: Latozinemab and AL101

LATOZINEMAB AND AL101 HAVE A DISTINCT BINDING EPITOPE ON SORT1

3D CRYSTALLOGRAPHY STRUCTURE OF SORT1

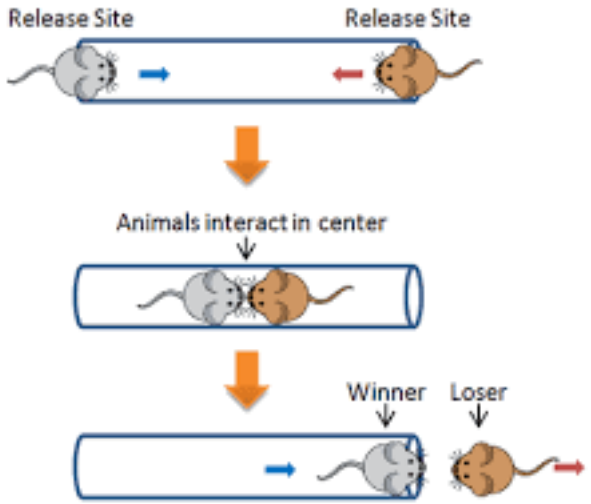


DRUG CANDIDATE PROFILES

- Latozinemab and AL101 are human anti-SORT1 antibodies.
- PK/PD profile distinguishes AL101 from latozinemab. **Longer half-life** provides the ability to optimize AL101 dosing regimens.
- Both Latozinemab and AL101 are generally **well-tolerated** in Phase 1 and 2 clinical trial results to date.
- AL101 is designed for more prevalent neurodegenerative diseases, including **AD** and **PD**.

Alector PGRN-Elevating Antibody Rescues Behavioral Deficit in Aged FTD-*GRN* Mice

SOCIAL INTERACTION TEST

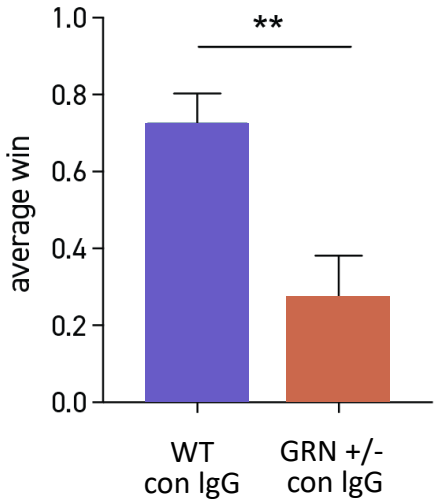


WT mice, control IgG

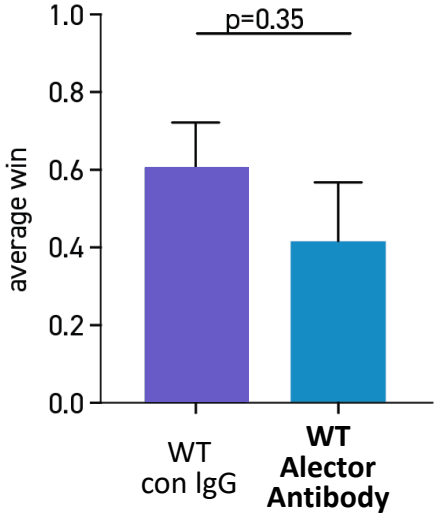
GRN +/- mice, control IgG

WT or GRN +/- mice, Alector PGRN-Elevating Antibody

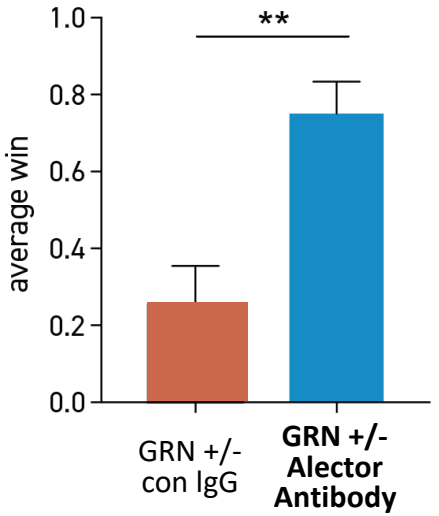
ALECTOR PGRN-ELEVATING ANTIBODY REVERSES BEHAVIORAL DEFICIT AFTER 4.5 WEEKS OF TREATMENT



Control-treated GRN mice lost majority of matches against control IgG-treated WT mice



Alector PRGN-Elevating Antibody-treated WT mice behave similar to control IgG-treated WT mice



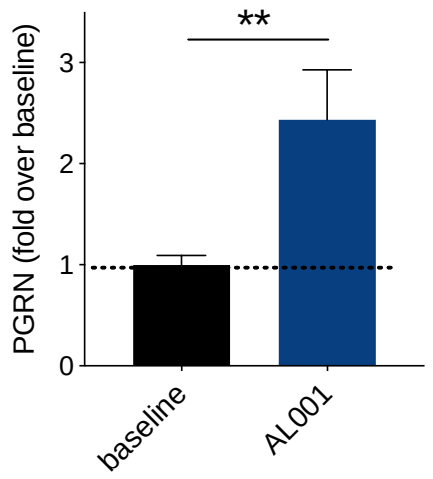
Alector PRGN-Elevating Antibody-treated GRN mice won majority of matches against control IgG-treated GRN mice

Mice treated with an Alector mouse cross-reacting SORT1 blocking antibody, dosed at 40 mg/kg once weekly for 4.5 weeks.
Collaboration with Dr. Erik D. Roberson University of Alabama.
Kurnellas, M.. et al. Latozinemab, a novel progranulin-elevating therapy for frontotemporal dementia. *J Transl Med* 21, 387 (2023).

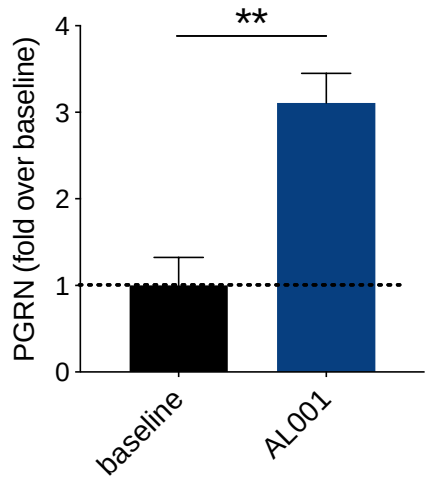
** indicates p< 0.01 by T-test.

Alector PGRN-Elevating Antibodies Increase PGRN in Serum, CSF in NHPs

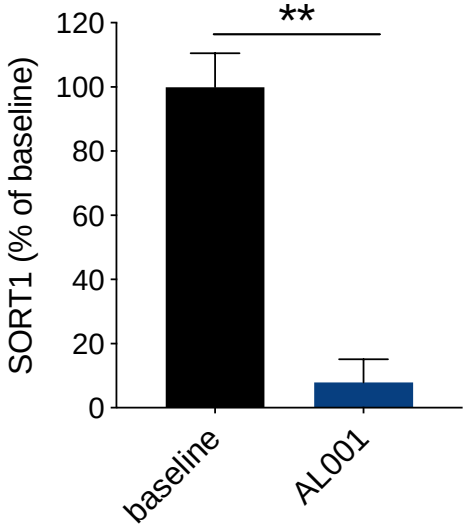
AL001: ~2.5-FOLD INCREASE IN CSF PGRN



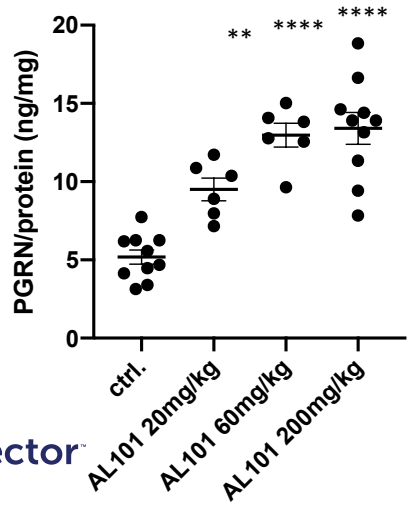
AL001: ~3-FOLD INCREASE IN SERUM PGRN



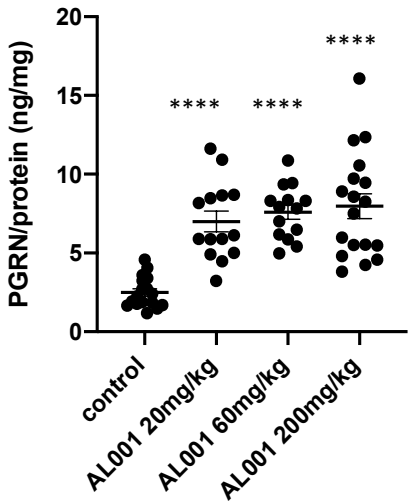
AL001: BLOCKS SORT1 IN WBC



AL101: INTRACELLULAR PGRN IN WBC



AL001: INTRACELLULAR PGRN IN WBC



PGRN = progranulin
CSF = cerebrospinal fluid
WBC = white blood cells
AL001 = latozinemab
SORT1 = sortilin

Alector data on file

AL001 4-week GLP study dosed at 200 mg/kg

* indicates p<0.05 by T-test.
** indicates p< 0.01 by T-test.
****indicated p<0.0001 by ANOVA

Latozinemab and AL101: Development of Novel Human mAbs That Elevate PGRN

MOST ADVANCED PGRN ELEVATING CANDIDATES IN CLNICAL DEVELOPMENT WORLDWIDE

	LATOZINEMAB	AL101
POTENTIAL INDICATIONS	Frontotemporal dementia with a progranulin gene mutation (FTD-*GRN*).	Larger indications, including Alzheimer's disease (AD).
CLINICAL SAFETY	**Phase 1 and 2:** Generally well tolerated following monthly IV administrations for a year or more in healthy volunteers and FTD-*GRN* patients.	**Phase 1:** Generally well tolerated following monthly IV and SC (q2w) administrations in healthy volunteers.
KEY CLINICAL OUTCOMES & BIOMARKERS	**Phase 1:** Increased PGRN in plasma and CSF in dose-dependent manner. **Phase 2:** Encouraging trends across biomarkers of disease activity. **Phase 3:** Pivotal trial designed to detect a minimal effect of 25% in CDR® plus NACC FTLD-SB.	**Phase 1:** Increased PGRN levels in plasma and CSF in a dose-dependent manner; PK/PD profile supports development in larger indications.
STATUS & UPCOMING MILESTONES	**Phase 3:** In October 2023, achieved target enrollment in INFRONT-3 pivotal Phase 3 trial in FTD-*GRN* for a treatment duration of 96 weeks.	**Phase 2:** Patient screening underway and anticipate dosing first participant in PROGRESS-AD Phase 2 clinical trial in early AD soon.

Portfolio: Advancing Novel First-in-Class Programs with Major Rights Retained

TARGET	CANDIDATE	RESEARCH	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	ALECTOR'S COMMERCIAL OWNERSHIP	PARTNERS
PGRN	Latozinemab	FTD-*GRN*					U.S. 50-50 profit share with co-promote and tiered double-digit royalties ex-U.S.	GSK
	AL101	AD						GSK
TREM2	AL002	AD					Global 50-50 profit share with opt-in	abbvie
UD	ADP054-ABC	ALS, AD, PD						
UD	UD-ABC	AD, PD						
GCase	ADP050-ABC	PD, LBD						
GPNMB	ADP027-ABC	PD						
UD	ADP056-ABC	AD						

IP portfolio contains 50+ patent families, which include 73 issued patents and >500 pending patent applications directed to more than 20 targets and/or technologies

alector™

ABC = Alector Brain Carrier Technology
UD = undisclosed

Latozinemab and AL101 are Currently Partnered in a Collaboration Agreement with GSK

Latozinemab and AL101

$700M upfront

$1.5B+ in potential milestone payments

U.S. 50-50 profit share

Tiered double-digit royalties ex-U.S.

$160 million for first commercial sale in the U.S.

$90 million for first commercial sale in at least two of the following countries: France, Germany, Italy, Spain, or the UK

PGRN: A Promising Target for FTD and AD

Fenghua Hu, Ph.D.

Associate Professor, Department of Molecular Biology and Genetics and Weill Institute for Cell and Molecular Biology, Cornell University

Progranulin: A promising target for FTD and AD

Fenghua Hu

Associate Professor

Department of Molecular Biology and Genetics

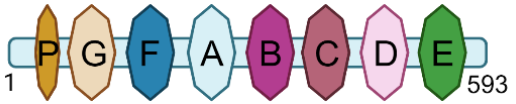
Weill Institute for Cell and Molecular Biology

Cornell University, Ithaca, NY, USA

Disclosures

- Dr. Fenghua Hu's contribution to this webinar is not related to her Cornell University duties or responsibilities.
- Dr. Fenghua Hu is a paid consultant of Alector Inc and Guidepoint. She serves on the SAB of Muna Therapeutics.
- Cornell University has filed a patent application (9987–01-US) for methods using sPLA$_2$-IIA inhibition to treat FTLD-GRN and other neurodegenerative diseases on behalf of Dr. Fenghua Hu's team.

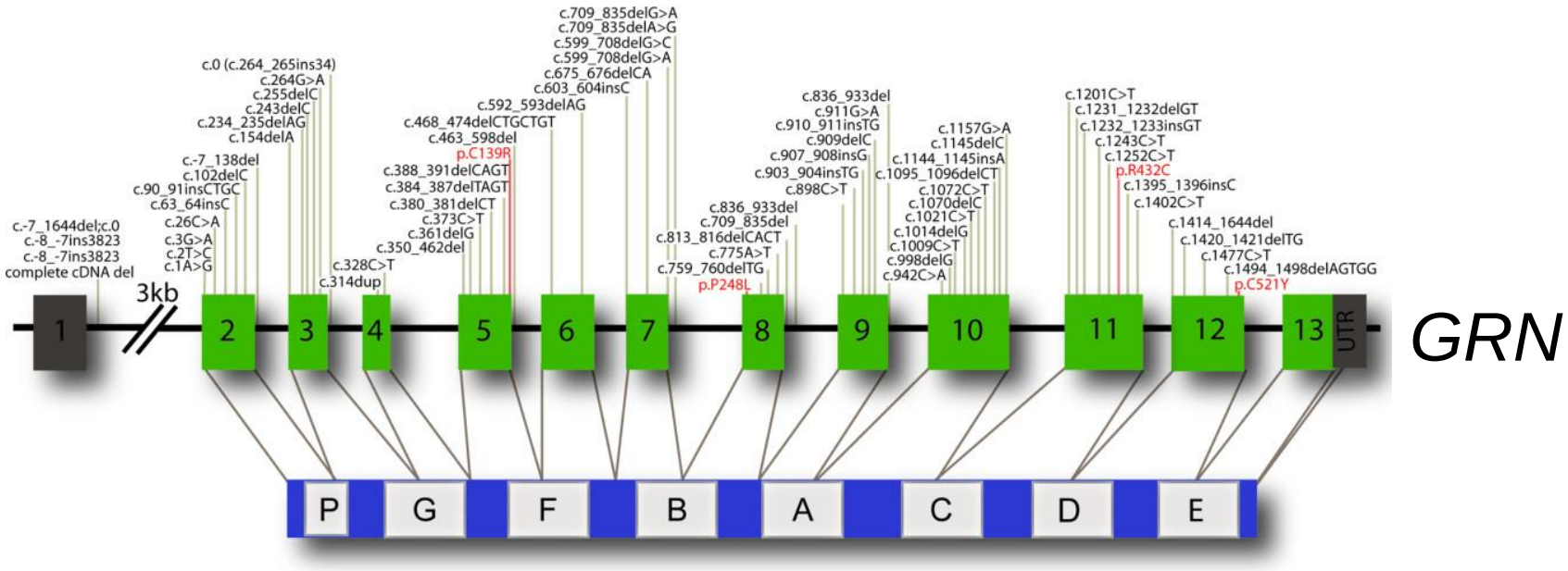
Progranulin (PGRN) is tightly associated with neurodegenerative diseases

GRN gene → 

PGRN protein

Mutations in the *GRN* gene	**Associated Disease**	**Penetrance**	**Age Onset**
Heterozygous LOF (+/-)	Frontotemporal Dementia (FTD)	>90%	~50-60s

Progranulin (PGRN) haploinsufficiency is a leading cause of FTD



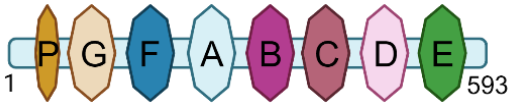
PGRN haplo-insufficiency

↓

FTD

Baker et al, Nature 2006
Cruts et al, Nature 2006
Gass et al, Hum Mol Genet 2006

Progranulin (PGRN) is tightly associated with neurodegenerative diseases

GRN gene → 

PGRN protein

Mutations in the *GRN* gene	Associated Disease	Penetrance	Age Onset
Heterozygous LOF (+/-)	Frontotemporal Dementia (FTD)	>90%	~50-60s
Homozygous LOF (-/-)	Neuronal Ceroid Lipofuscinosis (NCL)	100%	~20s

Smith et al, *Am J Hum Genet*. 2012
Almeida et al, *Neurobiol Aging* 2016

Neuronal Ceroid Lipofuscinosis (NCL): A class of lysosomal storage disorder

NEURAL REGENERATION RESEARCH
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Review

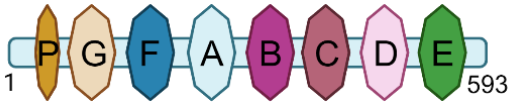
Table 1 | Neuronal ceroid lipofuscinoses

Disease	Typical age of manifestation*	Protein (gene)	Protein localization	Protein function
CLN1	Infantile (6–24 mon)	Palmitoyl protein thioesterase 1 (*PPT1*)	Lysosomal lumen, synaptic vesicles	S-depalmitoylase (long-chain fatty acyl hydrolase) (Camp and Hofmann, 1993; Vesa et al., 1995)
CLN2	Late infantile (2–4 yr)	Tripeptidyl peptidase 1 (*TPP1*)	Lysosomal lumen	Serine protease (Lin et al., 2001)
CLN3	Junvenile (4–10 yr)	CLN3 (*CLN3*)	Endolysosomal membrane	Unknown
CLN4	Adult (adult Kufs disease, Parry type)	Cysteine-string protein alpha, CSPα, DNAJC5 (*DNAJC5*)	Cytosol, association with endolysosomal membranes	Co-chaperone, conveys microautophagy and misfolding-associated protein secretion (Lee et al., 2022a)
CLN5	Late infantile (3–7 yr)	CLN5 (*CLN5*)	Endolysosomal	Cysteine based S-depalmitoylase (Luebben et al., 2022)
CLN6	Late infantile (1.5–8 yr)	CLN6 (*CLN6*)	Endoplasmic reticulum membrane	Involved in anterograde transport of lysosomal cargo (Bajaj et al., 2020)
CLN7	Late infantile (1.5–8 yr)	MFSD8 (*MFSD8*)	Endolysosomal membrane	Endolysosomal chloride channel (Wang et al., 2021)
CLN8	Late infantile (1.5–7 yr)	CLN8 (*CLN8*)	Endoplasmic reticulum/ endoplasmic reticulum Golgi intermediate compartment (ERGIC) membrane	Involved in anterograde transport of lysosomal cargo (di Ronza et al., 2018; Bajaj et al., 2020)
CLN10	Congenital (neonatal)	Cathepsin D (*CTSD*)	Lysosomal lumen	Aspartyl endoprotease (Steinfeld et al., 2006)
CLN11	Adult (early 20s)	Progranulin (*GRN*)	Lysosomal lumen, secretory pathway, secreted	Unknown (regulation of lysosomal enzyme activity?)
CLN12	Juvenile (8–12 yr)	ATP13A2, Park9 (*ATP13A2*)	Endolysosomal membrane	Polyamine transporter (van Veen et al., 2020)
CLN13	Adult (Kufs disease type B; 20+ yr)	Cathepsin F (*CTSF*)	Lysosomal lumen	Cysteine protease (Wang et al., 1998)
CLN14	Infantile/late infantile (8–9 mon)	Potassium channel tetramerization domain-containing protein 7 (*KCTD7*)	Cytosol	Cytosolic adaptor involved in transport and ubiquitin-proteasome degradation (Staropoli et al., 2012; Wang et al., 2022)

*The age of onset can deviate from the typical age of manifestation, as specific mutations can lead to a protracted course of the disease.

Klein, Marcel; Hermey, Guido, Neural Regeneration Research18(7):1463-1471, July 2023.

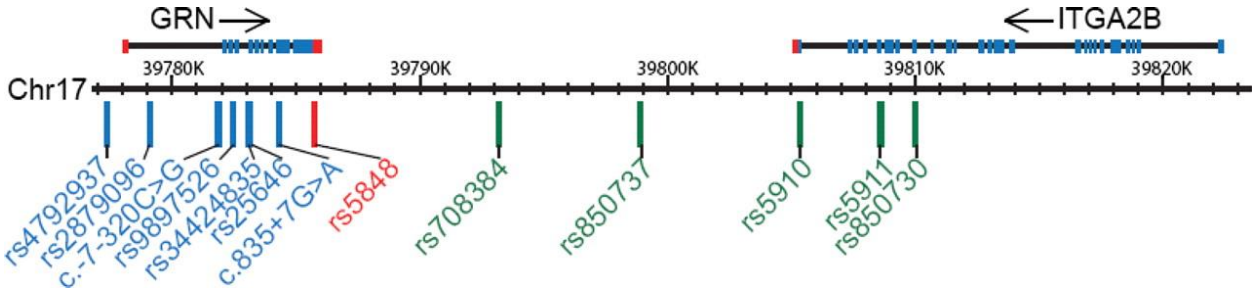
Progranulin (PGRN) is tightly associated with neurodegenerative diseases

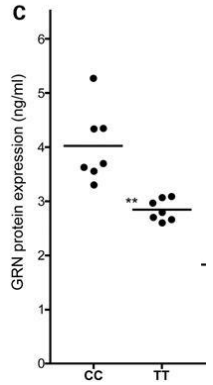
GRN gene → 

PGRN protein

Mutations in the *GRN* gene	**Associated Disease**	**Penetrance**	**Age Onset**
Heterozygous LOF (+/-)	Frontotemporal Dementia (FTD)	>90%	~50-60s
Homozygous LOF (-/-)	Neuronal Ceroid Lipofuscinosis (NCL)	100%	~20s
Polymorphisms	AD, PD	NA	~60s (40-90)

GRN polymorphisms are associated with AD





rs5848 TT allele locate in 3'UTR is associated with lower PGRN Levels

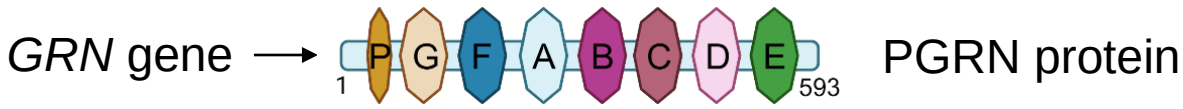
Rademakers et al, Hum Mol Genet 2008, Pages 3631–3642

Kamalainen et al, J Alzheimers Dis 2013

Hsiung et al, J Neurol Sci 2011

- The minor T allele of rs5848 was significantly associated with an increased risk of LOAD (Perry et al JAMA Neurol 2013; Sheng et al Gene 2014; Xu et al, Molecular Neurobiology, 2017).
- rs5848 is associated with hippocampal sclerosis and TDP-43 pathology, Braak stage and tau pathology in LOAD (Vardarajan et al, Alzheimer's and Dementia, 2022).

Progranulin (PGRN) is tightly associated with neurodegenerative diseases



Mutations in the *GRN* gene	Associated Disease	Penetrance	Age Onset
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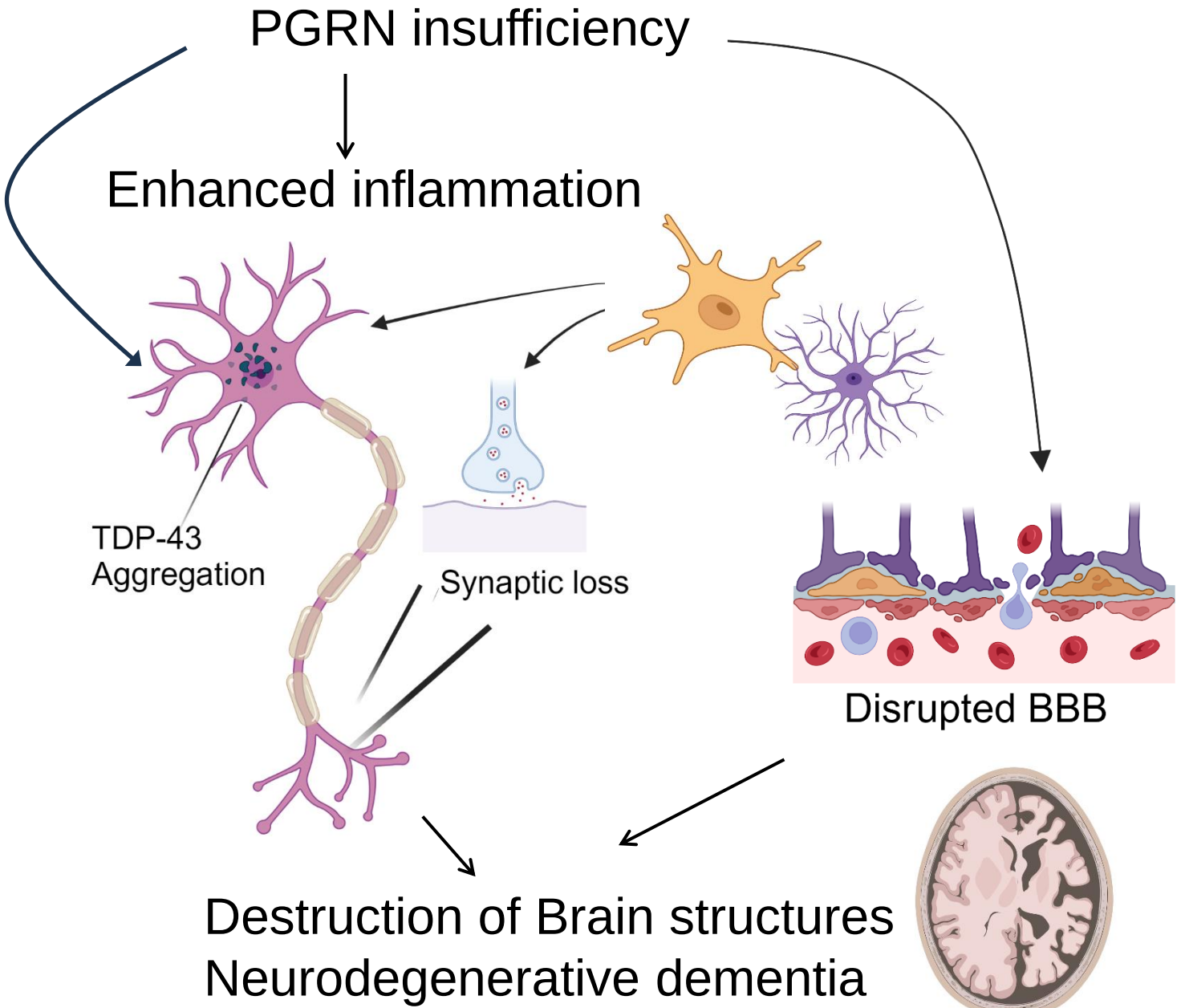
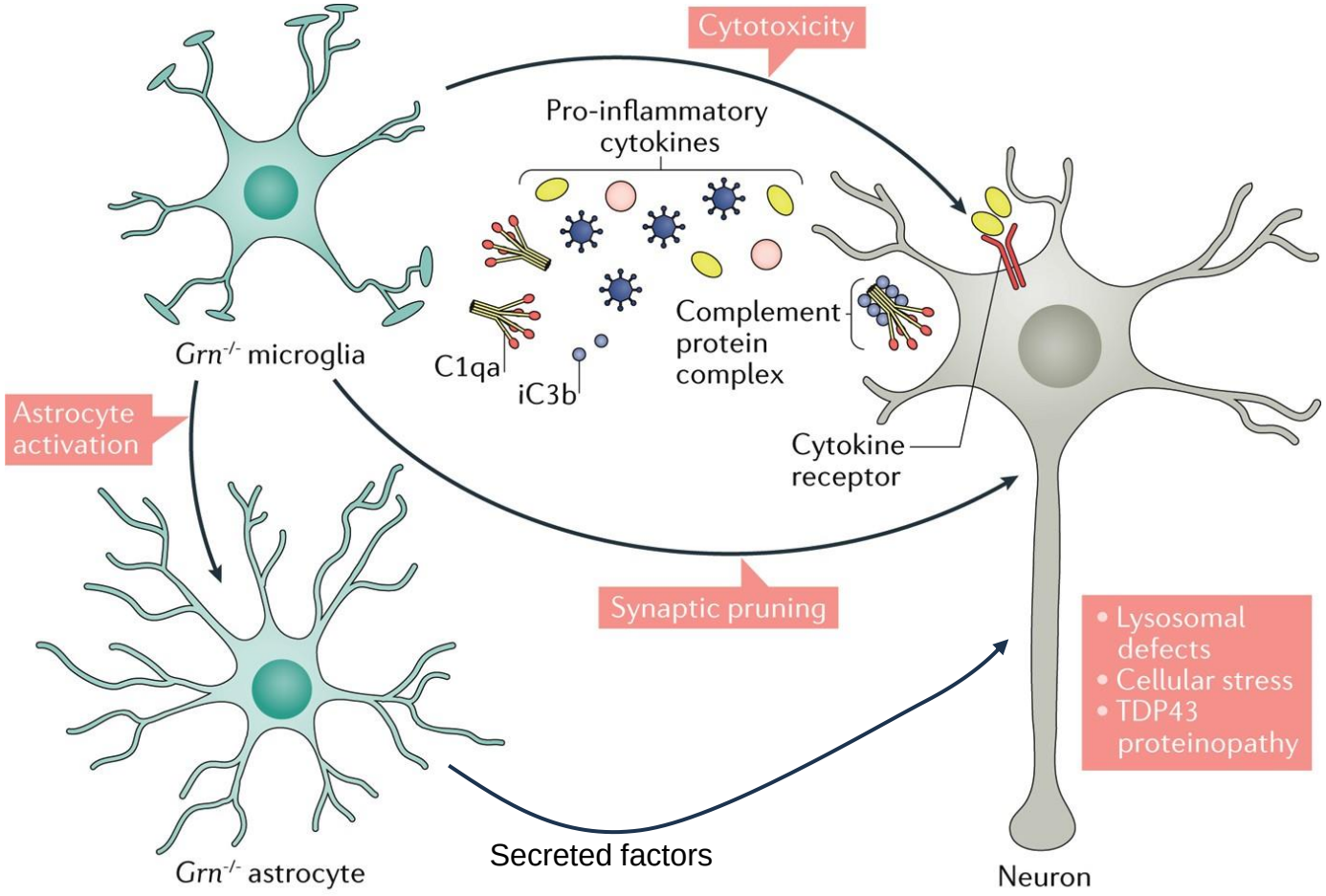
How does PGRN prevent neurodegeneration?

How does PGRN prevent neurodegeneration?



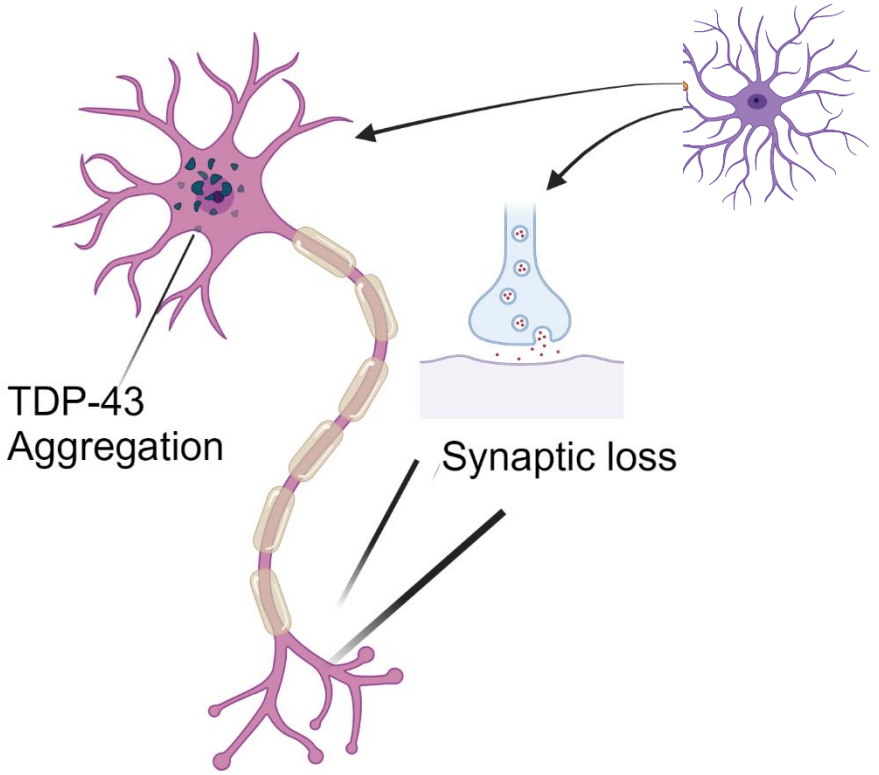
Function of PGRN as a critical immune regulator



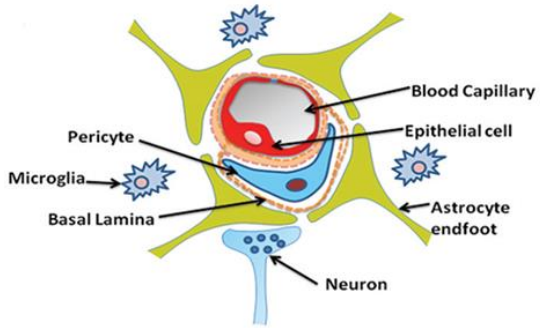
Adapted from Kao et al, Nature Review Neuroscience 2020

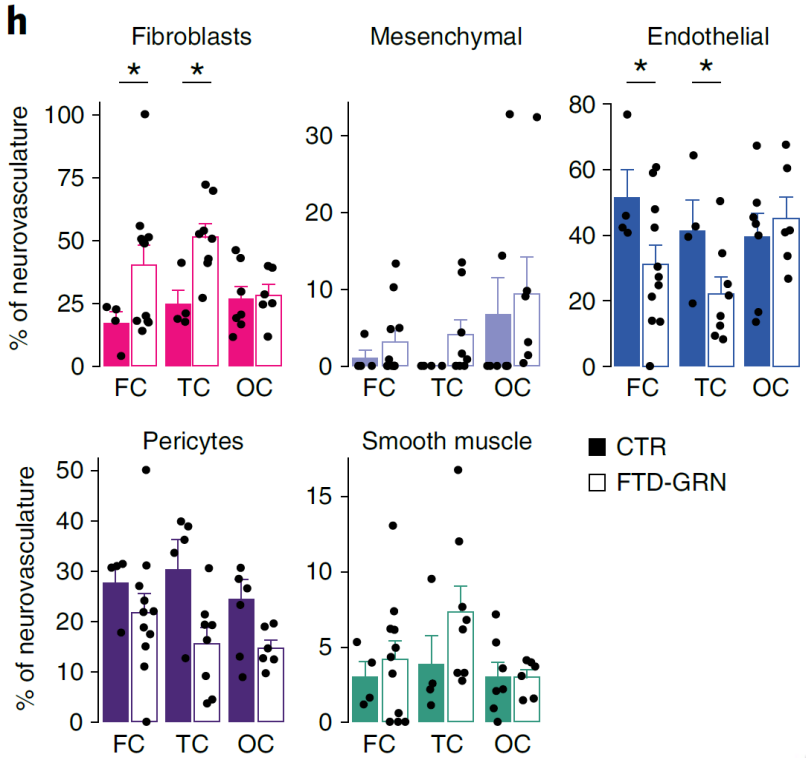
Astrocyte abnormalities due to PGRN deficiency drive neuropathology

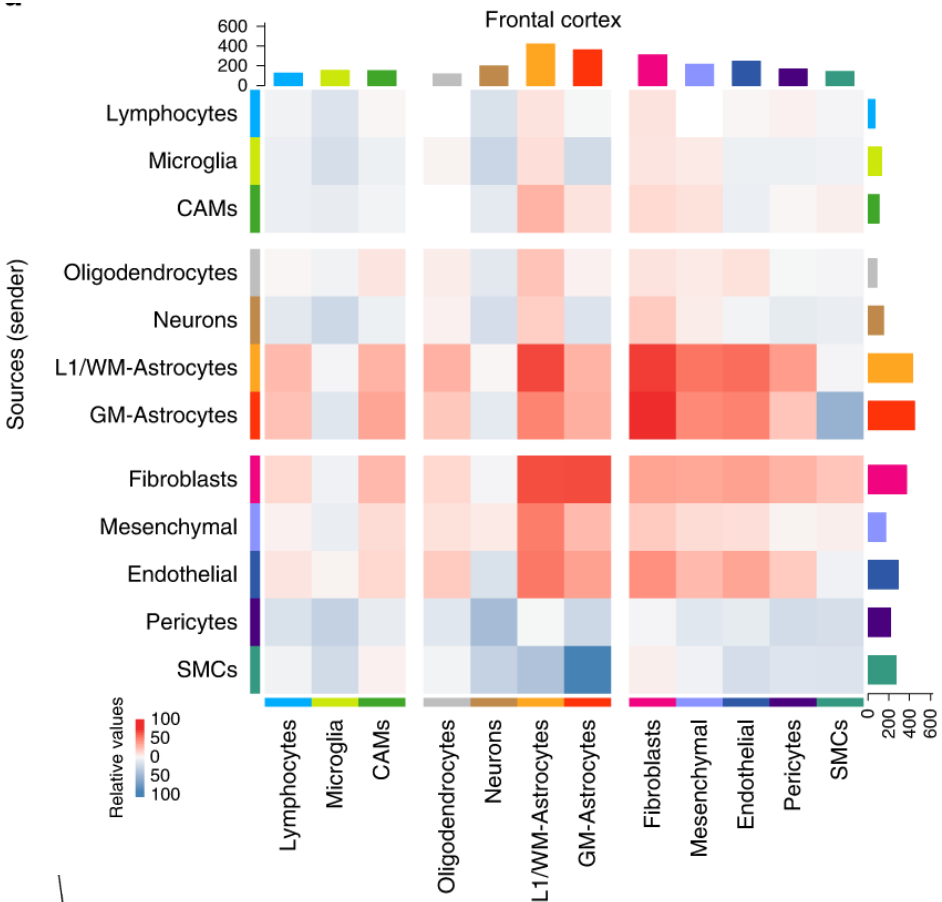
- hiPSC-derived *GRN*-deficient astrocytes delay spiking activity of developing neurons (Lee et al, Neurobiol Dis 2023).
- *GRN*$^{-/-}$ iAstrocyte are drivers for TDP-43 pathology in brain organoid. (Majo et al, Stem Cell Reports 2023).
- Astroglial toxicity promotes synaptic degeneration in the thalamocortical circuit in frontotemporal dementia with *GRN* mutations (Elise Marsan et al, J Clin Invest. 2023).

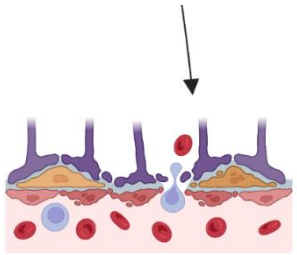


Neurovascular dysfunction in FTLD-*GRN*



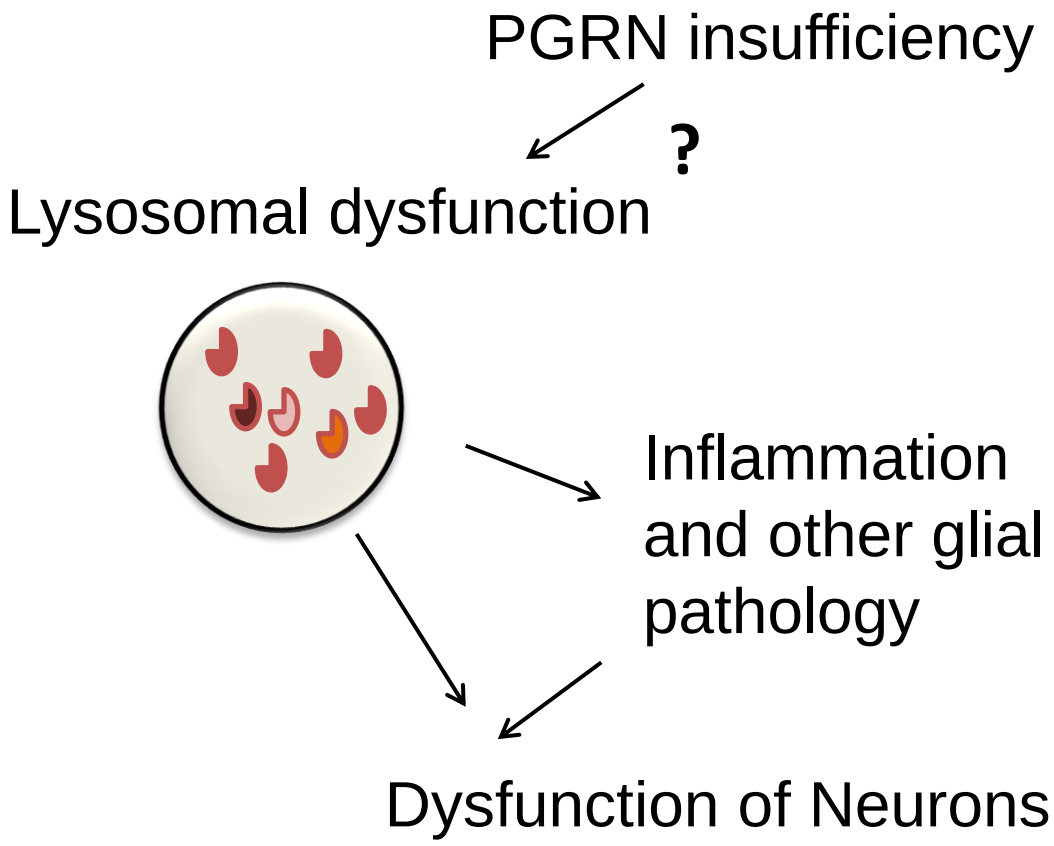




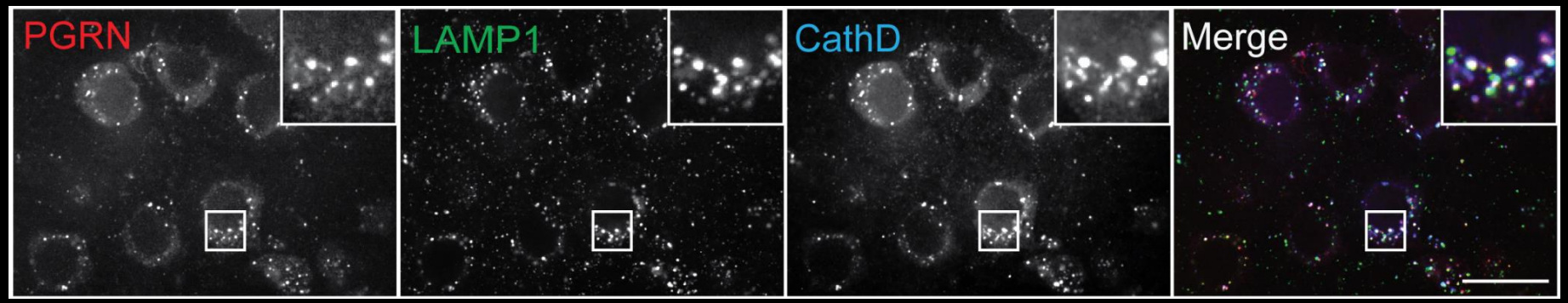


Gerrits et al, Nature Neuroscience 2022

How does PGRN prevent neurodegeneration at molecular and cellular levels?

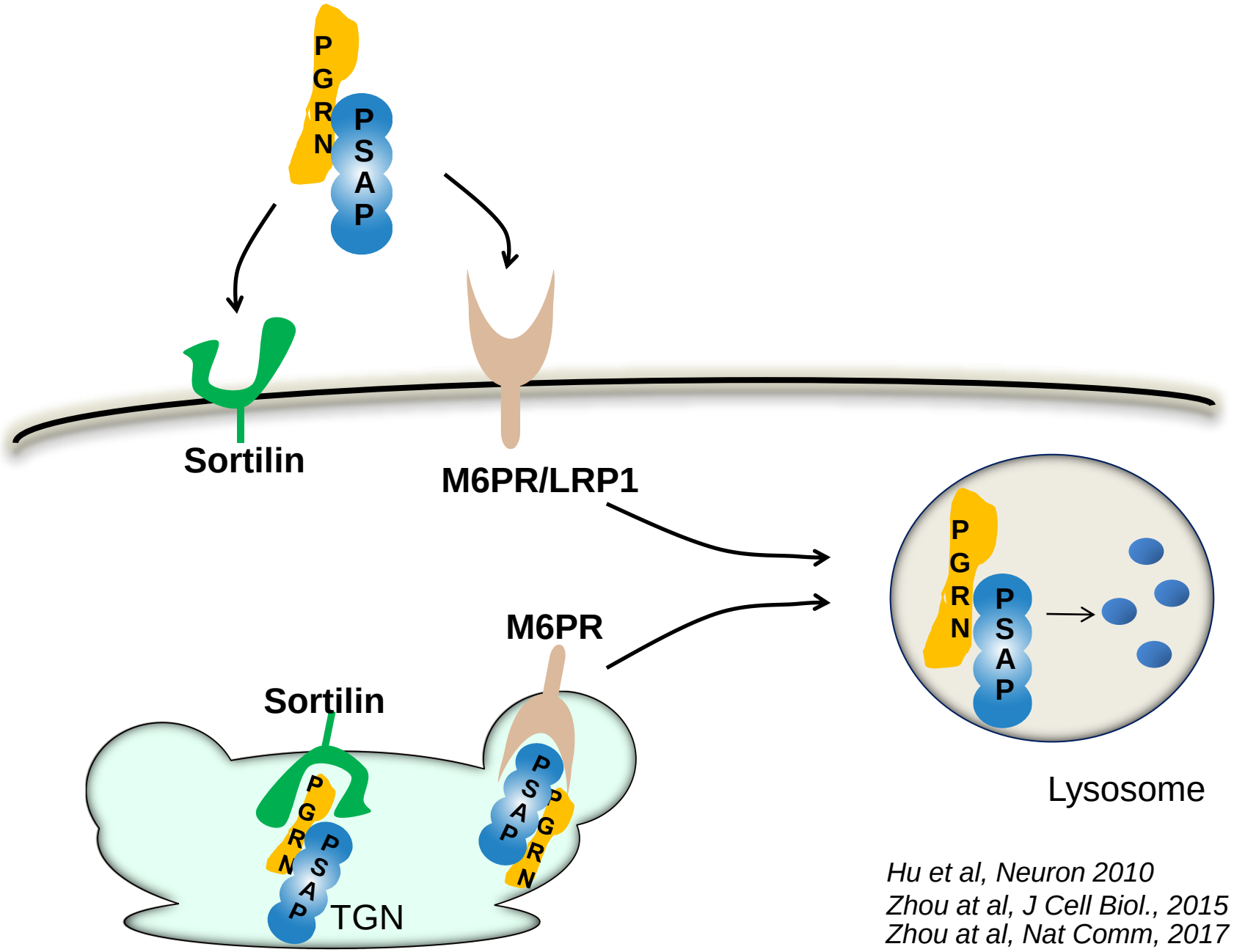


PGRN is a lysosomal resident protein



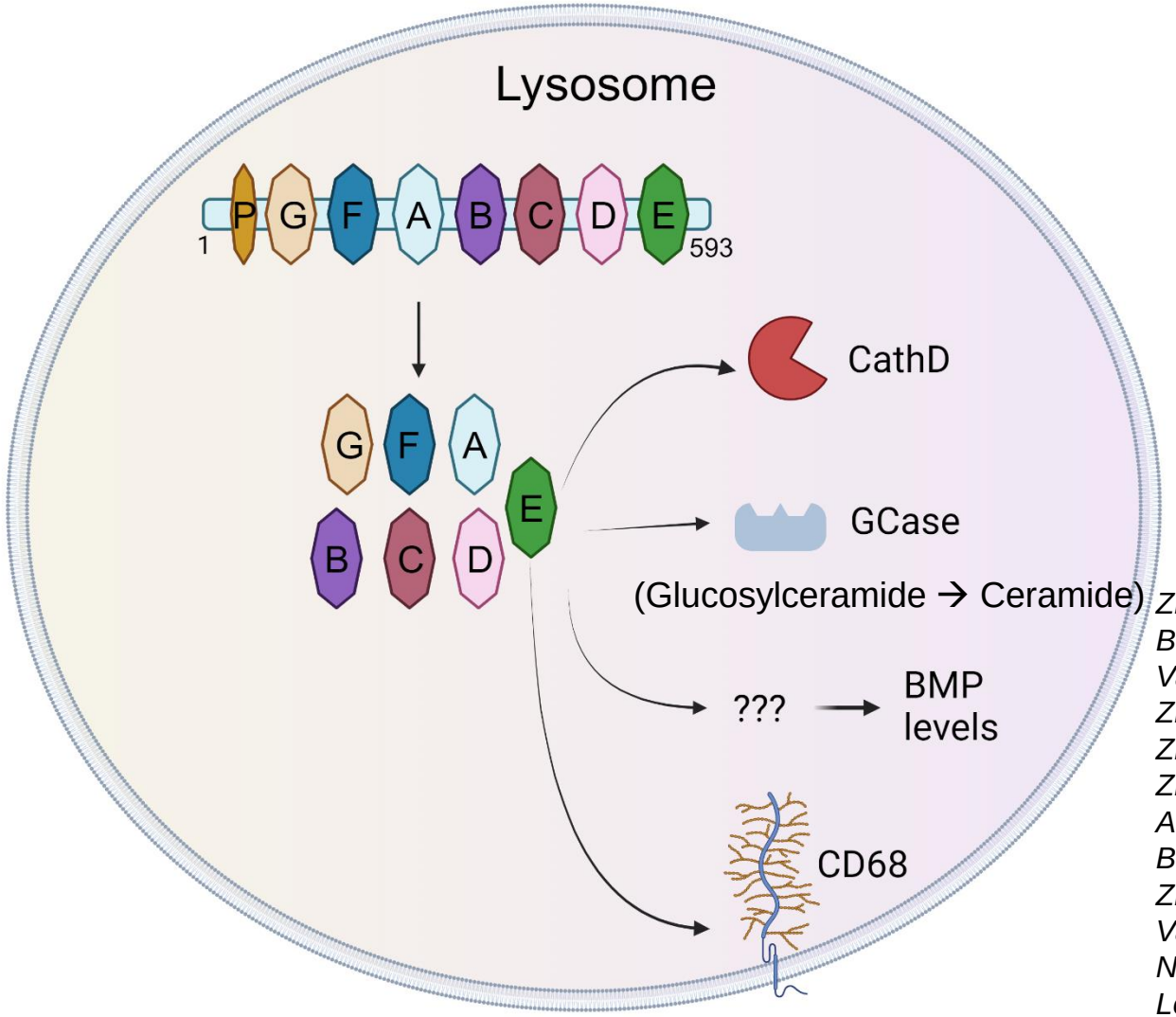
Paushter et al Acta Neuropathologica 2018

Lysosomal trafficking of progranulin



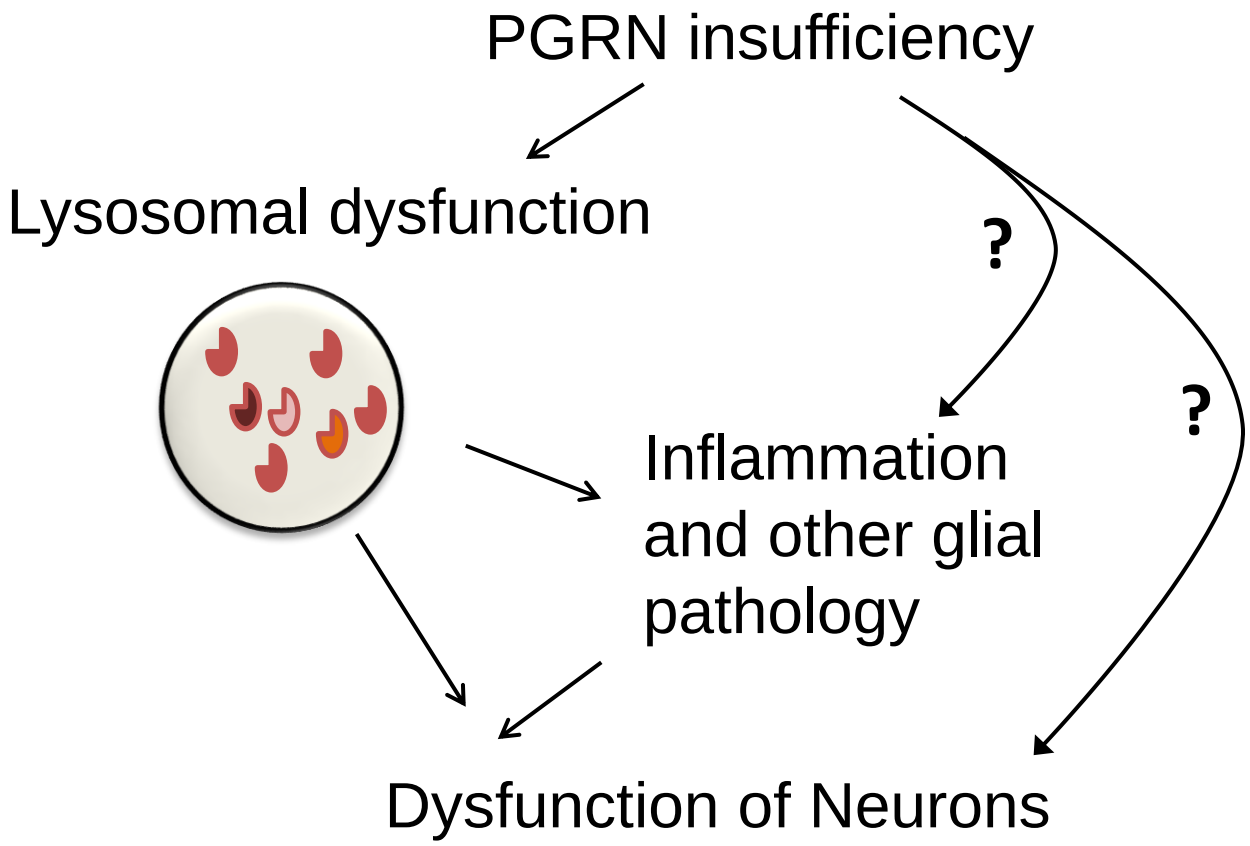
Hu et al, Neuron 2010
Zhou at al, J Cell Biol., 2015
Zhou at al, Nat Comm, 2017

How does PGRN function in the lysosome?

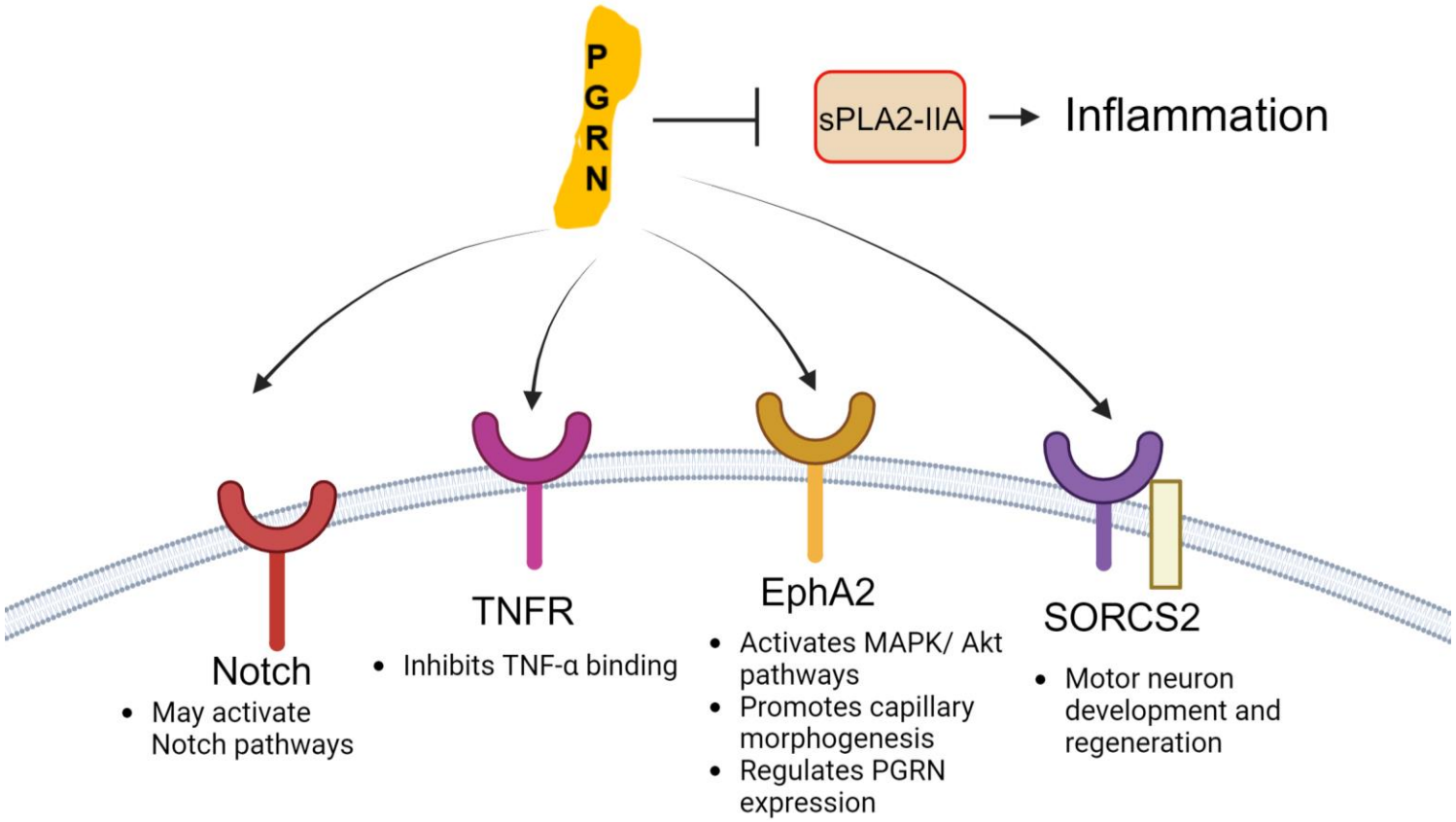


Zhou at al, J Cell Biol., 2015
Beel et al, Hum Mol Genet 2017
Valdez et al., Hum Mol Genet 2017
Zhou at al, Nat Comm, 2017
Zhou at al, Mol Neurodeg 2017
Zhou et al, Acta Neuropath 2017
Arrant et al, Acta Neuropathol Commun 2019
Butler et al, J Mol Biol 2019
Zhou et al, PLOS One 2019
Valdez et al, Hum Mol Genet 2019
Nunez Santos et al, JBC 2022
Logan et al, Cell 2021
Boland et al, Nature Communication 2022
Zhang at al, Mol Neurodeg 2022

How does PGRN prevent neurodegeneration?

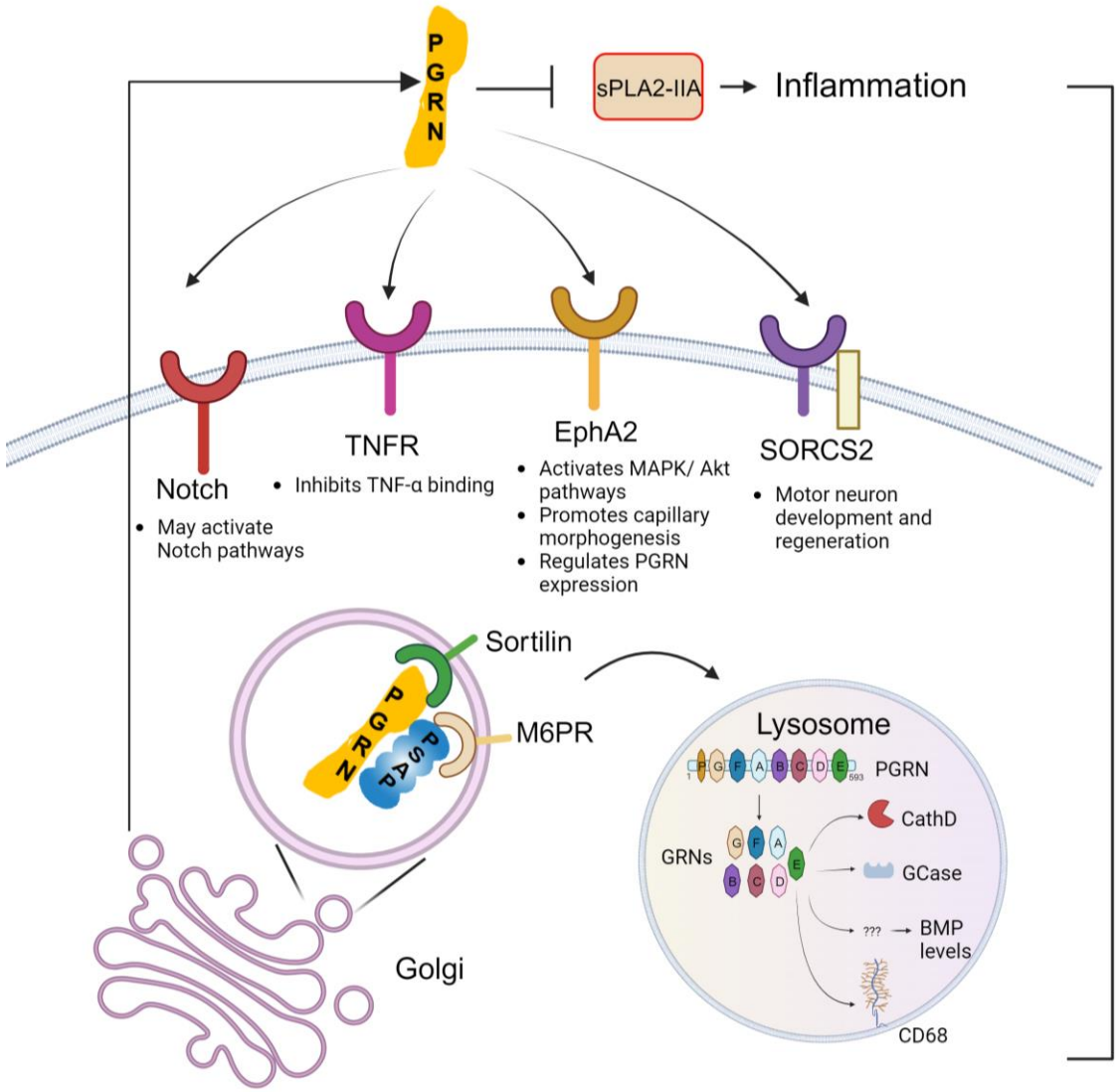


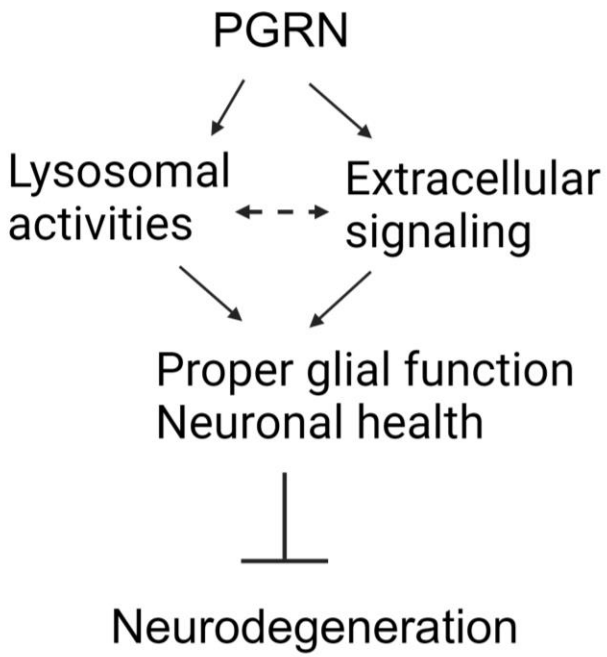
Extracellular functions of PGRN



Tang et al, Science 2011
Chen et al, J Neuroscience 2013
Altmann et al, Mol Neurodegener. 2016
Neill et al, J. Cell Bio 2016
Thomasen et al, Cell Rep 2023
Du et al, bioRxiv 2023

Summary





Created with BioRender.com

Latozinemab and AL101 Clinical Development

Lawrence Carter, Ph.D.

Vice President, Neurology

Alector

INFRONT-2: Phase 2 Trial in FTD

Open-Label, Single Arm

PRIMARY ENDPOINT

Safety and Tolerability

SECONDARY ENDPOINT

PK, PD

EXPLORATORY ENDPOINTS

CSF and Plasma Biomarkers (Lysosomal, inflammation, neurodegeneration)

Volumetric MRI (vMRI)

Clinical Outcome Assessment (CDR® plus NACC FTLD-SB[2])

1. Asymptomatic and symptomatic FTD-GRN enrollment closed; FTD-C9orf72 cohort currently enrolling
2. CDR® plus NACC FTLD-SB: Clinical Dementia Rating (CDR) dementia staging instrument plus National Alzheimer's Coordinating Center (NACC) behavior and language domains frontotemporal lobar degeneration (FTLD) sum of boxes (SB)

AL001 = latozinemab
FTD = frontotemporal dementia
GRN = granulin gene
C9orf72 = chromosome 9 open reading frame 72 gene
PK = pharmacokinetic, PD = pharmacodynamic
CSF = cerebrospinal fluid

INFRONT-2: Latozinemab was well tolerated in participants treated for up to 12 months

	aFTD-*GRN* (N=5) n (%)	FTD-*GRN* (N=12) n (%)	FTD-*C9orf72* (N=16) n (%)	Total (N=33) n (%)
Any TEAE	5 (100.0)	**11 (91.7)**	15 (93.8)	31 (93.9)
Any treatment-related TEAE[1]	2 (40.0)	**2 (16.7)**	8 (50.0)	12 (36.4)
Any SAE[2]	0	**3 (25.0)**	2 (12.5)	5 (15.2)
Any treatment-related SAE	0	**0**	0	0
Any TEAE leading to study drug discontinuation	0	**1 (8.3)**	1 (6.3)	2 (6.1)

Data cut: Electronic data capture extraction, Aug 28, 2023
TEAE = treatment emergent adverse event; SAE = serious adverse event
1. The 5 most common adverse events (>10%) were fall, urinary tract infection, COVID-19, headache, syncope
2. SAEs observed in study: deep vein thrombosis, pneumothorax, syncope, ALS

INFRONT-2: Clinical Outcome Assessments Supported by Biomarkers in FTD-*GRN*

Key biomarkers and clinical outcome assessments reflect underlying disease activity in FTD-*GRN* patients

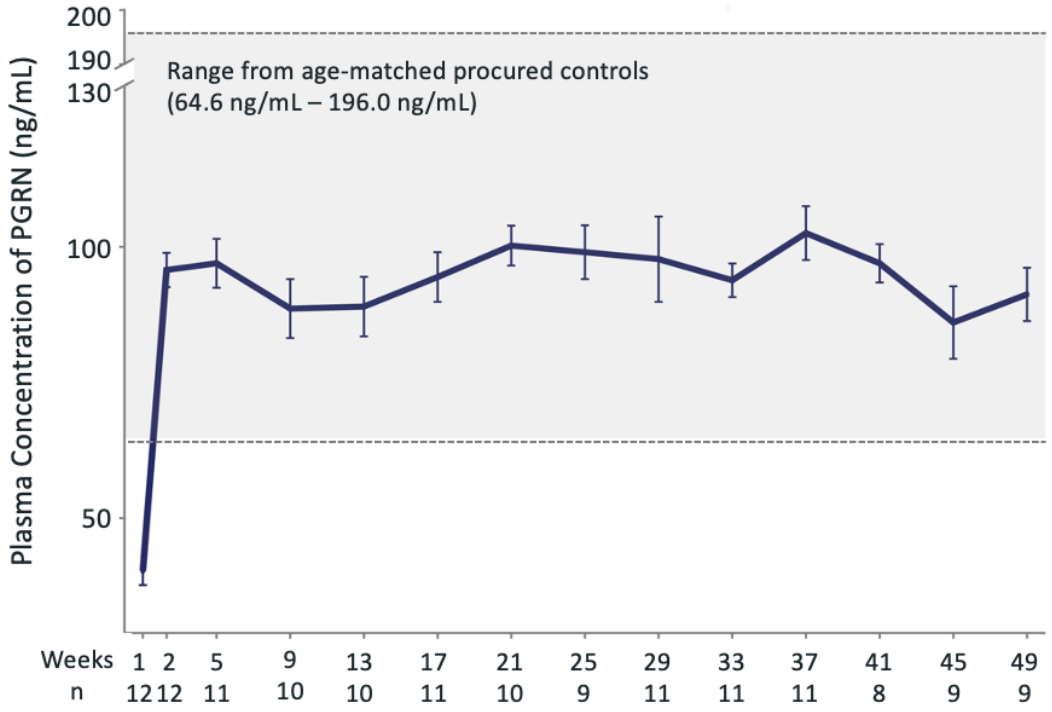
TARGET ENGAGEMENT	BIOMARKERS OF DISEASE ACTIVITY					CLINICAL BENEFIT
PGRN (Plasma and CSF)	Lysosomal Dysfunction	Inflammation	Brain Health	Neuronal Health	Brain Atrophy	Clinical Outcome Assessments
PGRN CSF and plasma PGRN levels	**e.g. CTSD, LAMP1** Dysfunctional lysosomes are hallmarks of FTD-*GRN*	**e.g. C1QB** Elevation of complement proteins occurs in FTD-*GRN*	**GFAP** Elevation of GFAP is a hallmark of FTD-*GRN* and correlates with cognitive decline	**NfL** NfL is a measure of axonal damage	**MRI** Accelerated brain tissue loss is a hallmark of FTD-*GRN* and corr elates with cognitive decline	**CDR® plus NACC FTLD-SB** FDA approvable endpoint for measuring clinical decline in FTD

CTSD = cathepsin D; LAMP1 = lysosomal associated membrane protein 1; C1QB = complement C1q B chain; GFAP = glial fibrillary acidic protein; NfL = neurofilament light chain; CDR® plus NACC FTLD-SB = Clinical Dementia Rating (CDR) dementia staging instrument plus National Alzheimer's Coordinating Center (NACC) behavior and language domains frontotemporal lobar degeneration (FTLD) sum of boxes (SB)

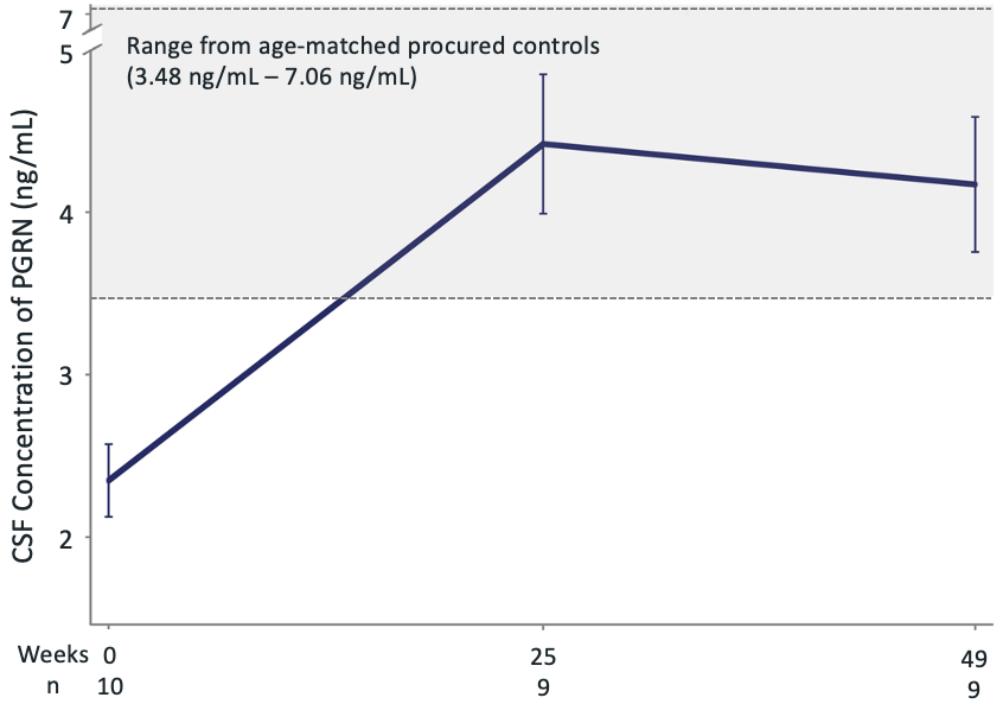
INFRONT-2: Latozinemab Restores PGRN in Plasma and CSF to Levels Seen in Healthy Volunteer Age-Matched Controls

ACHIEVED FULL AND SUSTAINED PGRN RESTORATION IN FTD-*GRN* PARTICIPANTS

PGRN Plasma Concentration



PGRN CSF Concentration



Data cut-off June 15, 2021
Mean +/- SEM
Source: AAIC 2021.

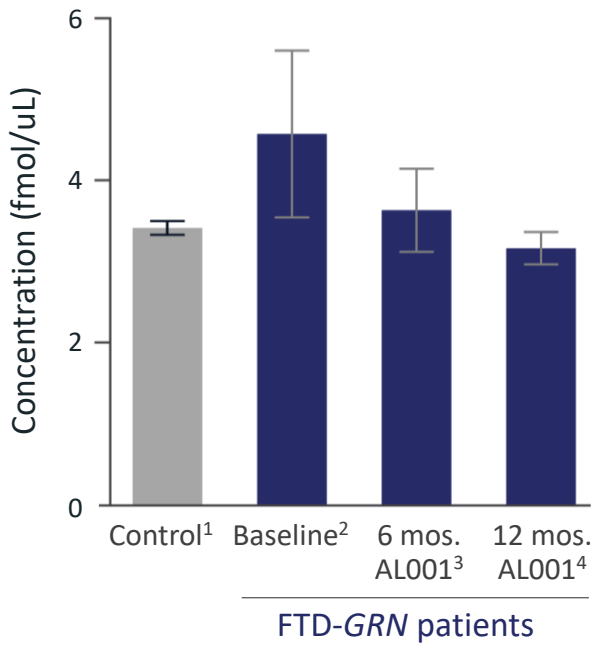
INFRONT-2: Latozinemab Treatment Normalizes Lysosomal and Inflammatory Biomarkers Towards Levels Seen in Control Subjects

FLUID BIOMARKERS OF DISEASE ACTIVITY

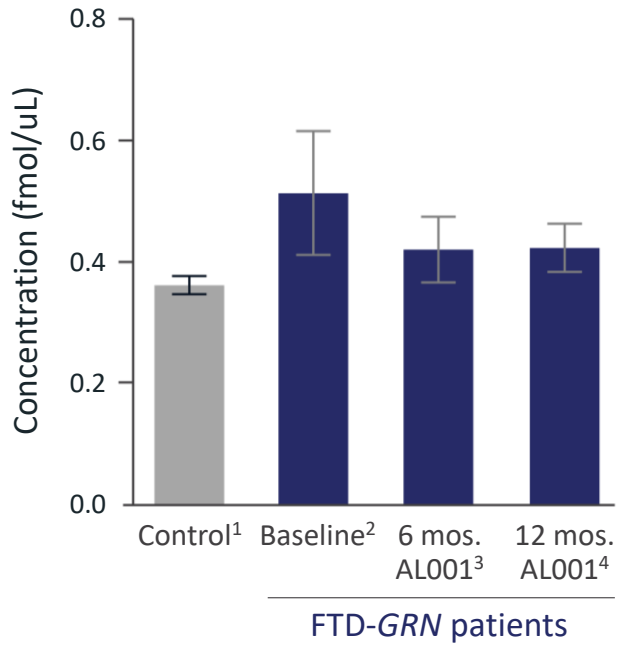
Symptomatic FTD-*GRN* patients at 12 months

Normalization of lysosomal and inflammatory biomarkers

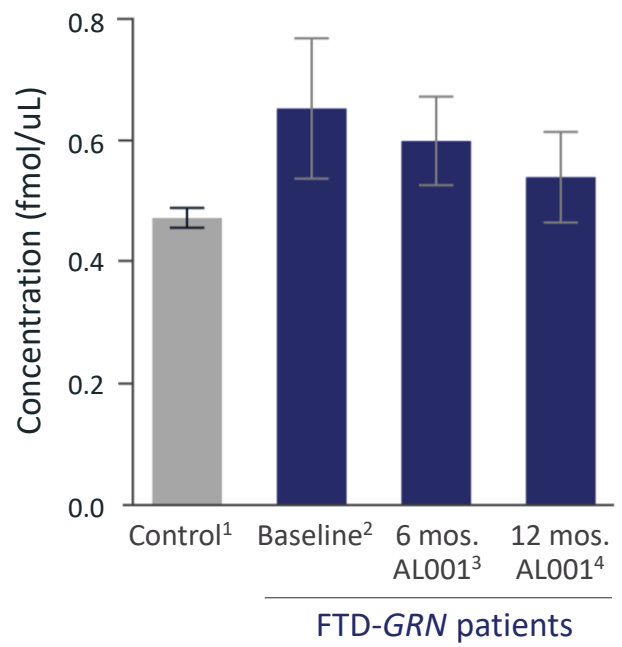
Lysosomal dysfunction - CTSD



Lysosomal dysfunction - LAMP1



Complement activation - C1QB



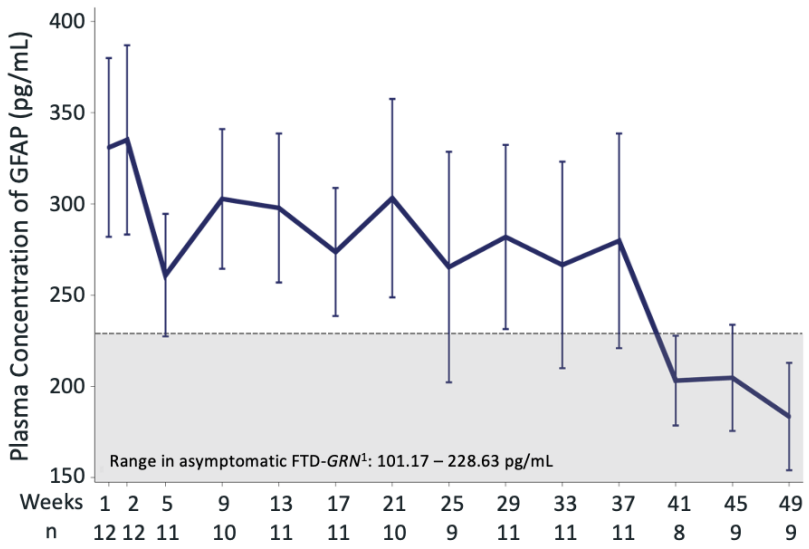
1. Age-matched procured control samples (N=44)
2. N = 11
3. N=9
4. N=10

Mean +/- SEM
CTSD = cathepsin D protein
LAMP1= lysosomal-associated membrane protein 1
C1QB = gene that encodes the B-chain polypeptide of serum complement subcomponent C1q
Source: AAIC 2021.

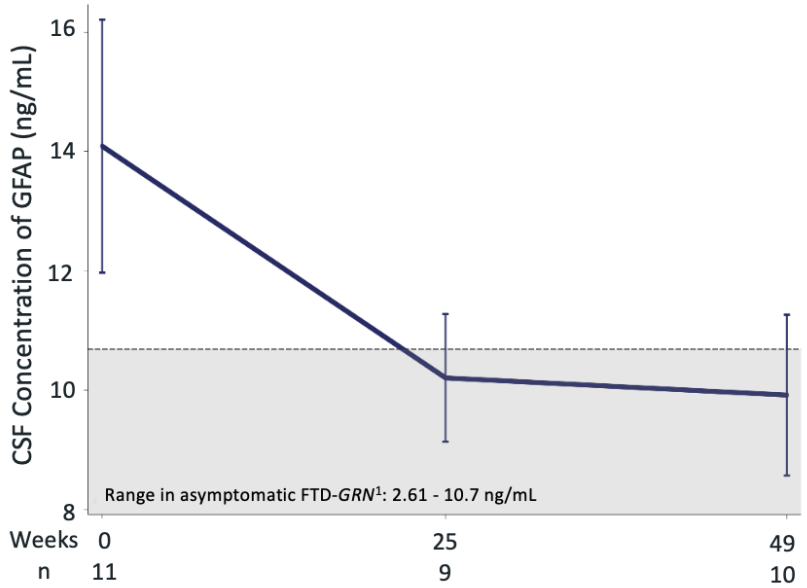
INFRONT-2: Latozinemab Treatment Decreases Glial Fibrillary Acidic Protein (GFAP) Levels Towards Range Seen in Asymptomatic Carriers of FTD-*GRN* Mutation

BIOMARKERS OF DISEASE ACTIVITY – ASTROGLIOSIS

GFAP Plasma Concentration



GFAP CSF Concentration



GRN Literature Shows that Plasma GFAP is Significantly Correlated with Temporal Atrophy in Symptomatic FTD-*GRN* Patients[1]

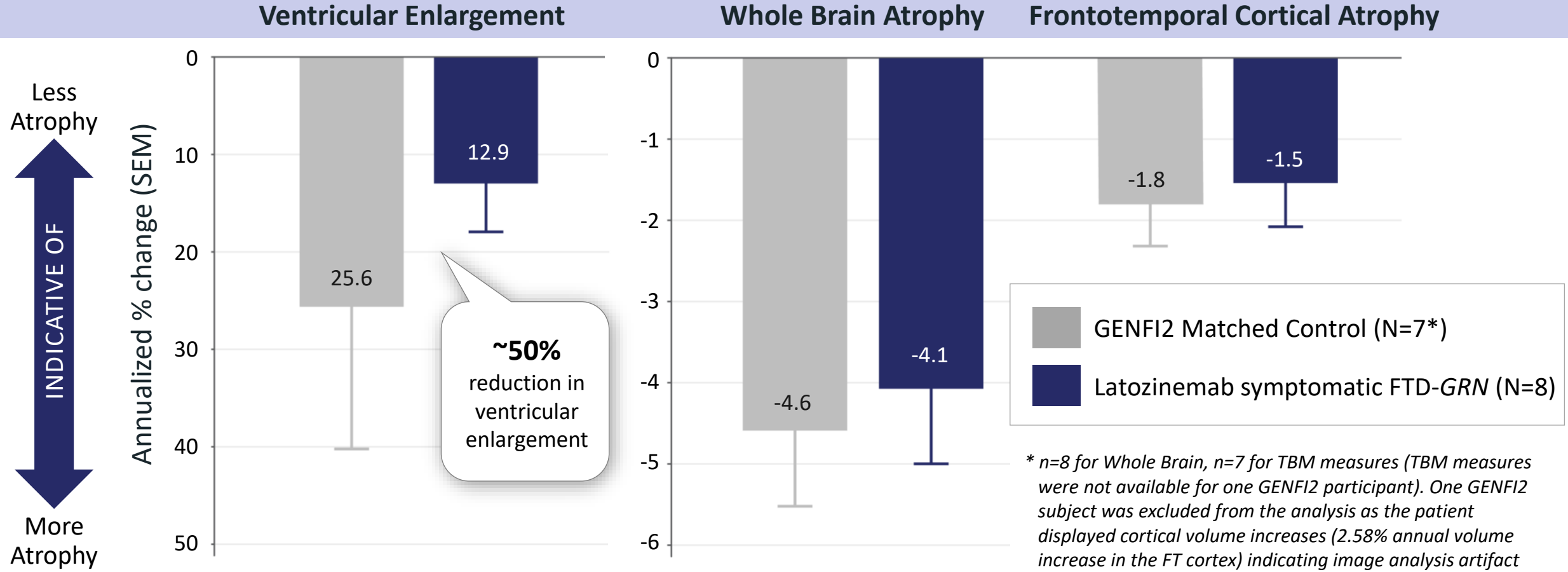
		GRN PS	*GRN* S
Whole brain	r	0.02	0.07
	p-value	0.906	0.805
Frontal	r	-0.08	0.20
	p-value	0.608	0.493
Temporal	r	0.13	**0.66**
	p-value	0.373	**0.010**
Parietal	r	0.05	0.40
	p-value	0.762	0.159
Occipital	r	0.10	0.24
	p-value	0.503	0.401
Cingulate	r	-0.17	0.55
	p-value	0.264	0.052
Insula	r	0.15	0.18
	p-value	0.328	0.533

Data cut-off June 15, 2021
Mean +/- SEM
Range is of baseline GFAP levels in asymptomatic FTD-GRN patients enrolled in INFRONT-2 Source: AAIC 2021.

1. Heller C, Foiani MS, Moore K, et al. J Neurol Neurosurg Psychiatry 2020;91:263–270

INFRONT-2: vMRI Data Showing Reduced Ventricular Enlargement and Reduced Brain Atrophy in Latozinemab-Treated FTD-*GRN* Patients vs. Matched Historical Controls

BIOMARKERS OF DISEASE ACTIVITY – BRAIN VOLUME CHANGES



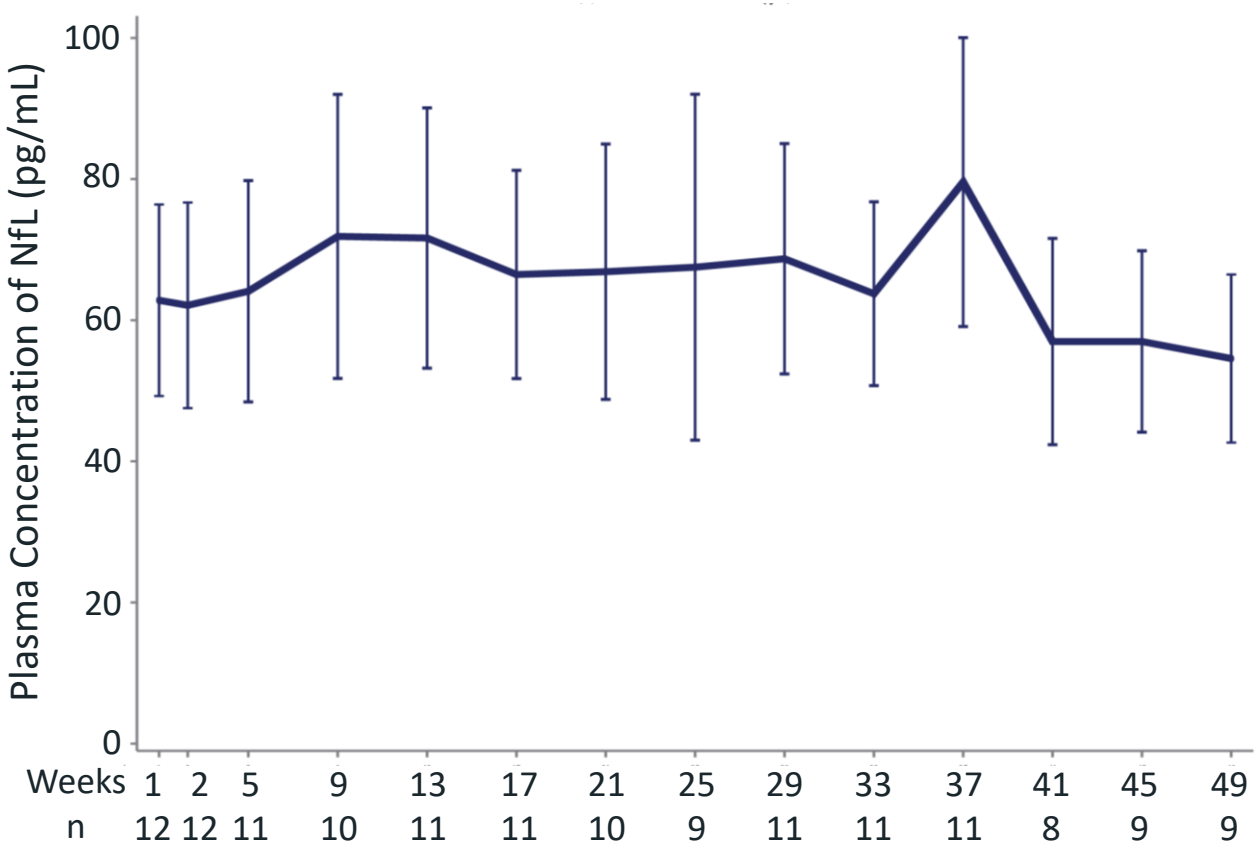
** n=8 for Whole Brain, n=7 for TBM measures (TBM measures were not available for one GENFI2 participant). One GENFI2 subject was excluded from the analysis as the patient displayed cortical volume increases (2.58% annual volume increase in the FT cortex) indicating image analysis artifact*

TBM = Tensor-based Morphometry (TBM) used for frontotemporal cortex and ventricles
Source: AAIC 2021.

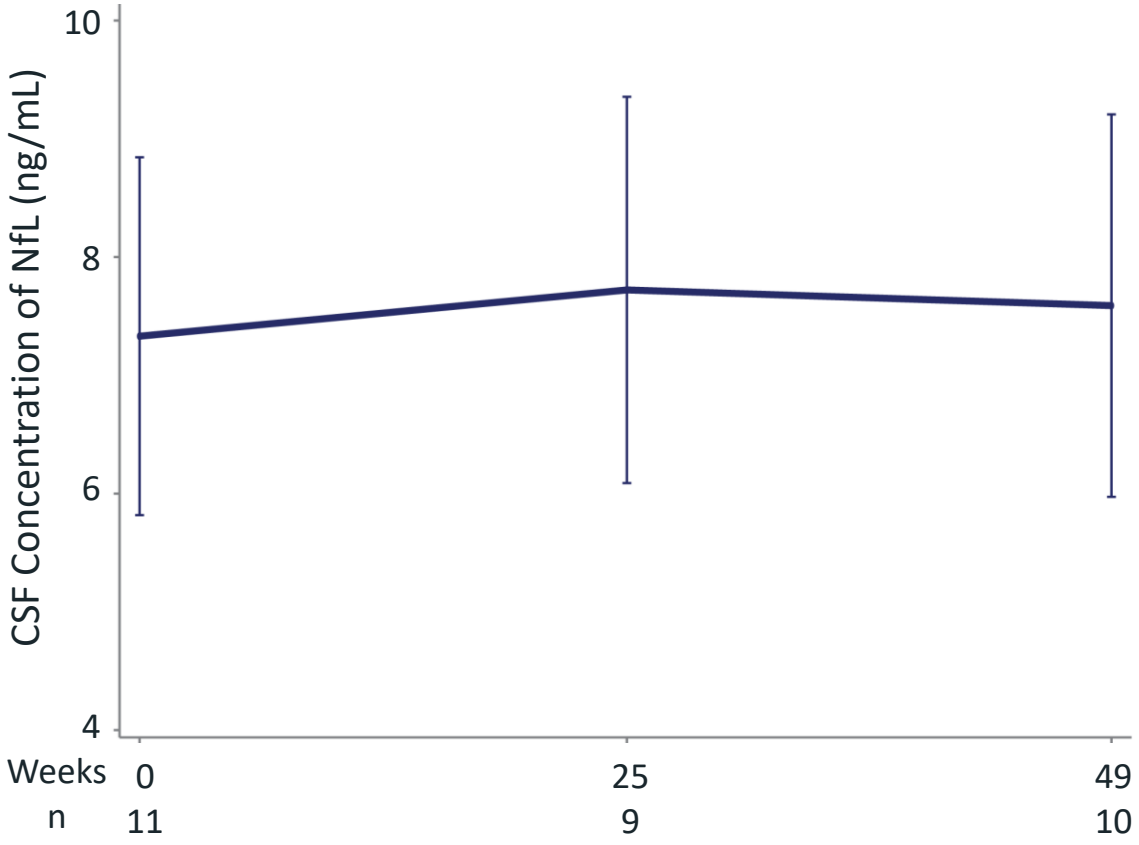
INFRONT-2: NfL Levels in Plasma and CSF Are Stable Over 12 Months in Latozinemab-treated FTD-*GRN* Patients

BIOMARKERS OF DISEASE ACTIVITY – NEURONAL HEALTH

NfL Plasma Concentration



NfL CSF Concentration



alector

Data cut-off June 15, 2021
Mean +/- SEM

Contextualizing INFRONT-2 Clinical Results with GENFI2 Matched Controls

- INFRONT-2 clinical results compared against comparable, GENFI2 matched controls
- Comparable baseline characteristics established between INFRONT-2 FTD-*GRN* symptomatic cohort and GENFI2 controls in two-steps:
  - Propensity score matching[1] based on CDR® plus NACC FTLD-SB at baseline
  - Matching refined by age, gender, baseline plasma NfL levels, and FTD disease variant at baseline[2]

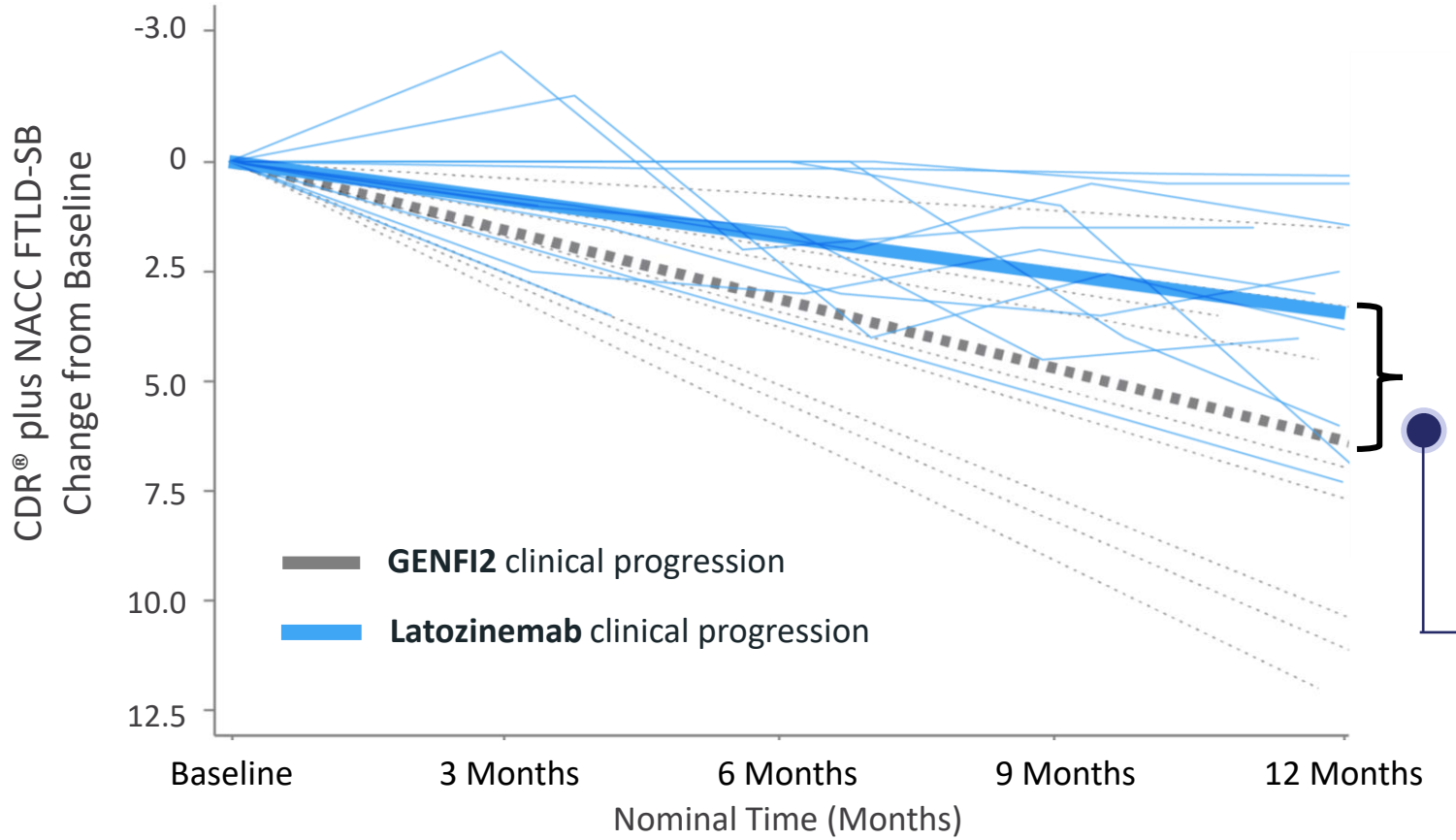
Baseline characteristics		**INFRONT-2** (N=12)	**GENFI2 Matched Controls** (N=10)
CDR® plus NACC FTLD-SB	**Mean (SD)**	**5.9 (3.74)**	**5.2 (3.60)**
	Min, Max	**0.5, 11**	**0.5, 11.5**
AGE (Years)	Mean (SD)	63.2 (9.71)	62.1 (6.74)
	Min, Max	49, 79	52, 72
GENDER	Male	8 (67%)	3 (30%)
PLASMA NfL (pg/mL)	N	12	9
	Mean (SD)	62.8 (47.00)	40.3 (27.28)
	Min, Max	11.2, 148.8	9.3, 99.9
FTD DISEASE VARIANT	bvFTD	5 (42%)	5 (50%)
	PPA	3 (25%)	3 (30%)
	Both	3 (25%)	0
	Other	1 (8%)	1 (10%)

GENFI = The Genetic Frontotemporal Initiative
GENFI2 refers to the longitudinal FTD registry dataset
1. Propensity score matching is a well-established statistical method intended to mimic randomization
2. Clinical reviewers blinded to outcome data

INFRONT-2: Preliminary Data Suggests Latozinemab Slows Disease Progression in FTD-*GRN* Participants Compared to Matched Historical Controls

CLINICAL MEASURE

CDR® plus NACC FTLD-SB



Parameter	Estimate[1]	95% CI
Annual Change in **GENFI2** (n=10)	6.4	[4.35,8.42]
Annual Change in **Latozinemab** (n=12)	3.3	[1.38,5.28]
Difference in Annual Change (GENFI2 – Latozinemab)	**3.1**	**[0.24,5.88]**

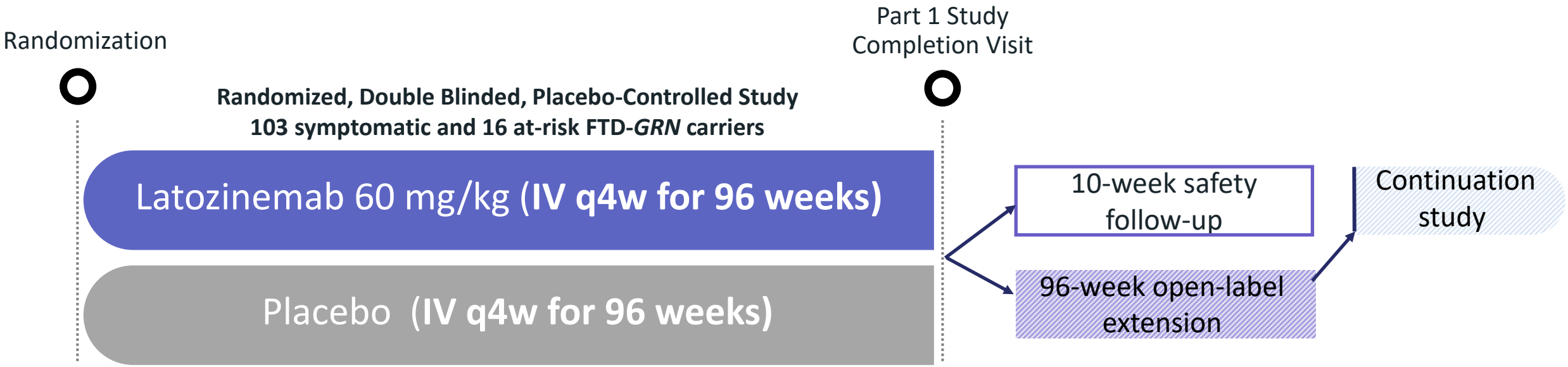
Estimated to slow annual disease progression by ~48% (3.1 point change)

1. Random Coefficient Model with Repeated Measurements including baseline & all available post-baseline measurements up to 12 months. Data cut-off Sep 8, 2021.
Phase 2 data presented at CTAD 2021 and ADPD 2022
NCT03987295

GENFI = The Genetic Frontotemporal Initiative
GENFI2 refers to the longitudinal FTD registry dataset

INFRONT-3: Ongoing Pivotal Phase 3 Study with Latozinemab

ACHIEVED TARGET ENROLLMENT IN Q4 2023



PRIMARY ENDPOINT	SECONDARY CLINICAL OUTCOMES ASSESSMENTS:	EXPLORATORY ENDPOINTS
CDR® plus NACC FTLD-SB	CGI-S, CGI-I, FRS, RBANS	vMRI, Plasma Biomarkers

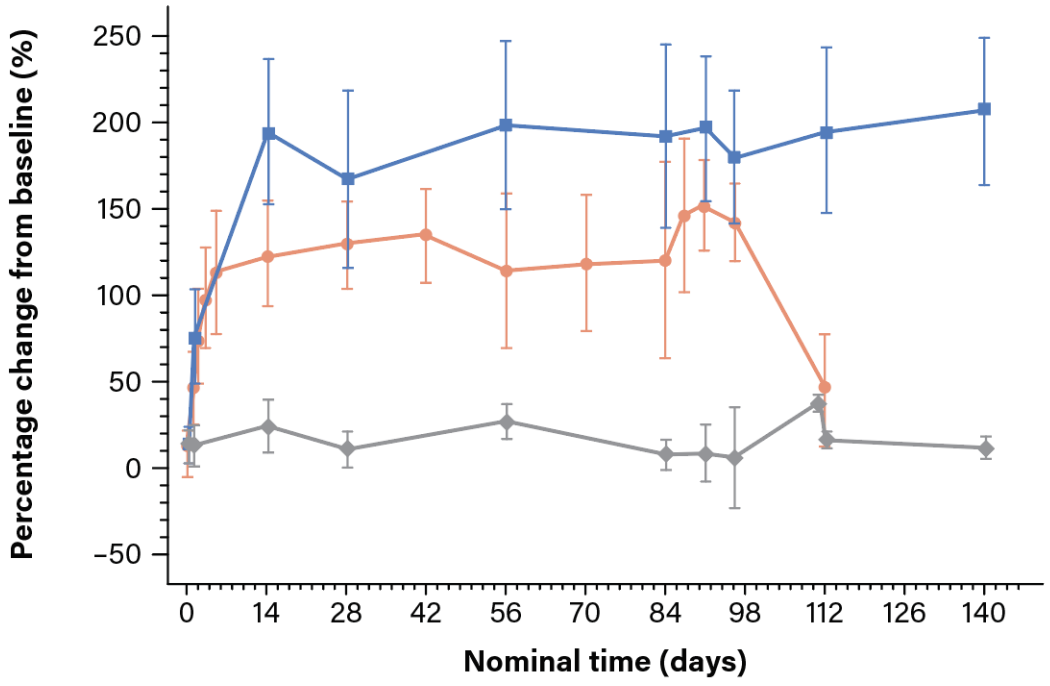
"At risk" = GRN carriers who are pre-symptomatic and meet a pre-specified NfL threshold for enrollment in the Phase 3
CDR® plus NACC FT1. LD-SB = Clinical Dementia Rating Dementia Staging Instrument PLUS National Alzheimer's Disease Coordinating Center Frontotemporal Lobar Degeneration Behavior and Language Domains Sum of Boxes; CGI-S = Clinician's Global Impression-Severity; CGI-I = Clinician's Global Impression-Improvement; FRS = Frontotemporal Dementia Rating Scale;
RBANS = Repeatable Battery for the Assessment of Neuropsychological Status

AL101 Elevated Progranulin Levels in Plasma and CSF in Phase 1

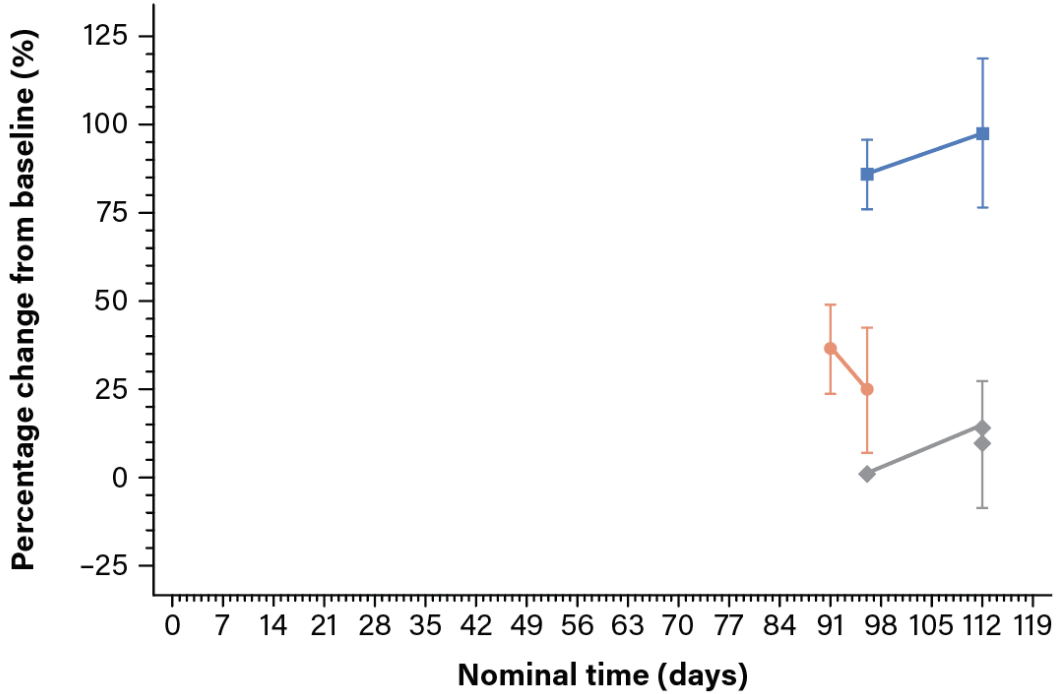
DEVELOPED TO ALIGN WITH NEEDS OF LARGER INDICATIONS, INCLUDING ALZHEIMER'S DISEASE

Mean (±SD) Percentage Change from Baseline in Plasma (A) and CSF (B) Concentrations of Progranulin as a Function of Time After Multiple-Dose Administration of AL101

Plasma PGRN



CSF PGRN

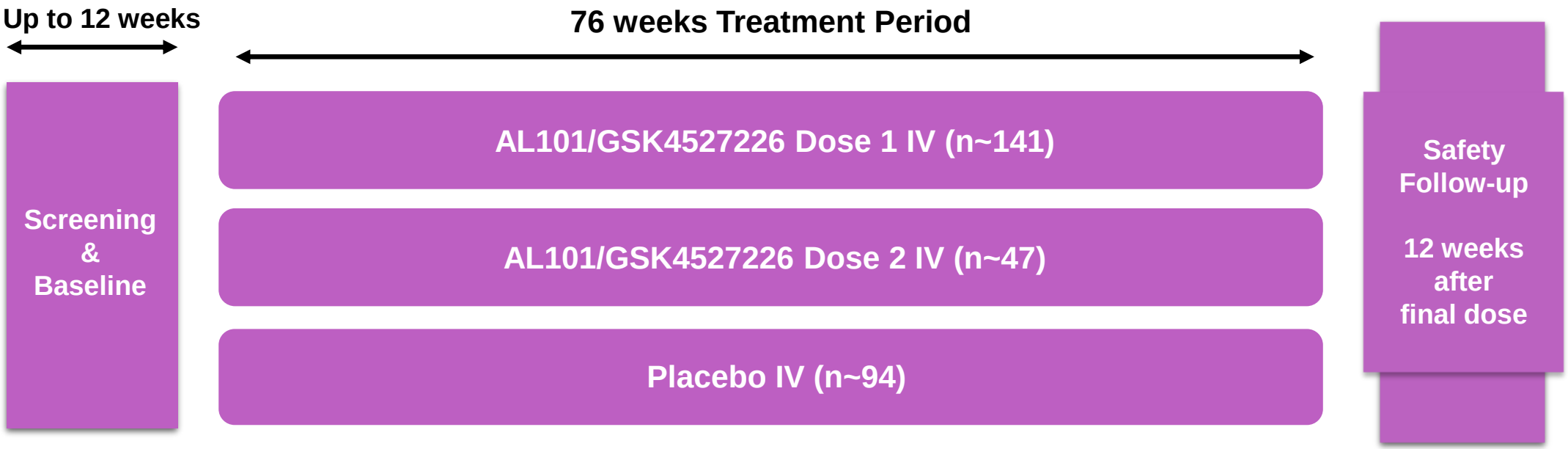


AL101 300 mg MD SC AL101 30 mg/kg MD IV Pooled Placebo MD IV

CSF =cerebrospinal fluid; IV = intravenous; MD = multiple-dose; PGRN = progranulin; SC = subcutaneous; SD = standard deviation
Source: Ward et al. CTAD 2022.

AL101 / GSK4527226 PROGRESS-AD Study Design

PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF AL101 / GSK4527226 IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE



Key inclusion criteria
- Age 50-85 years, inclusive
- Diagnosis of MCI due to AD up to mild AD dementia
- Amyloid positivity (by PET or CSF)

Primary endpoint
Change from Baseline in CDR-SB across Weeks 52, 64 and 76.

Key secondary endpoints
Change from Baseline across Weeks 52, 64 and 76 for iADRS, ADAS-Cog14, ADCS-iADL, ADCS-ADL-MCI, ADCOMS

Biomarkers: Amyloid PET, Tau PET, CSF and Plasma

Promising Advances in PGRN Therapeutic Development

Adam Boxer, M.D., Ph.D.

Endowed Professor of Neurology, University of California San Francisco, Weill Institute for Neurosciences

UCSF Weill Institute for Neurosciences

Memory and Aging Center

The past and future of progranulin clinical trials

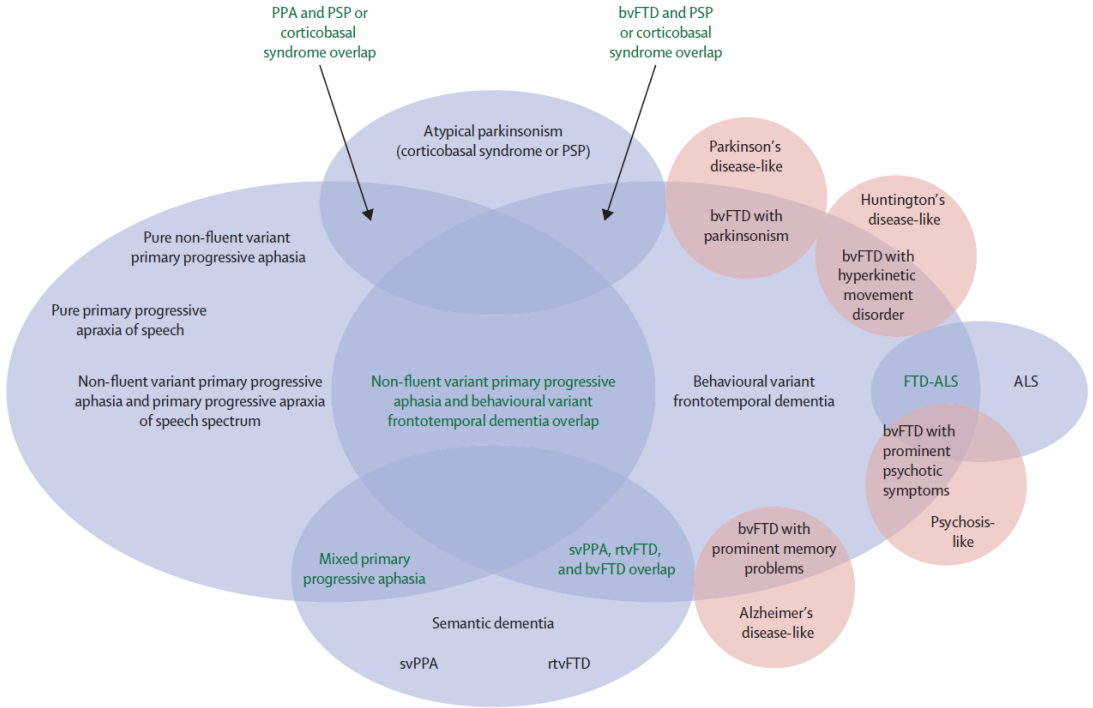
Adam Boxer, MD, PhD
Endowed Professor in Memory and Aging
University of California, San Francisco

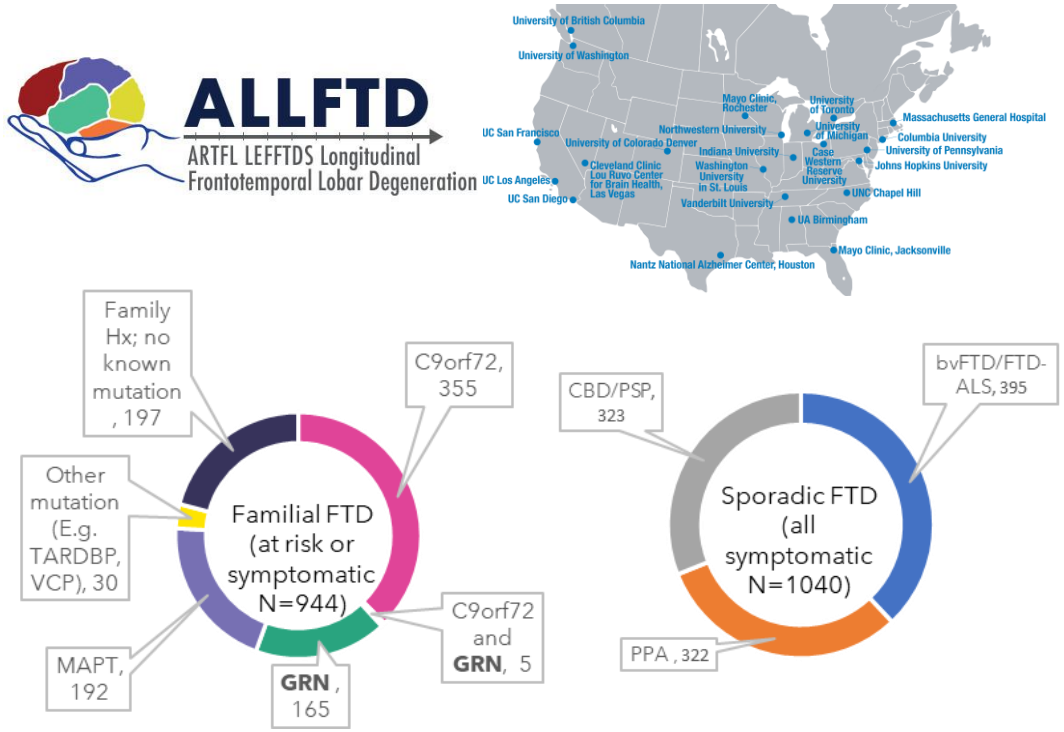
Outline

- Frontotemporal dementia & progranulin
- Progranulin biology & relationship to other diseases
- Early FTD trials and biomarkers
- Progranulin as a therapeutic target
- Early FTD-*GRN* trials
- Other potential uses of progranulin therapies

Frontemporal (lobar) Degeneration (FTD/FTLD)

- FTD rare disease (~10-20/100,000); common cause of early-onset (<65 years)
- Classic form: behavioral variant frontotemporal dementia (bvFTD; Pick's)
  - insidious onset, personality, behavioral changes → cognitive, motor
- 40% strong family history; ~30% identifiable autosomal dominant

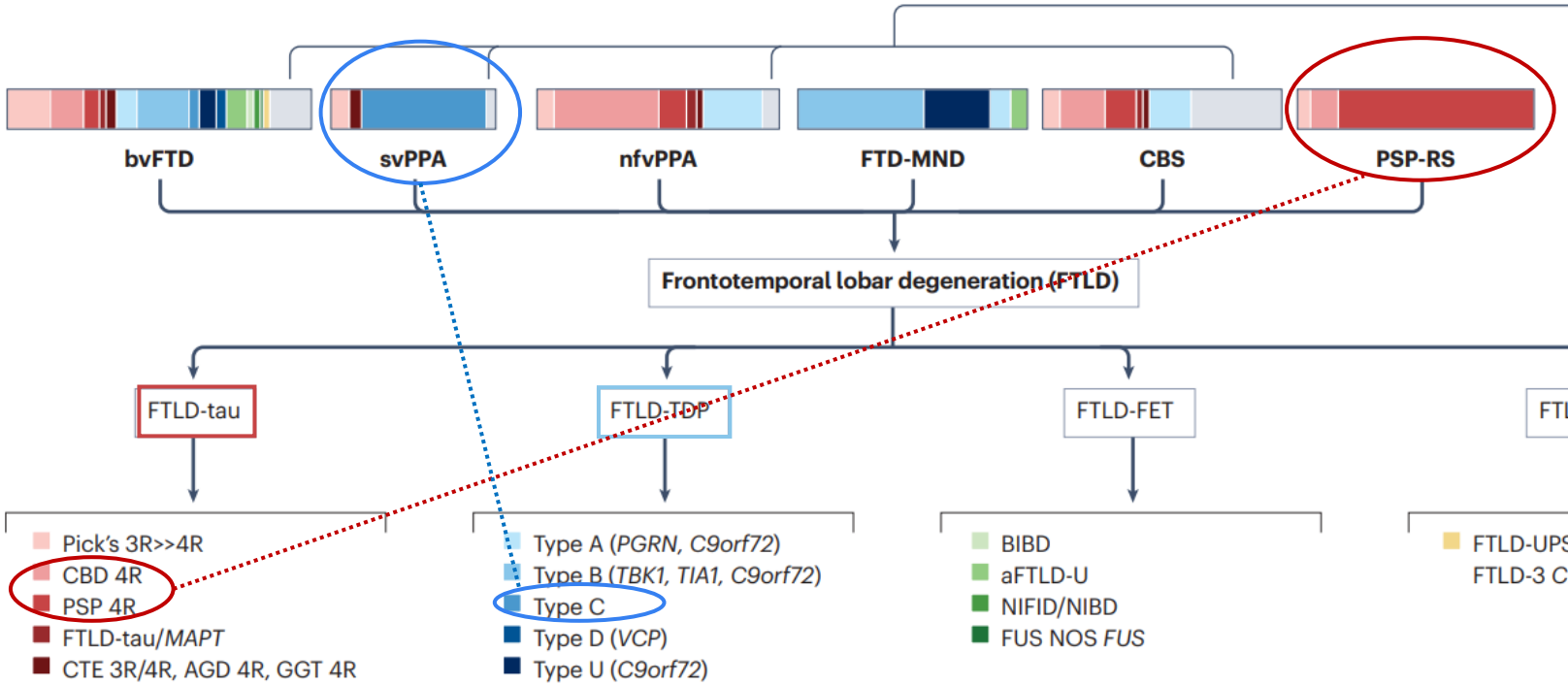




Boeve, et al, *Lancet Neurol*, 2023; Boxer presentation at 2022 NAPA-ADRD Summit

UCSF

FTLD trials in genetically-defined or clinically predictive syndromes



Biomarkers

CSF: 4R MTBR fragments (?)

Nonspecific

CSF/Blood: NfL
MRI: structural, FLAIR
PET: FDG-PET

CSF: *C9orf72* DPRs, progranulin, BMP's
Blood: Progranulin

CSF/Blood: NfL
MRI: structural, FLAIR
PET: FDG-PET

Biomarkers

Soluble proteins

CSF: Aβ42/40, P-tau181, MTBR-tau
Blood: Aβ42/40, P-tau181, -217, other P-tau's & ratios; MTBR-tau,

Insoluble proteins

PET: Aβ (multiple FDA approved ligands); tau (FTP, others soon?)

Nonspecific

MRI: structural, FLAIR, SWI
PET: FDG-PET

CSF/Blood: GFAP, NfL

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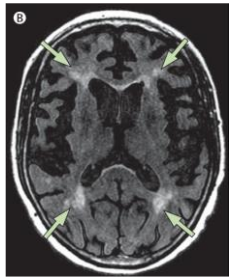
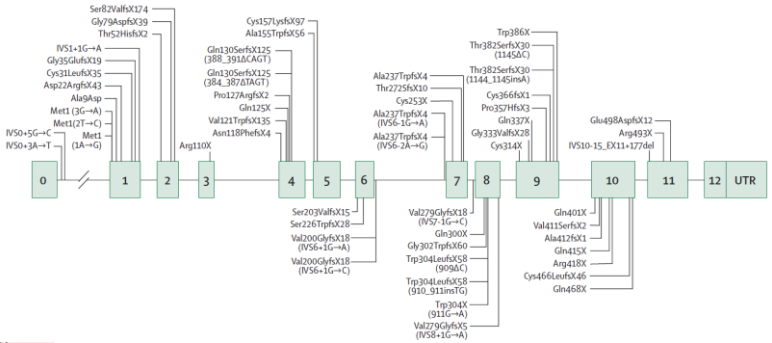
Progranulin (*GRN*) mutations cause FTD

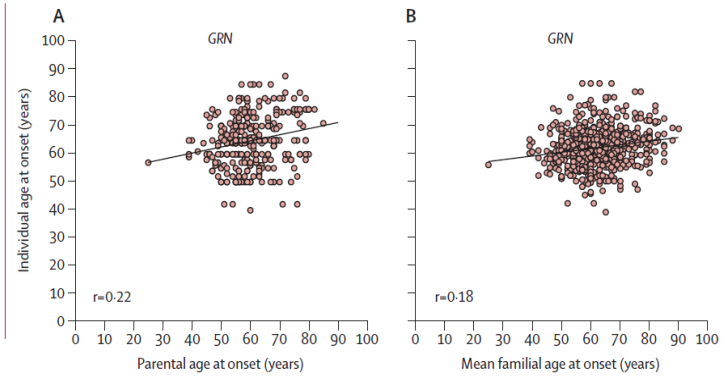
- *C9orf72* (2011) > *GRN* (2006) ~ *MAPT* (1998) most common genetic FTD causes (founder effects)
- Progranulin previously studied: inflammation, wound healing, cancer



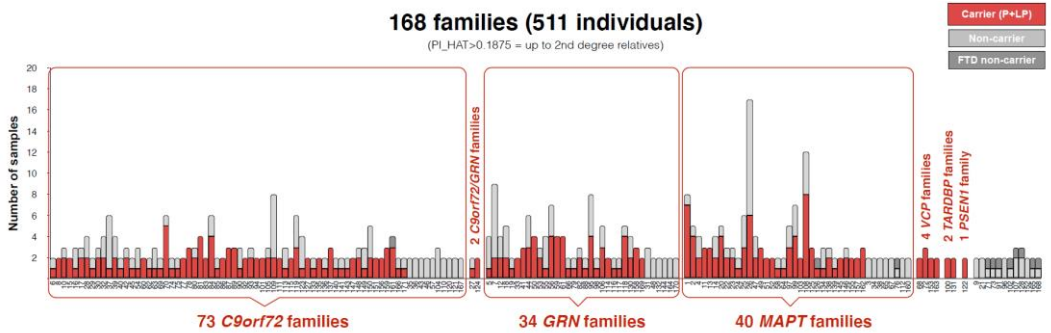


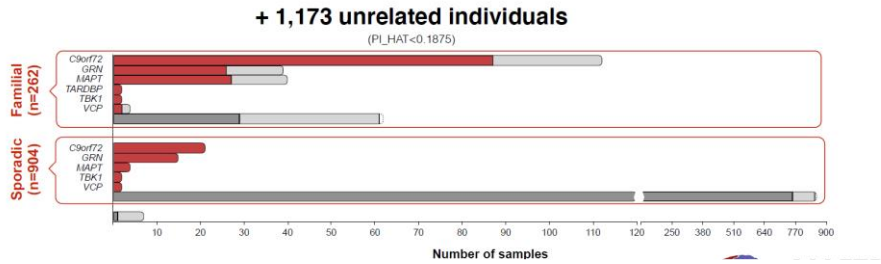
	GRN (n=1179)
Diagnoses within the frontotemporal dementia spectrum	
Behavioural variant frontotemporal dementia	446 (37·8%)
Non-fluent variant primary progressive aphasia	107 (9·1%)
Semantic variant primary progressive aphasia	13 (1·1%)
Logopenic variant primary progressive aphasia	4 (0·3%)
Primary progressive aphasia not otherwise specified*	36 (3·1%)
Frontotemporal dementia with amyotrophic lateral sclerosis	7 (0·6%)
Amyotrophic lateral sclerosis	7 (0·6%)
Corticobasal syndrome	47 (4·0%)
Progressive supranuclear palsy†	0 (0%)
Diagnoses outside the frontotemporal dementia spectrum	
Alzheimer's disease	97 (8·2%)
Huntington's disease	0 (0%)
Parkinson's disease	16 (1·4%)
Dementia with Lewy Bodies	4 (0·3%)
Vascular dementia	9 (0·8%)
Dementia not otherwise specified*	361 (30·6%)
Other	25 (2·1%)

Individual age of onset hard to predict



Familial relatedness in autosomal dominant FTD from ALLFTD



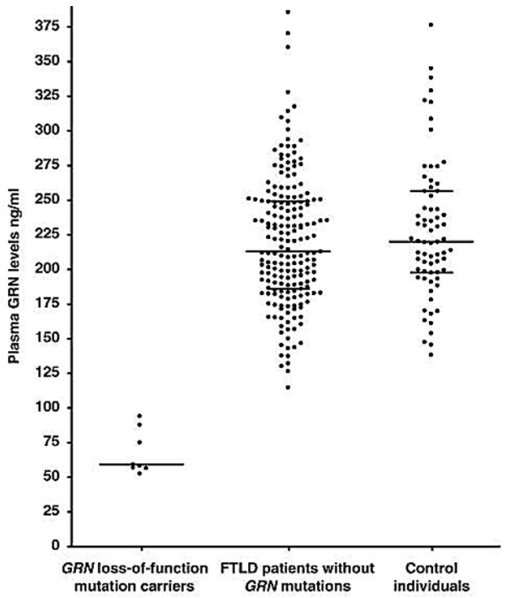


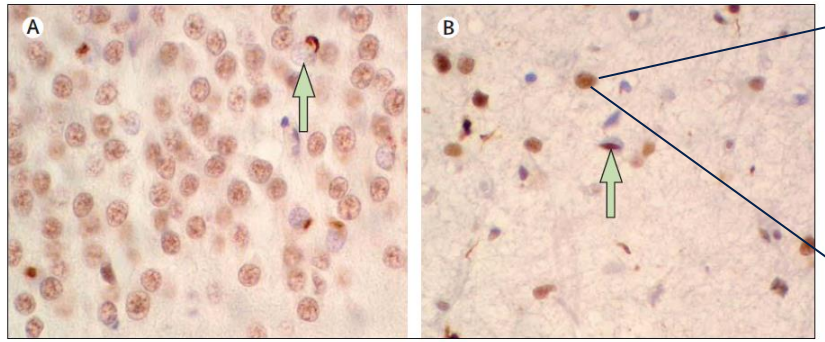
(2022 ALLFTD data)

Baker, et al, *Nature*, 2006; Van Swieten and Heutnik, *Lancet Neurol*, 2008; Moore et al, *Lancet Neurol*, 2019; DaSilva-Ramos, et al. in prep

UCSF

Biological effects of *GRN* haploinsufficiency

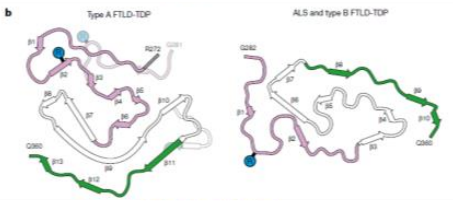




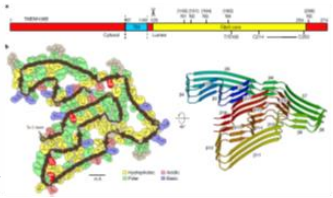
FTLD TDP type A

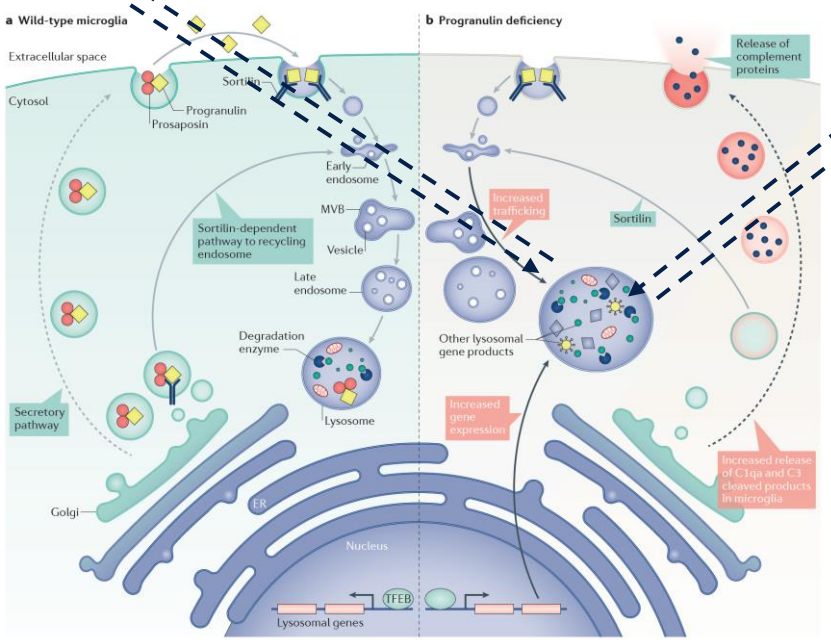
Insoluble amyloid aggregates

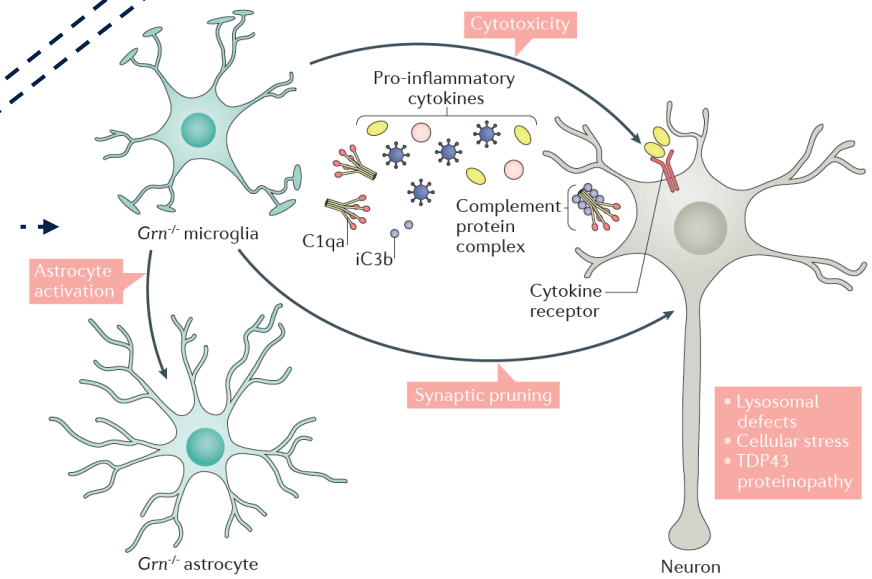
TDP-43 (Type A & B)



TMEM103b







Lysosomal dysfunction

***TMEM106b* protective allele**

TMEM106b is lysosomal protein

***TMEM106b* healthy brain aging**

***TMEM106b* risk for LATE (AD co-path)**

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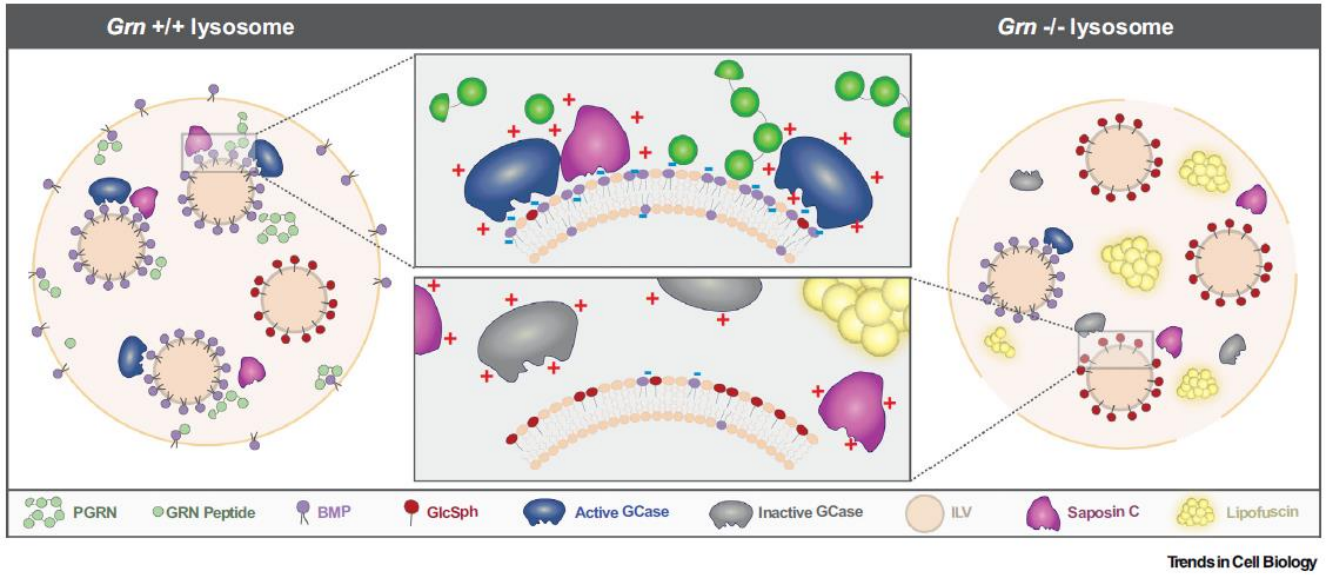
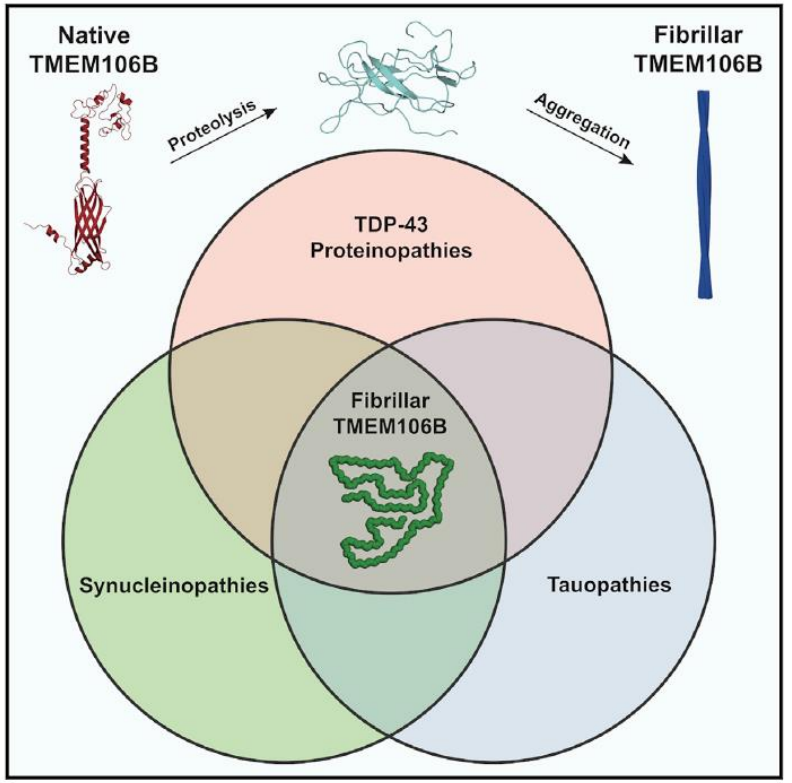
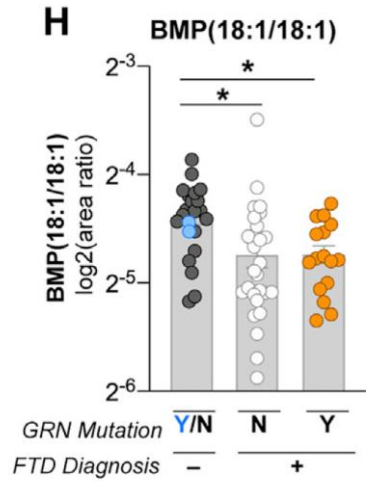
Progranulin biology: lysosomal function & biomarker discovery

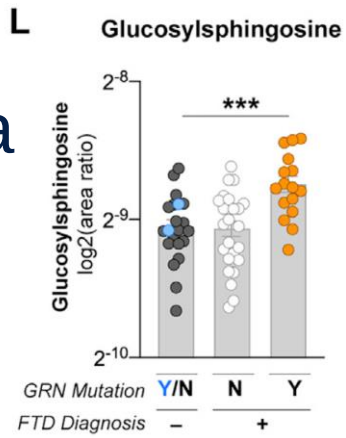


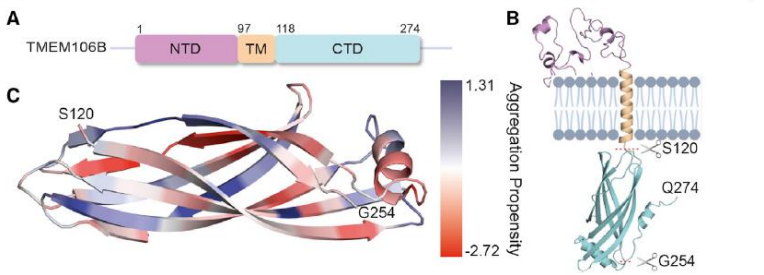


CSF



plasma

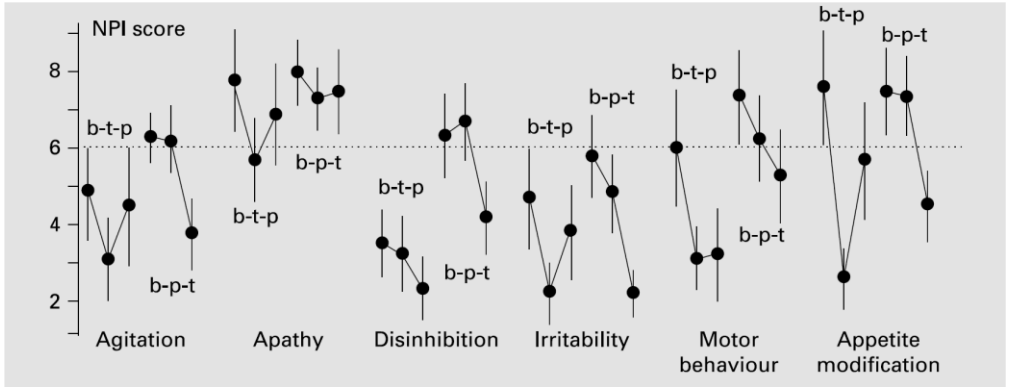




Logan et al, *Cell*, 2021; Logan et al, *Trends in Cell Biol*, 2022; Chang et al, *Cell*, 2022

UCSF

Randomized, placebo controlled, crossover trial of trazodone for FTD



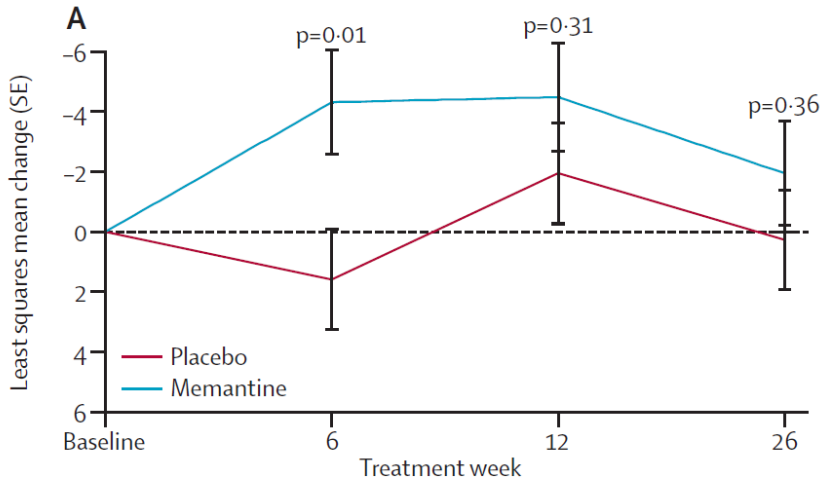
- n=26 evaluable FTD (Lund/Manchester)
- 6 wks trazodone (up to 300 mg) vs. placebo
- primary endpoint: NPI (p = 0.028); n= 10 with > 50% reduction in NPI
- OL experience SSRIs similar

Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial

Adam L Boxer, David S Knopman, Daniel I Kaufer, Murray Grossman, Chiadi Onyike, Neill Graf-Radford, Mario Mendez, Diana Kerwin, Alan Lerner, Chuang-Kuo Wu, Mary Koestler, Jill Shapira, Kathryn Sullivan, Kristen Klepac, Kristine Lipowski, Jerin Ullah, Scott Fields, Joel H Kramer, Jennifer Merrilees, John Neuhaus, M Marsel Mesulam, Bruce L Miller

	Placebo			Memantine		
	bvFTD (n=33)	Semantic dementia (n=9)	All (n=42)	bvFTD (n=31)	Semantic dementia (n=8)	All (n=39)
Characteristics						
Men (%)*	28 (85%)	4 (44%)	32 (76%)	14 (45%)	5 (62%)	19 (49%)
Age (years)	65·6 (62·8 to 68·4)	68·6 (63·4 to 73·7)	66·2 (63·8 to 68·6)	65·6 (62·7 to 68·3)	67·0 (62·5 to 71·5)	65·8 (63·5 to 68·1)
Education (years)	15·4 (14·4 to 16·4)	15·0 (12·8 to 17·2)	15·3 (14·5 to 16·2)	15·7 (14·8 to 16·7)	15·8 (13·0 to 18·5)	15·7 (14·9 to 16·6)
Disease duration (years)	3·5 (2·6 to 4·4)	2·8 (1·3 to 4·3)	3·3 (2·6 to 4·1)	3·0 (2·1 to 4·0)	2·8 (1·6 to 3·9)	3·0 (2·2 to 3·7)
Weight (kg)	90·6 (83·4 to 97·8)	71·1 (64·9 to 77·2)	86·2 (80·0 to 92·4)	81·8 (75·3 to 88·3)	76·2 (61·4 to 90·9)	80·6 (74·9 to 86·3)
Primary outcomes						
NPI	22·2 (16 to 28·3)	18·6 (13·8 to 23·4)	21·5 (15·7 to 27·3)	21·1 (16 to 26·2)	18·8 (15 to 22·6)	20·6 (15·8 to 25·4)
CGIC	3·3 (3·1 to 3·5)	3·3 (3·2 to 3·4)	3·3 (3·1 to 3·5)	3·5 (3·2 to 3·8)	3·4 (3·2 to 3·6)	3·5 (3·2 to 3·8)

NPI



www.thelancet.com/neurology **Published online January 2, 2013** http://dx.doi.org/10.1016/S1474-4422(12)70320-4

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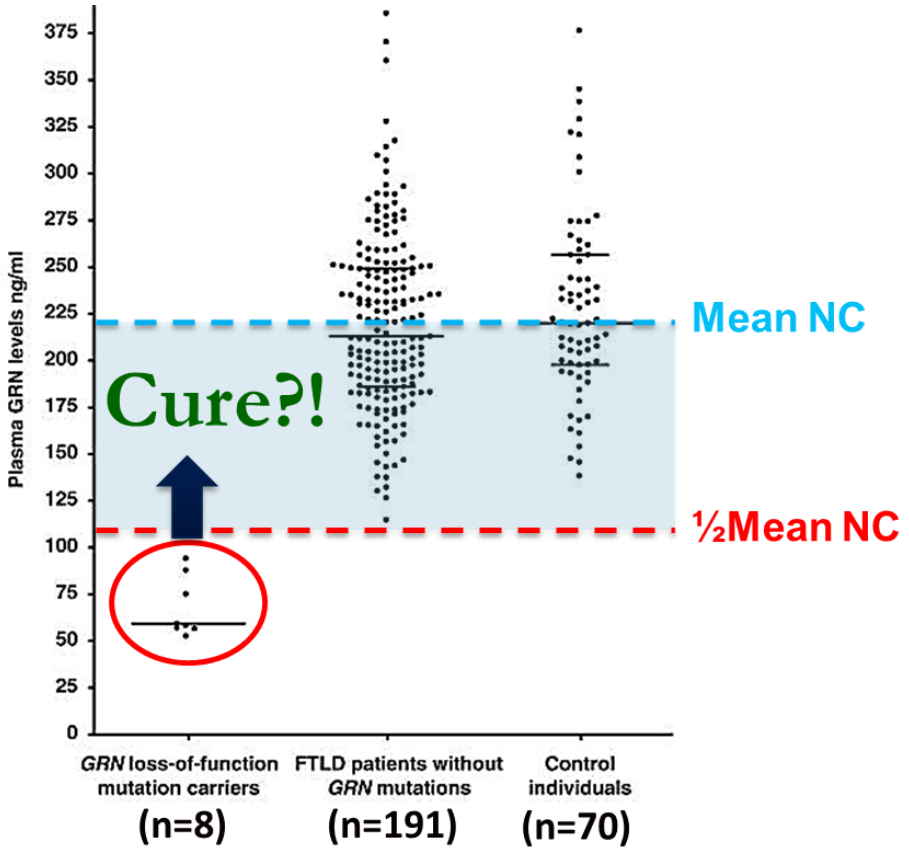
GRN haploinsufficiency: low hanging fruit?

- Consortium for FTD Research → Bluefield Project
- Led by CV researchers: analogous to familial hypercholesterolemia?
- HTS identifies SAHA (histone deacetylase inhibitor [HDACi]) as raising progranulin
- Envivo Therapeutics publicly announces it has a BBB permeant HDACi
- FTD Treatment Study Group (FTSG) formed in 2010 to attract industry to FTD therapeutics
- 2011- 2014 small OL studies of other drugs : amiodarone, chloroquine, nimodipine
- Envivo (renamed Forum) starts FRM-334 Phase 2a in 2015



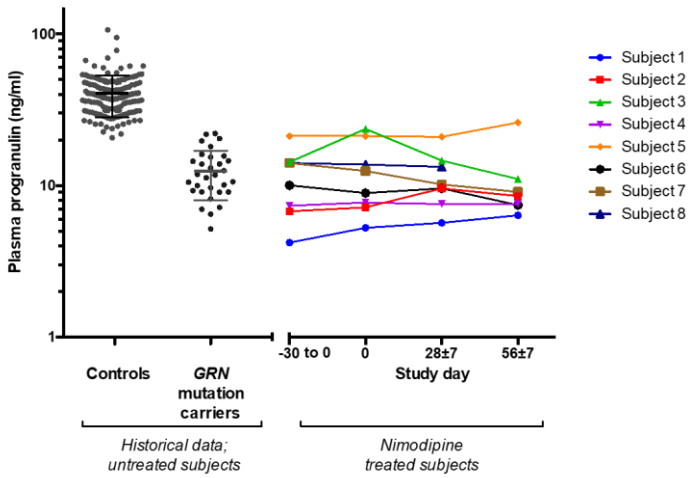
Cenik et al, *JBC*, 2011; Boxer et al, *Alz & Dementia*, 2012a, b, Finch et al, Brain, 2009

UCSF

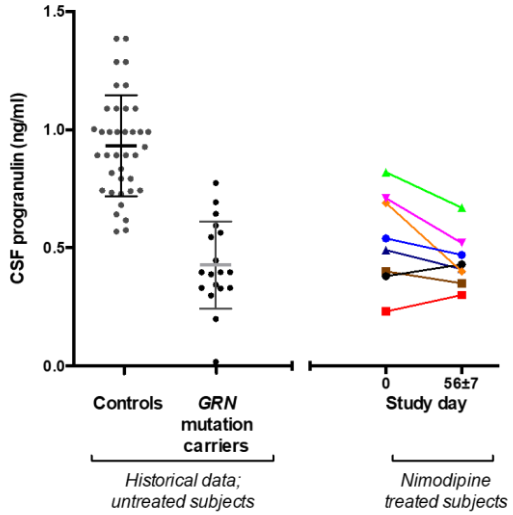
Nimodipine for *GRN* haploinsufficiency

Enrolled carriers	8
***GRN* mutations**	T52HfsX2, R110X (3), Q300X, Q406X, E421fs, R493X
Symptomatic	2/8
Age ±SD (y)	57.3 ±11.4
Sex (M/F)	4/4
Education (y)	
Completed 8 weeks	7/8
Adverse events	**All mild severity** (swelling in extremities, headache, light headed, insomnia, UTI, syncope, flushed sensation in lower extremities, episodic fast heart rate, dizziness, flu-like symptoms, redness on legs, palpitations, lassitude, upper respiratory tract infection, depression, lower extremity edema)

Plasma progranulin

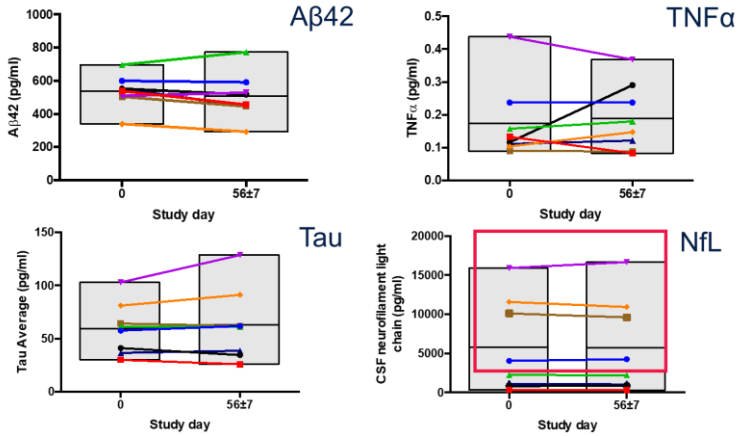


CSF progranulin

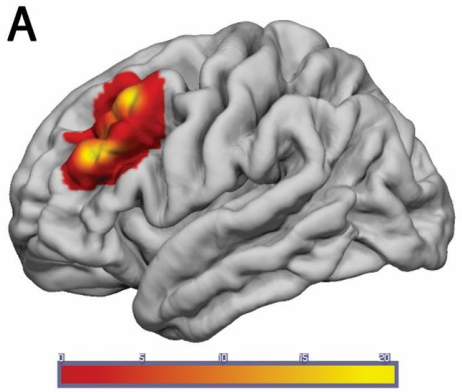


Measure	Dose escalation phase					Maintenance phase			
	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Plasma PGRN, cytokines	X	X			X				X
CSF PGRN, cytokines	X								X
EKG, Vitals, AEs	X	X	X	X	X				X
Clin labs (CBC, Chem, etc.)	X								X
MRI (rsfMRI, pASL)	X								X
Total dose mg/day	0	90	180*	270*	360*	360*	360*	360*	360*

* Or highest tolerated dose



Symptomatic participants



Sha et al, *Alz & Dement*, 2018

UCSF

Ph2a trial of HDACi for *GRN* haploinsufficiency

JAMA Network Open

Original Investigation | Neurology

Effect of the Histone Deacetylase Inhibitor FRM-0334 on Progranulin Levels in Patients With Progranulin Gene Haploinsufficiency

A Randomized Clinical Trial

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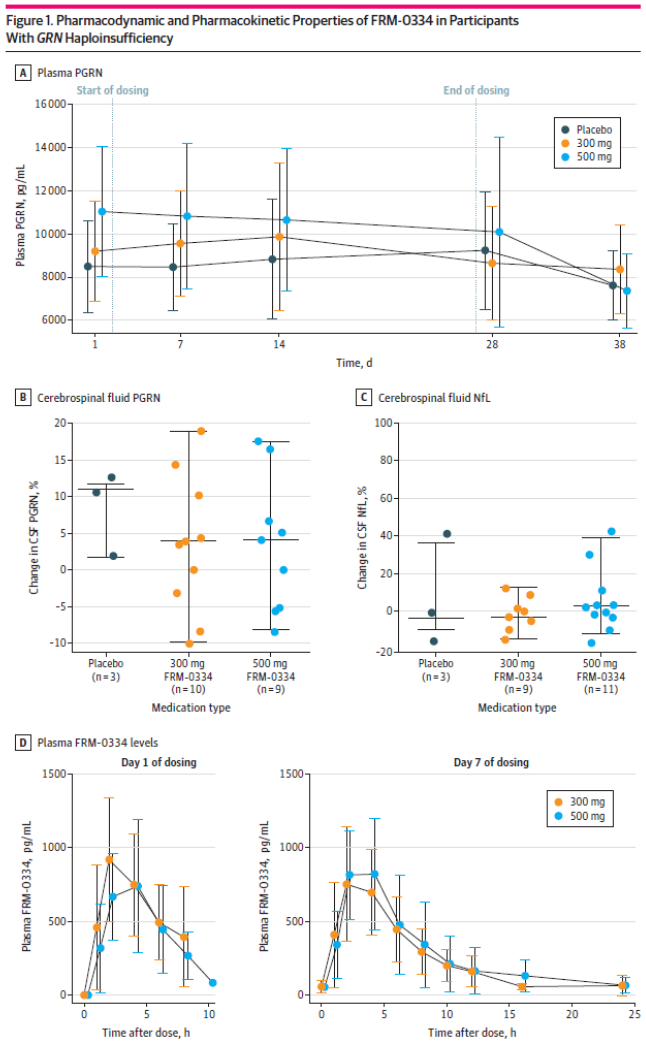
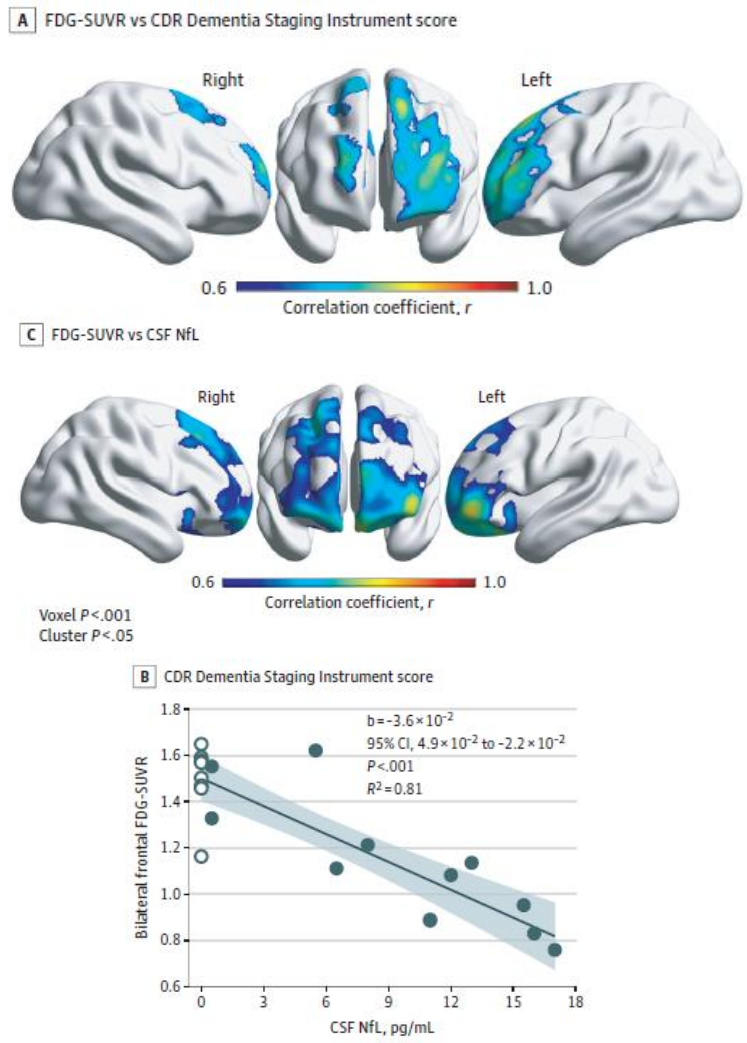
Characteristic	Mean (SD)[a]				
	GRN variation carriers by treatment assignment			*GRN* variation carriers	
		FRM-0334			
	Placebo (n = 5)	300 mg (n = 11)	500 mg (n = 11)	Prodromal (n = 8)	Symptomati (n = 19)
Placebo, No. (%)	NA	NA	NA	1 (12.5)	4 (21.1)
FRM-0334 300 mg, No. (%)	NA	NA	NA	2 (25.0)	9 (47.4)
FRM-0334 500 mg, No. (%)	NA	NA	NA	5 (62.5)	6 (31.6)
Sex, No. (%)					
Women	3 (60.0)	7 (63.6)	6 (54.5)	4 (50.0)	12 (63.2)
Men	2 (40.0)	4 (36.4)	5 (45.5)	4 (50.0)	7 (36.8)
Age, y	55.6 (5.9)	59 (9.7)	54.2 (11.1)	51.6 (10.5)	58.4 (8.8)
Baseline clinical severity					
Prodromal/symptomatic	1/4	2/9	5/6	NA	NA
CDR plus NACC FTLD, sum of boxes	4.2 (6.8)	8 (6.1)	4.1 (7)	0	9.9 (5.4)[c]





Ljubenkov et al, *JAMA Network Open*, 2021

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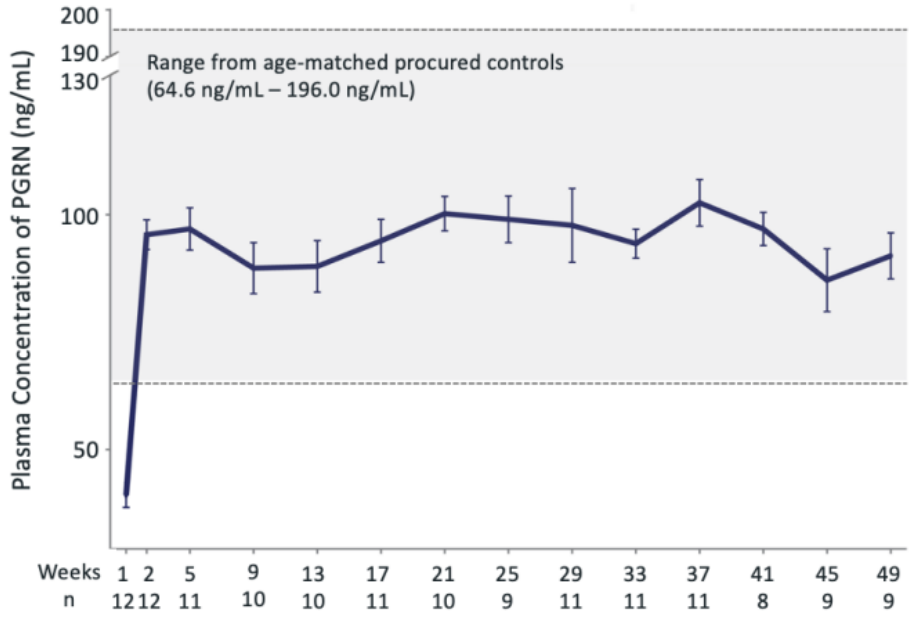
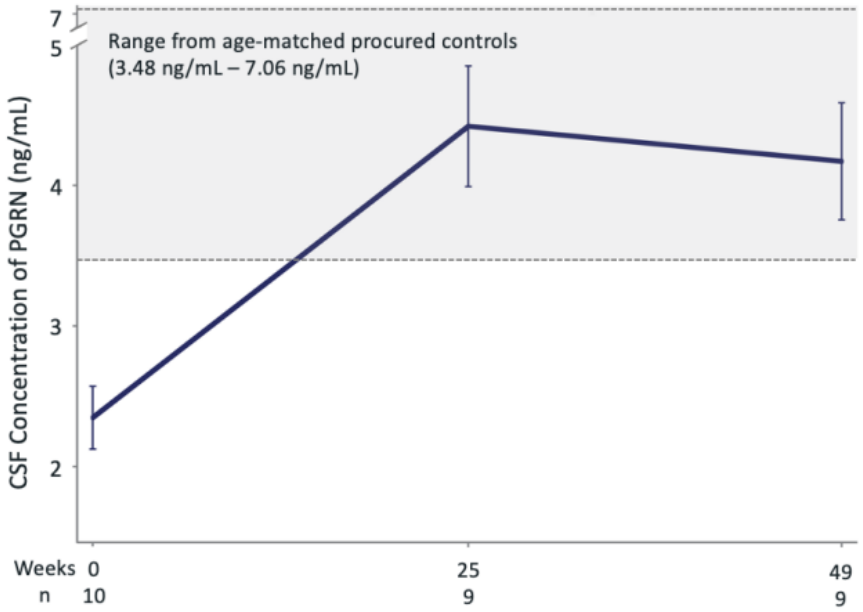
Plasma and CSF progranulin: pharmacodynamic biomarkers

Latozinemab (anti-sortilin)

PGRN Plasma Concentration



PGRN CSF Concentration



Making the most of a limited sample

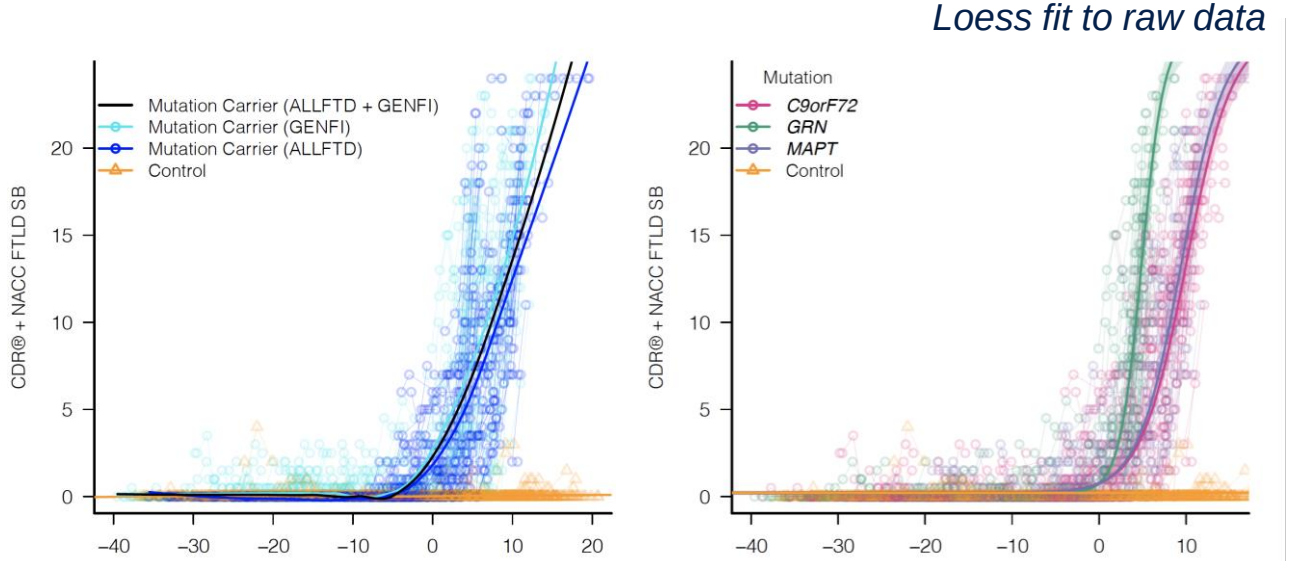
Bayesian Disease Progression Models (DPMs)

- Harmonized clinical endpoints & biomarkers in ALLFTD & GENFI in *C9orf72*, *GRN*, and *MAPT*
  - CDR® + NACC FTLD SB
  - UDS v3 neuropsychological measures and Revised Self Monitoring Scale (RSMS)
  - Plasma NfL & Volumetric ROIs (4 lobes, MTL, striatum, thalamus, insula, cerebellum)
  - *Motor score (updated model)*
- Jointly modeled all endpoints to estimate latent "disease age"
  - Years since clinical onset
  - Participants are aligned on this variable
- Bayesian priors included estimated years since onset based on clinician report (Sx) or age relative to mutation's mean (PreSx)

nature medicine ARTICLES https://doi.org/10.1038/s41591-022-01942-9 Check for updates

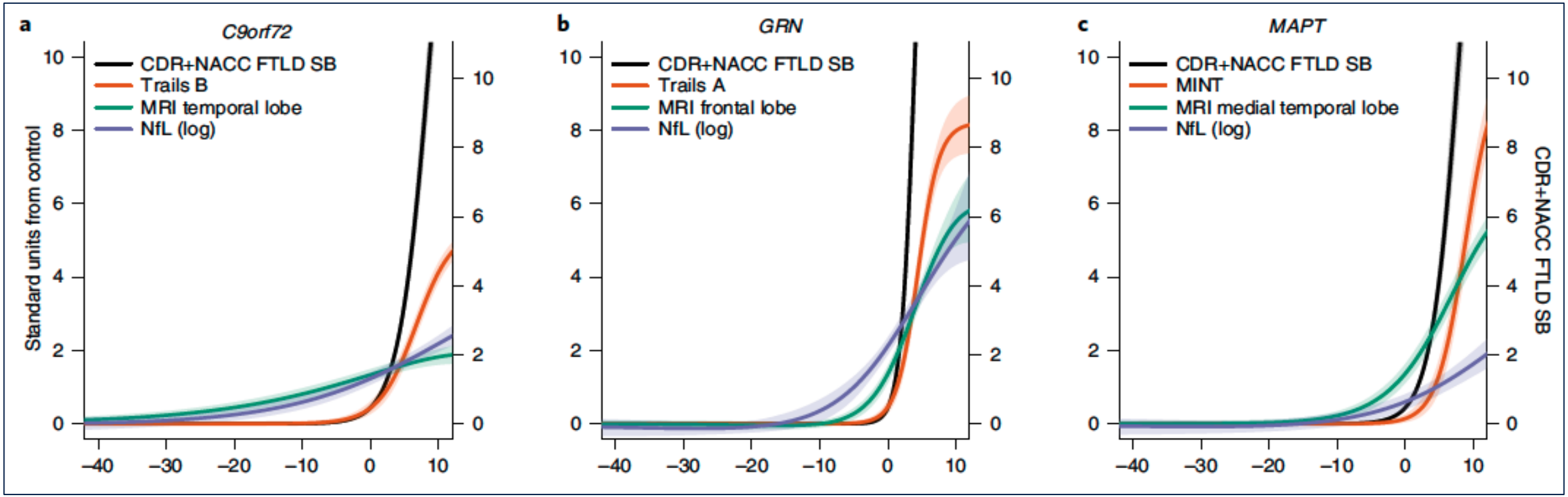
Temporal order of clinical and biomarker changes in familial frontotemporal dementia

Loess fit to raw data

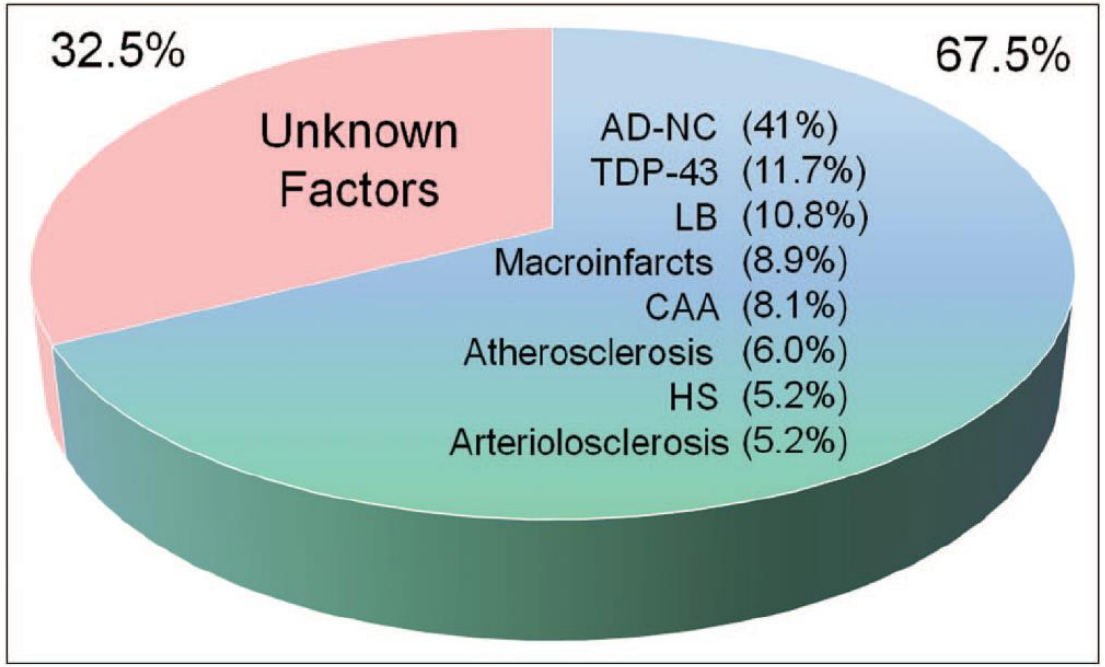


Staffaroni et al., *Nature Medicine,* 2022

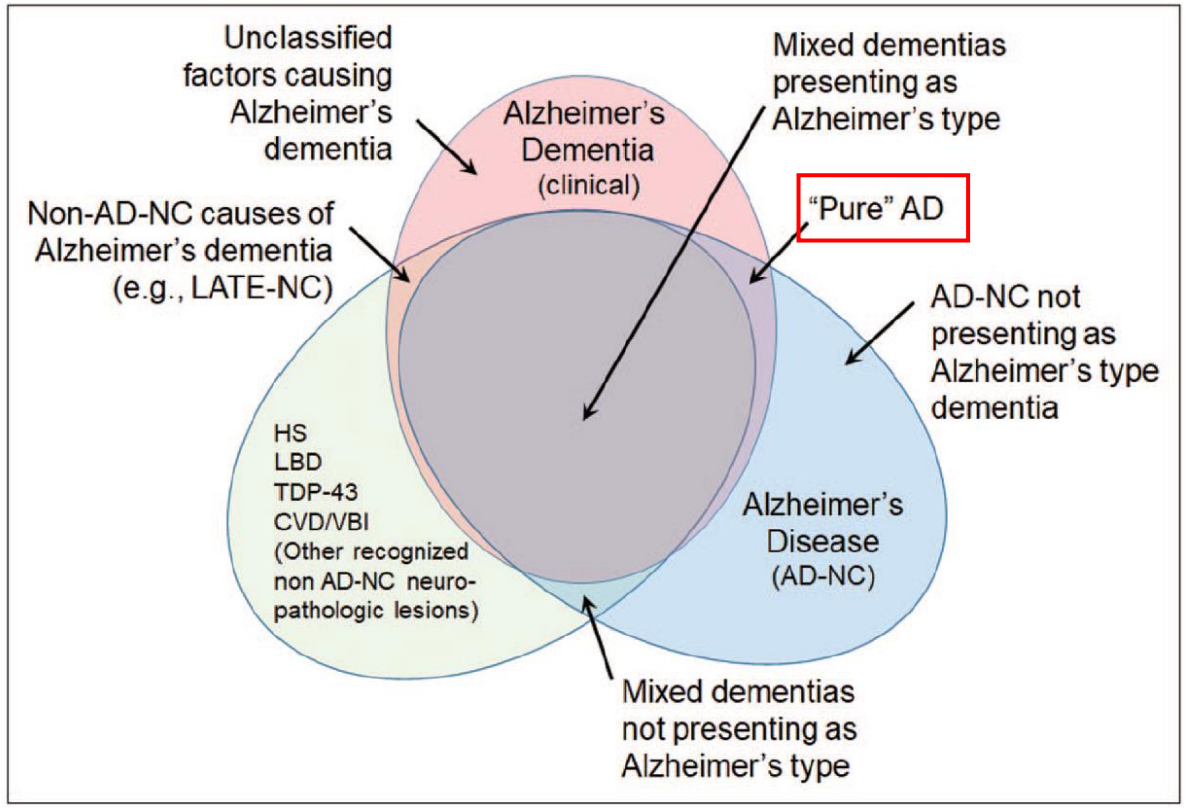
DPM's to identify best clinical trial endpoints



The clinical Alzheimer's Dementia syndrome often includes "Related Dementia" pathologies



Neuropathology of 'Alzheimer's Dementia' (n=1162) from 2 longitudinal aging studies



Mehta and Schneider, *Curr Opin Neurol*, 2021

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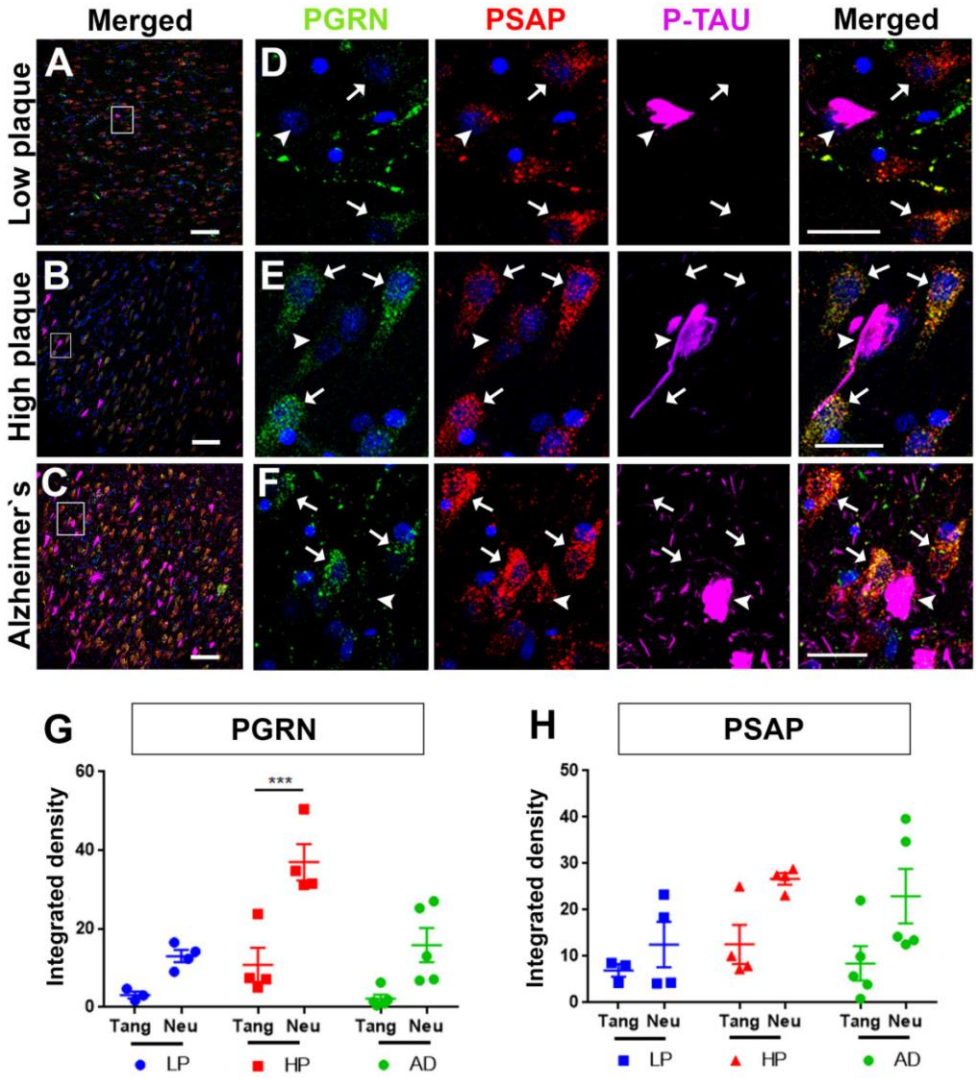
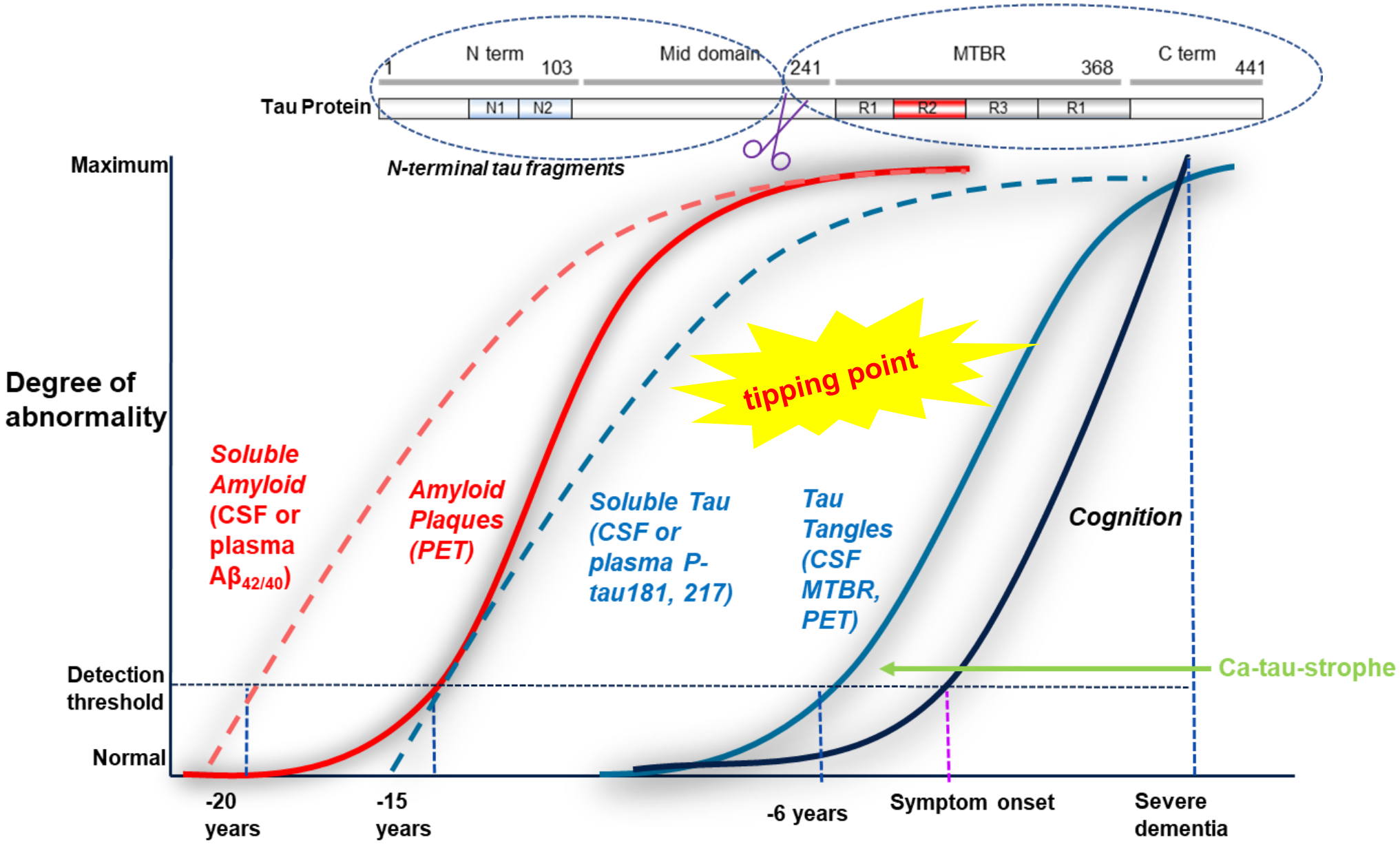
Progranulin is associated with Aβ plaques, but not tangles in AD



LP= low plaques
HP= high plaques
AD= ADNC prob AD

Mendsaikhan, et al, *J. Neuropath Exp Neurol*, 2021

UCSF



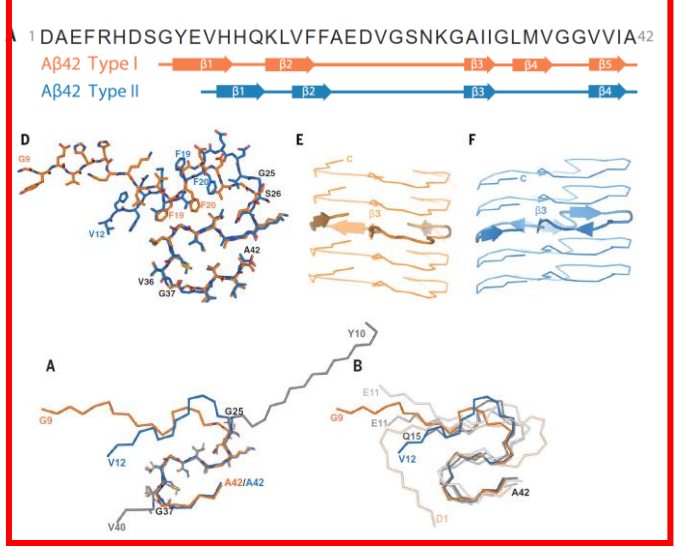
Boxer and Sperling, *Cell*, 2023

UCSF

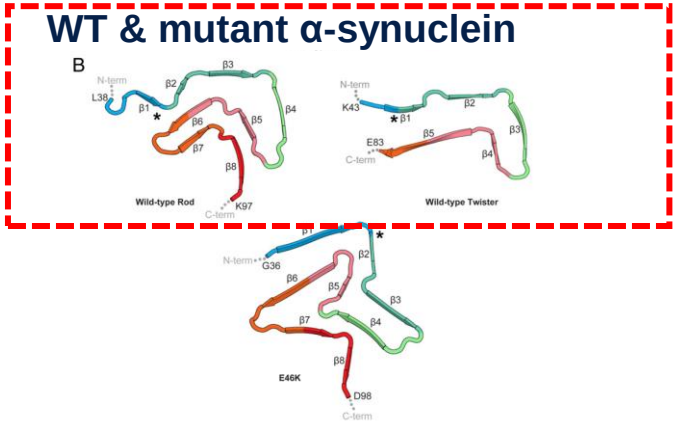
Pathological aggregates consist of amyloids (cryo-EM)

AD

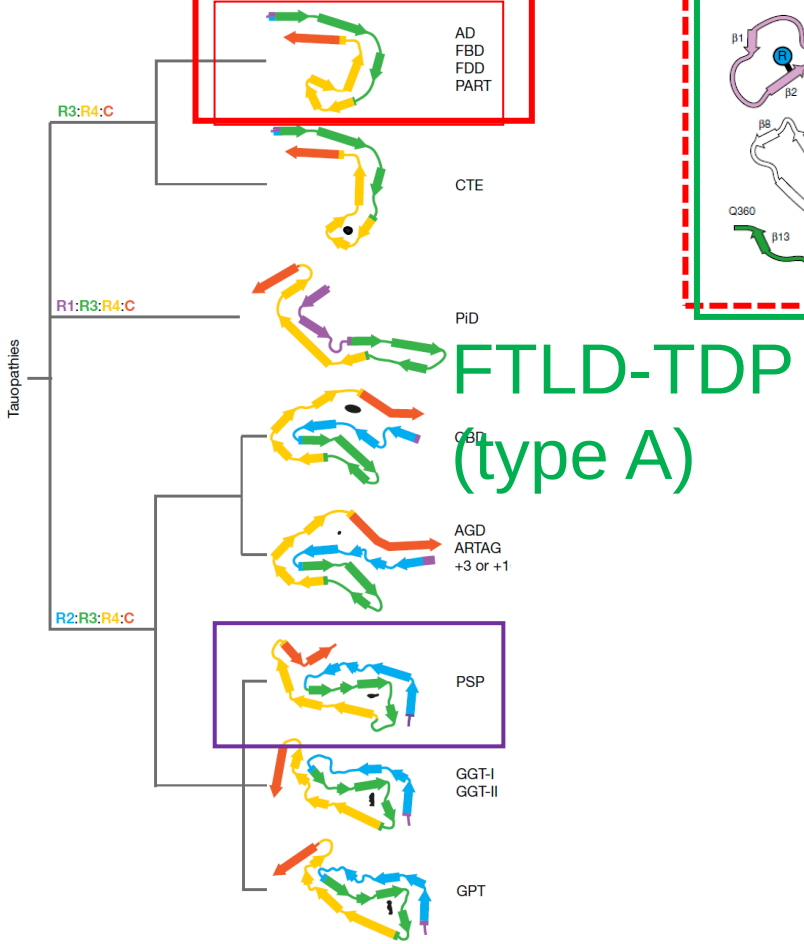
Beta amyloid ($A\beta_{1-42}$)



WT & mutant α-synuclein

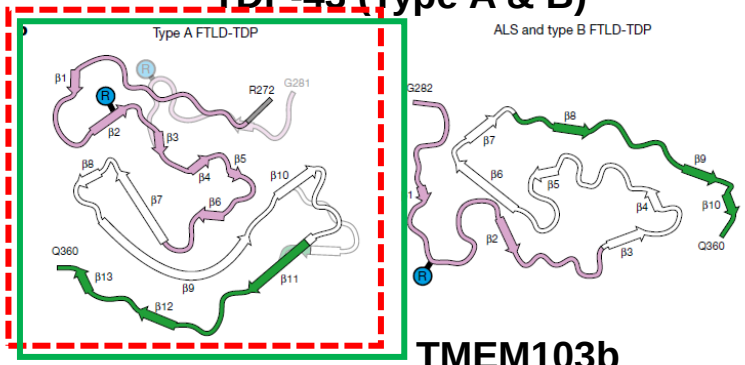


Tau

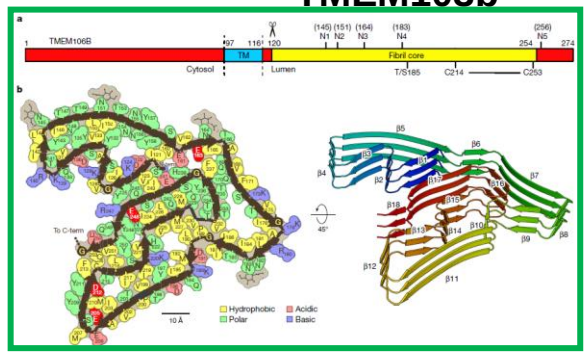


FTLD-TDP (type A)

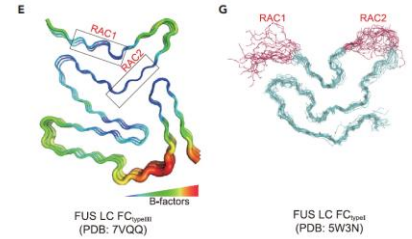
TDP-43 (Type A & B)



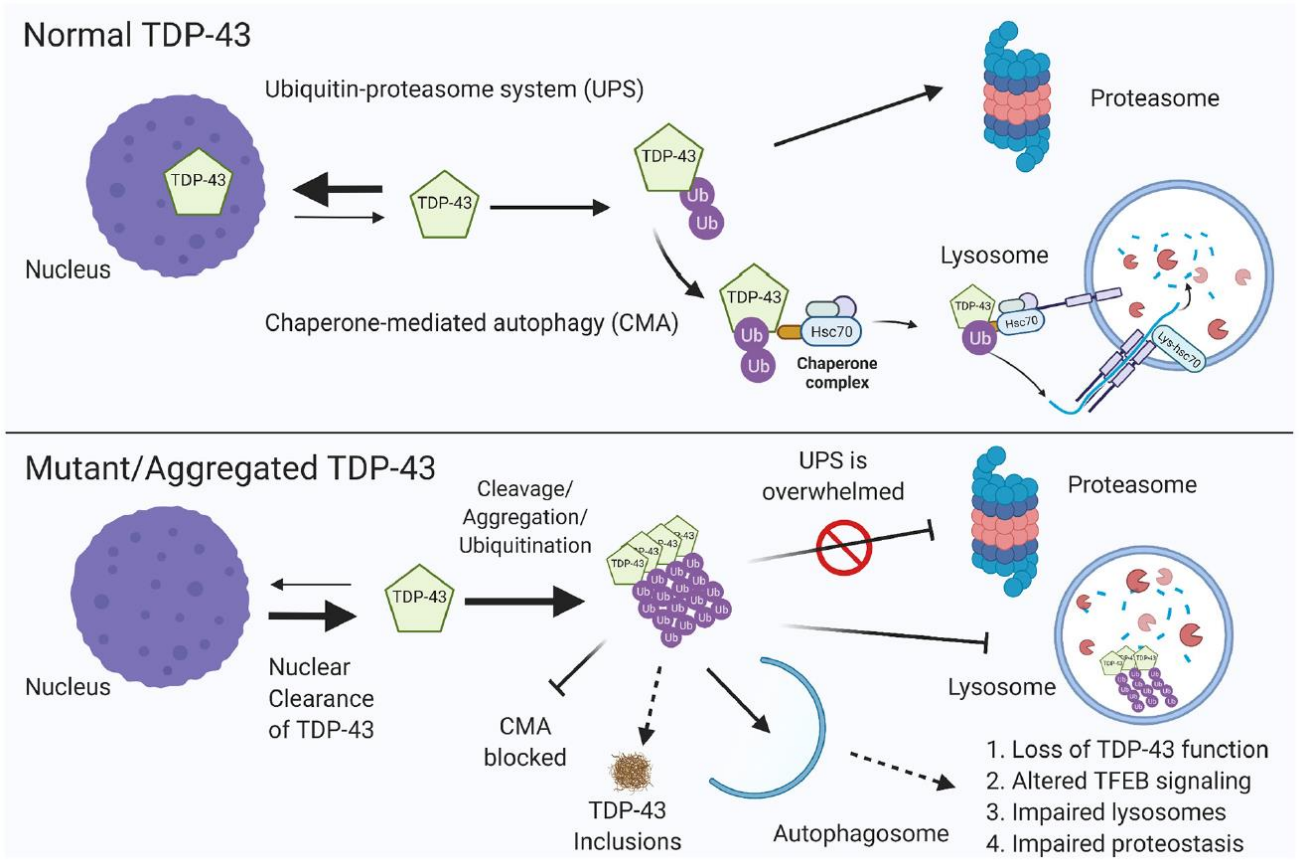
TMEM103b



FUS (fused in sarcoma)



Impaired protein clearance may be a common ND mechanism



Root et al, *Neurobiol Dis*, 2021

UCSF

TDP-43 pathology and hippocampal atrophy in AD

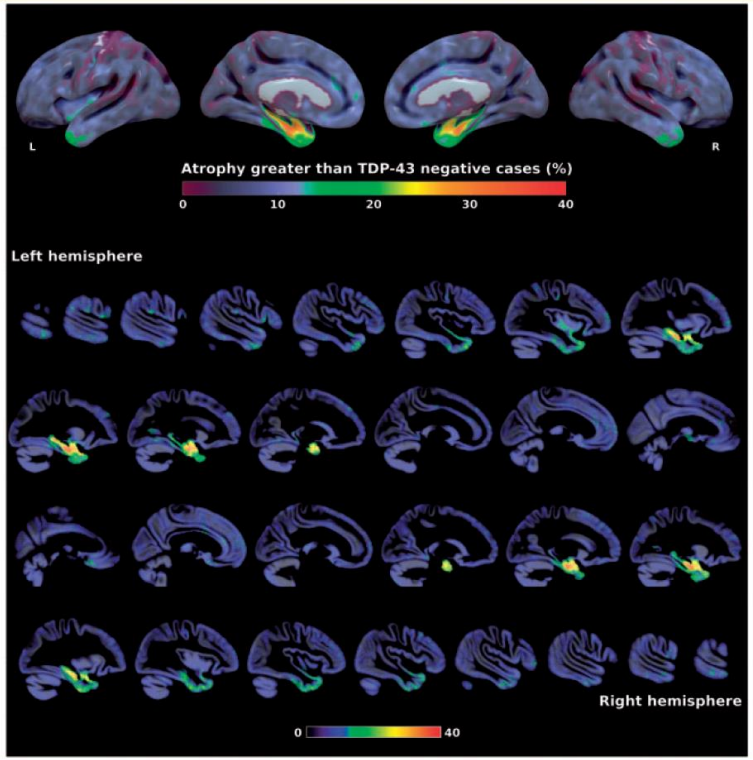


Figure 5 Frequency map of grey matter atrophy in TDP-43-positive cases compared to TDP-43-negative cases. Values represent

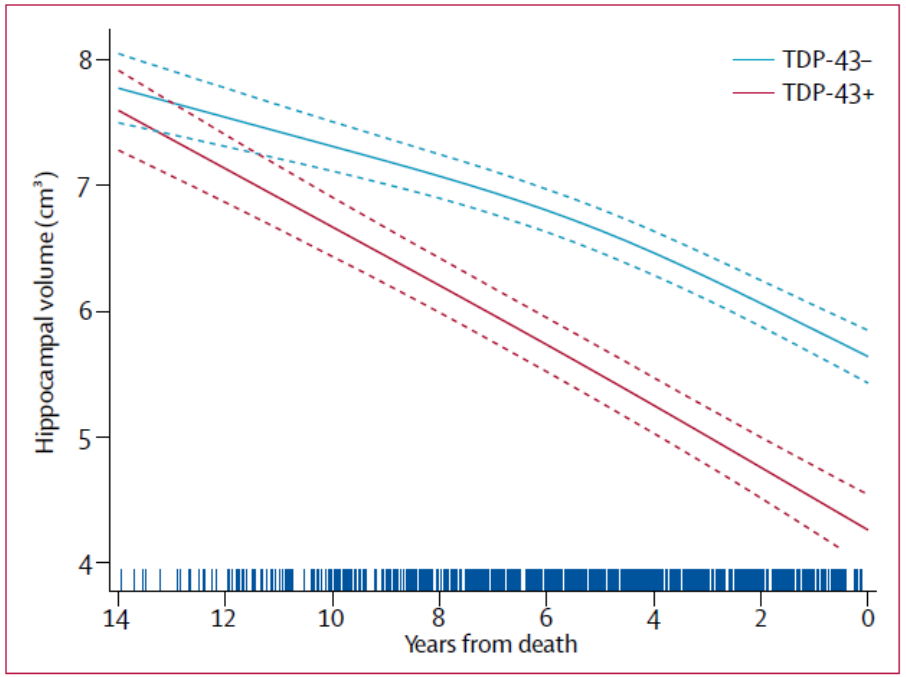
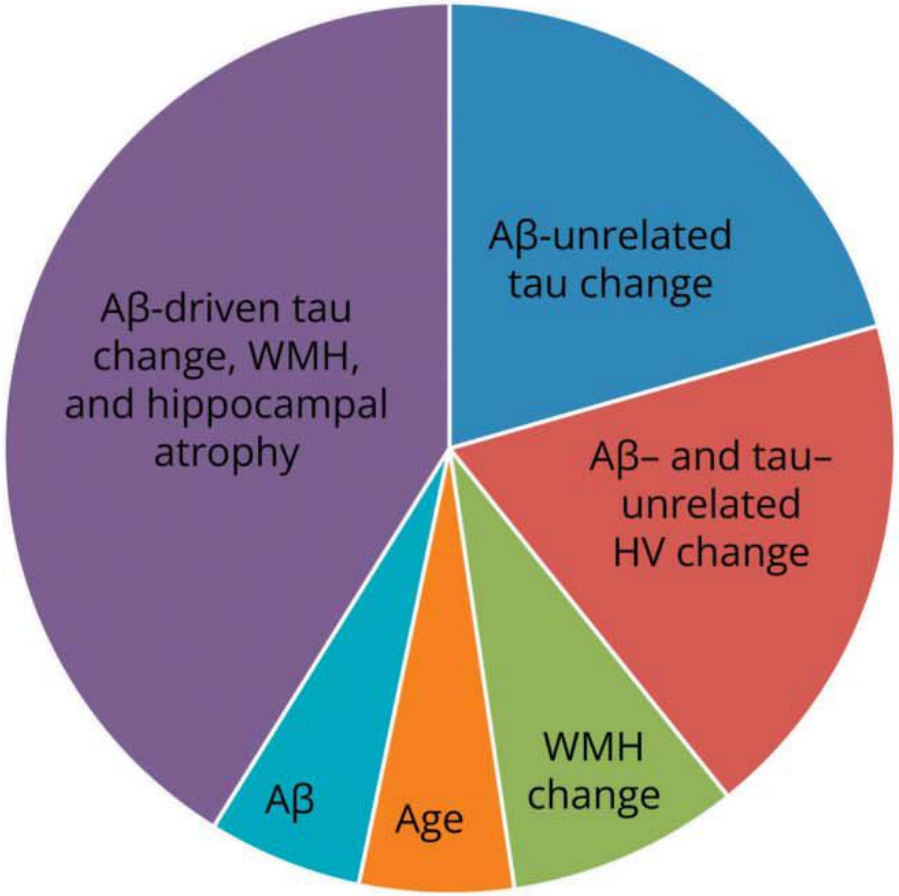


Figure 3: Trajectories of hippocampal volumes for individuals with and without hippocampal TDP-43 based on linear mixed-effects regression modelling (FreeSurfer analysis)

10% of age-related cognitive decline is likely TDP-43 related

Decomposition of the variance in cognitive decline

Total variance explained by changes in imaging markers = 48%



Cognitive impact of neuropathologies:

1. Aβ: **2%** as a unique pathology
   +22% mediated by other pathologies
2. Tau: **11%** as a unique pathology **+22%** with Aβ
3. Suspected LATE: **10%** (HV unique pathology)
4. Cerebrovascular disease: **3%** (WMH alone)
   +6% with Aβ and tau

Data from Harvard Aging Brain Study (HABS)

Hanseeuw et al, *Neurology*, 2023

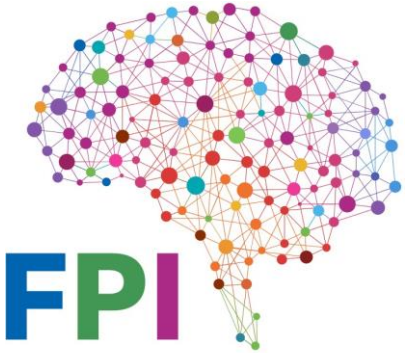
UCSF

Conclusions

- Rapid progress in understanding *GRN* biology and disease
- Progranulin haploinsufficiency → lysosomal dysfunction & TDP-43 proteinopathy → multiple cellular effects; inflammation
- FTD-*GRN* low hanging fruit for therapeutics (replacement)
- Previous clinical trials were challenging to complete
- Biomarkers: progranulin (CSF, blood); BMP species? (CSF); NfL (CSF, blood); MRI
- Elevating progranulin may improve lysosomal in other multi-proteinopathies, including AD

Special thanks to:

ALLFTD & GENFI research participants

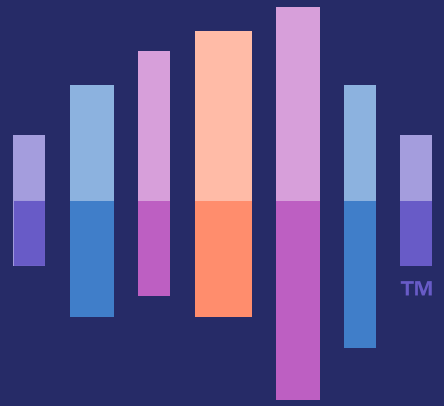


Closing Remarks and Q&A

Latozinemab and AL101: Milestones and Opportunities

MOST ADVANCED PGRN ELEVATING CANDIDATES IN CLINICAL DEVELOPMENT WORLDWIDE

LATOZINEMAB MILESTONE	In October 2023, achieved target enrollment of 103 symptomatic and 16 at-risk FTD-*GRN* participants in the pivotal INFRONT-3 Phase 3 trial for a treatment duration of 96 weeks.
AL101 MILESTONE	Patient screening underway and anticipate dosing first participant with early Alzheimer's disease in PROGRESS-AD Phase 2 clinical trial in Q4 2023.
EXPANSION TO OTHER INDICATIONS	Potential to expand into other indications including amyotrophic lateral sclerosis (ALS), Parkinson's disease, and other neurodegenerative diseases.
COMMERCIAL RIGHTS	U.S. 50-50 profit share with GSK co-promote and tiered double-digit royalties ex-U.S.
POTENTIAL GSK MILESTONE PAYMENT(S)	$160 million for first commercial sale in the U.S. $90 million for first commercial sale in at least two of the following countries: • France, Germany, Italy, Spain, or the UK.



Thank you