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 preclinical 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 on 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.

This presentation contains statistical data based on independent industry publications or other publicly available information, as well as other information based on our internal sources. We have not independently verified the accuracy or completeness of the data contained in these industry publications and other publicly available information. Accordingly, we make no representations as to the accuracy or completeness of that data.

Except as required by law, we undertake no obligation to update any statements in this presentation for any reason after the date of this presentation. We have filed Current Reports on Form 8-K, Quarterly Reports on Form 10-Q, Annual Reports on Form 10-K, and other documents with the SEC. You should read these documents for more complete information about us. You may obtain these documents for free by visiting EDGAR on the SEC website at www.sec.gov.
## Today’s Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
</table>
| 8:00-8:15 am | **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 |
| 8:15-8:35 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 |
| 8:35-8:55 am | **03** Latozinemab/AL101 Overview and Clinical Development  
Lawrence Carter, Ph.D., Vice President of Clinical Development, Neurology |
| 8:55-9:15 am | **04** Promising Advances in PGRN Therapeutic Development  
Adam Boxer, M.D., Ph.D., Professor, Neurology, UCSF, Weill Institute for Neurosciences |
| 9:15-9:30 am | **05** Closing Remarks and Q&A  
Sara Kenkare-Mitra, Ph.D., President and Head of Research and Development, Alector |
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
Frontotemporal Dementia (FTD)

A rapidly progressive form of dementia, with no approved treatment

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
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

GRN Mutations Are Causal or Increase Risk for Multiple Neurodegenerative Diseases

NEURONAL CEROID LIPOFUSCINOSIS
NCL

FTD-GRN
Associated w/ Increased Risk
50% PGRN loss

FTD
FRONTOTEMPORAL DEMENTIA
FRONTOTEMPORAL DEMENTIA WITH GRN MUTATIONS

AD
ALZHEIMER’S DISEASE

ALS
AMYOTROPHIC LATERAL SCLEROSIS

PD
PARKINSON’S DISEASE

100% PGRN loss

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


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**

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 COMPARTMENT²,³

- 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 RECEPTORS²

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 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

* indicates p<0.05 by T-test.
### Latozinemab and AL101: Development of Novel Human mAbs That Elevate PGRN

#### Most Advanced PGRN Elevating Candidates in Clinical 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

<table>
<thead>
<tr>
<th>TARGET</th>
<th>CANDIDATE</th>
<th>RESEARCH</th>
<th>PRECLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>ALECTOR’S COMMERCIAL OWNERSHIP</th>
<th>PARTNERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGRN</td>
<td>Latozinemab</td>
<td>FTD-GRN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>U.S. 50-50 profit share with co-promote and tiered double-digit royalties ex-U.S.</td>
<td>GSK</td>
</tr>
<tr>
<td></td>
<td>AL101</td>
<td>AD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TREM2</td>
<td>AL002</td>
<td>AD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Global 50-50 profit share with opt-in</td>
<td>abbvie</td>
</tr>
</tbody>
</table>

- **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.

**ABC** = Alector Brain Carrier Technology
**UD** = undisclosed
Latozinemab and AL101 are Currently Partnered in a Collaboration Agreement with GSK

- **$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

<table>
<thead>
<tr>
<th>Mutations in the GRN gene</th>
<th>Associated Disease</th>
<th>Penetrance</th>
<th>Age Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterozygous LOF (+/-)</td>
<td>Frontotemporal Dementia (FTD)</td>
<td>&gt;90%</td>
<td>~50-60s</td>
</tr>
</tbody>
</table>
Progranulin (PGRN) haploinsufficiency is a leading cause of 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

<table>
<thead>
<tr>
<th>Mutations in the <strong>GRN</strong> gene</th>
<th>Associated Disease</th>
<th>Penetrance</th>
<th>Age Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterozygous LOF (+/-)</td>
<td>Frontotemporal Dementia (FTD)</td>
<td>&gt;90%</td>
<td>~50-60s</td>
</tr>
<tr>
<td>Homozygous LOF (-/-)</td>
<td>Neuronal Ceroid Lipofuscinosis (NCL)</td>
<td>100%</td>
<td>~20s</td>
</tr>
</tbody>
</table>

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

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

*The age of onset can deviate from the typical age of manifestation, as specific mutations can lead to a protracted course of the disease.*
Progranulin (PGRN) is tightly associated with neurodegenerative diseases

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

How does PGRN prevent neurodegeneration?

<table>
<thead>
<tr>
<th>Mutations in the GRN gene</th>
<th>Associated Disease</th>
<th>Penetrance</th>
<th>Age Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterozygous LOF (+/-)</td>
<td>Frontotemporal Dementia (FTD)</td>
<td>&gt;90%</td>
<td>~50-60s</td>
</tr>
<tr>
<td>Homozygous LOF (-/-)</td>
<td>Neuronal Ceroid Lipofuscinosis (NCL)</td>
<td>100%</td>
<td>~20s</td>
</tr>
<tr>
<td>Polymorphisms</td>
<td>AD, PD</td>
<td>NA</td>
<td>~60s (40-90)</td>
</tr>
</tbody>
</table>

*GRN* gene → PGRN protein

![Diagram of GRN gene with mutations](image)
How does PGRN prevent neurodegeneration?

- PGRN insufficiency
- Enhanced inflammation
- TDP-43 Aggregation
- Synaptic loss
- Disrupted BBB
- Destruction of Brain structures
- Neurodegenerative dementia
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 insufficiency
- Lysosomal dysfunction
- Inflammation and other glial pathology
- Dysfunction of Neurons
PGRN is a lysosomal resident protein

Paushter et al Acta Neuropathologica 2018
Lysosomal trafficking of progranulin

Hu et al, Neuron 2010
Zhou et al, Nat Comm, 2017
How does PGRN function in the lysosome?
How does PGRN prevent neurodegeneration?

PGRN insufficiency

Lysosomal dysfunction

Inflammation and other glial pathology

Dysfunction of Neurons
Extracellular functions of PGRN

- **Notch**
  - May activate Notch pathways

- **TNFR**
  - Inhibits TNF-α binding

- **EphA2**
  - Activates MAPK/ Akt pathways
  - Promotes capillary morphogenesis
  - Regulates PGRN expression

- **SORCS2**
  - Motor neuron development and regeneration

References:
- Tang et al, Science 2011
- Chen et al, J Neuroscience 2013
- Thomasen et al, Cell Rep 2023
- Du et al, bioRxiv 2023
Summary

PGRN
Lysosomal activities ➔ Extracellular signaling

Proper glial function
Neuronal health

Neurodegeneration

Notch
- May activate Notch pathways
- Inhibits TNF-α binding

TNFR
- Inhibits TNF-α binding

EphA2
- Activates MAPK/ Akt pathways
- Promotes capillary morphogenesis
- Regulates PGRN expression

SORCS2
- Motor neuron development and regeneration

Sortilin
- M6PR

Golgi

Lysosome
- PGRN
- CathD
- GCase
- BMP levels
- CD68

Inflammation
Latozinemab and AL101 Clinical Development

Lawrence Carter, Ph.D.
Vice President, Neurology
Alector
INFRONT-2: Phase 2 Trial in FTD

Open-Label, Single Arm

**Asymptomatic FTD-GRN\(^1\)**
- N = 5
- AL001 60 mg/kg q4w for 96 weeks

**Symptomatic FTD-GRN\(^1\)**
- N = 12
- AL001 60 mg/kg q4w for 96 weeks

**Symptomatic FTD-C9orf72\(^1\)**
- N = 16
- AL001 60 mg/kg q4w for 96 weeks

---

1. Asymptomatic and symptomatic FTD-GRN enrollment closed; FTD-C9orf72 cohort currently enrolling
2. CDR\(^\circ\) 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)

---

**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\(^\circ\) plus NACC FTLD-SB\(^2\))

---

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**

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

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

<table>
<thead>
<tr>
<th>TARGET ENGAGEMENT</th>
<th>BIOMARKERS OF DISEASE ACTIVITY</th>
<th>CLINICAL BENEFIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGRN (Plasma and CSF)</td>
<td>Lysosomal Dysfunction</td>
<td>Inflammation</td>
</tr>
<tr>
<td><strong>PGRN</strong></td>
<td><strong>e.g. CTSD, LAMP1</strong></td>
<td><strong>e.g. C1QB</strong></td>
</tr>
<tr>
<td>CSF and plasma PGRN levels</td>
<td>Dysfunctional lysosomes are hallmarks of FTD-GRN</td>
<td>Elevation of complement proteins occurs in FTD-GRN</td>
</tr>
</tbody>
</table>

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**

![Graph of PGRN Plasma Concentration](image)

- **Range from age-matched procured controls**
  - 64.6 ng/mL – 196.0 ng/mL

**PGRN CSF Concentration**

![Graph of PGRN CSF Concentration](image)

- **Range from age-matched procured controls**
  - 3.48 ng/mL – 7.06 ng/mL

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

<table>
<thead>
<tr>
<th>Lysosomal dysfunction - CTSD</th>
<th>Lysosomal dysfunction - LAMP1</th>
<th>Complement activation - C1QB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Baseline</td>
<td>6 mos. AL001</td>
</tr>
<tr>
<td>Concentration (fmol/ul)</td>
<td>Concentration (fmol/ul)</td>
<td>Concentration (fmol/ul)</td>
</tr>
</tbody>
</table>

| FTD-GRN patients | FTD-GRN patients | FTD-GRN patients |

Mean +/- SEM

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

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**

### 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.


**GFAP Plasma Concentration**

**GFAP CSF Concentration**

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

<table>
<thead>
<tr>
<th></th>
<th>GRN PS</th>
<th>GRN S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole brain</td>
<td>r</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.606</td>
</tr>
<tr>
<td>Frontal</td>
<td>r</td>
<td>-0.08</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.608</td>
</tr>
<tr>
<td>Temporal</td>
<td>r</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.373</td>
</tr>
<tr>
<td>Parietal</td>
<td>r</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.762</td>
</tr>
<tr>
<td>Occipital</td>
<td>r</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.503</td>
</tr>
<tr>
<td>Cingulate</td>
<td>r</td>
<td>-0.17</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.264</td>
</tr>
<tr>
<td>Insula</td>
<td>r</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>0.328</td>
</tr>
</tbody>
</table>

Used with permission of BMJ Publishing Group, from Plasma glial fibrillary acidic protein is raised in progranulin-associated frontotemporal dementia, Heller, C et al, 91, 3, ©2020; permission conveyed through Copyright Clearance Center, Inc.
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**

<table>
<thead>
<tr>
<th>Ventricular Enlargement</th>
<th>Whole Brain Atrophy</th>
<th>Frontotemporal Cortical Atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENFI2 Matched Control (N=7*)</td>
<td>Latozinemab symptomatic FTD-GRN (N=8)</td>
<td></td>
</tr>
<tr>
<td>Less Atrophy</td>
<td>More Atrophy</td>
<td></td>
</tr>
<tr>
<td>Annualized % change (SEM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular Enlargement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GENFI2 Matched Control</td>
<td>25.6</td>
<td>Latozinemab symptomatic FTD-GRN</td>
</tr>
<tr>
<td>Latozinemab symptomatic FTD-GRN</td>
<td>-4.6</td>
<td></td>
</tr>
<tr>
<td>GENFI2 Matched Control</td>
<td>-4.1</td>
<td></td>
</tr>
<tr>
<td>Latozinemab symptomatic FTD-GRN</td>
<td>-1.8</td>
<td></td>
</tr>
<tr>
<td>GENFI2 Matched Control</td>
<td>-1.5</td>
<td></td>
</tr>
</tbody>
</table>

* 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.

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

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

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

Biomarkers of Disease Activity – Neuronal Health

NfL Plasma Concentration

NfL CSF Concentration
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\(^\circ\) plus NACC FTLD-SB at baseline
  - Matching refined by age, gender, baseline plasma NfL levels, and FTD disease variant at baseline\(^2\)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>INFRONT-2 (N=12)</th>
<th>GENFI2 Matched Controls (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR(^\circ) plus NACC FTLD-SB</td>
<td>Mean (SD)</td>
<td>5.9 (3.74)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0.5, 11</td>
<td>0.5, 11.5</td>
</tr>
<tr>
<td>AGE (Years)</td>
<td>Mean (SD)</td>
<td>63.2 (9.71)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>49, 79</td>
<td>52, 72</td>
</tr>
<tr>
<td>GENDER</td>
<td>Male</td>
<td>8 (67%)</td>
</tr>
<tr>
<td>PLASMA NfL (pg/mL)</td>
<td>N</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>62.8 (47.00)</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>11.2, 148.8</td>
</tr>
<tr>
<td>FTD DISEASE VARIANT</td>
<td>bvFTD</td>
<td>5 (42%)</td>
</tr>
<tr>
<td></td>
<td>PPA</td>
<td>3 (25%)</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>3 (25%)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

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

**CDR® plus NACC FTLD-SB**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Change in GENFI2 (n=10)</td>
<td>6.4</td>
<td>[4.35, 8.42]</td>
</tr>
<tr>
<td>Annual Change in Latozinemab (n=12)</td>
<td>3.3</td>
<td>[1.38, 5.28]</td>
</tr>
<tr>
<td>Difference in Annual Change (GENFI2 – Latozinemab)</td>
<td>3.1</td>
<td>[0.24, 5.88]</td>
</tr>
</tbody>
</table>

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


NCT03987295

**GENFI = The Genetic Frontotemporal Initiative**

GENFI2 refers to the longitudinal FTD registry dataset

**Estimated to slow annual disease progression by ~48% (3.1 point change)**
INFRONT-3: Ongoing Pivotal Phase 3 Study with Latozinemab

ACHIEVED TARGET ENROLLMENT IN Q4 2023

Randomization

Randomized, Double Blinded, Placebo-Controlled Study
103 symptomatic and 16 at-risk FTD-GRN carriers

Latozinemab 60 mg/kg (IV q4w for 96 weeks)

Placebo (IV q4w for 96 weeks)

Part 1 Study Completion Visit

10-week safety follow-up

Continuation study

96-week open-label extension

PRIMARY ENDPOINT

CDR® plus NACC FTLD-SB

SECONDARY CLINICAL OUTCOMES ASSESSMENTS:

CGI-S, CGI-I, FRS, RBANS

EXPLORATORY ENDPOINTS

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

Randomized, Double Blinded, Placebo-Controlled Study

103 symptomatic and 16 at-risk FTD-GRN carriers

Latozinemab 60 mg/kg (IV q4w for 96 weeks)

Placebo (IV q4w for 96 weeks)

Part 1 Study Completion Visit

10-week safety follow-up

Continuation study

96-week open-label extension

PRIMARY ENDPOINT

CDR® plus NACC FTLD-SB

SECONDARY CLINICAL OUTCOMES ASSESSMENTS:

CGI-S, CGI-I, FRS, RBANS

EXPLORATORY ENDPOINTS

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

CSF = cerebrospinal fluid; IV = intravenous; MD = multiple-dose; PGRN = progranulin; SC = subcutaneous; SD = standard deviation

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**

**Up to 12 weeks**

- **Screening & Baseline**

**76 weeks Treatment Period**

- **AL101/GSK4527226 Dose 1 IV (n~141)**
- **AL101/GSK4527226 Dose 2 IV (n~47)**
- **Placebo IV (n~94)**

**Safety Follow-up**

- 12 weeks after final dose

**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
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
Fronttemporal (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
FTLD trials in genetically-defined or clinically predictive syndromes

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
- PET: FDG-PET

Biomarkers
- CSF: 4R MTBR fragments (?)
- CSF: C9orf72 DPRs, progranulin, BMP’s
- Blood: Progranulin
- CSF/Blood: NfL
- MRI: structural, FLAIR
- PET: FDG-PET

CSF/Blood: GFAP, NIL
Progranulin (GRN) mutations cause FTD

- Progranulin previously studied: inflammation, wound healing, cancer

Familial relatedness in autosomal dominant FTD from ALLFTD

Individual age of onset hard to predict

Biological effects of GRN haploinsufficiency

Lysosomal dysfunction

**TMEM106b protective allele**

**TMEM106b is lysosomal protein**

**TMEM106b healthy brain aging**

**TMEM106b risk for LATE (AD co-path)**
Progranulin biology: lysosomal function & biomarker discovery

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


- Table showing characteristics of patients and outcomes for Placebo and Memantine

- Graph showing least squares mean change in NPI scores over treatment weeks for Placebo and Memantine
**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
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, insomia, 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)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Dose escalation phase</th>
<th>Maintenance phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 1</td>
</tr>
<tr>
<td>Plasma PGRN, cytokines</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CSF PGRN, cytokines</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>EKG, Vitals, AEs</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clin labs (CBC, Chem, etc.)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>MRI (rsfMRI, pASL)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Total dose mg/day</td>
<td>0</td>
<td>90</td>
</tr>
</tbody>
</table>

* Or highest tolerated dose

Sha et al, Alz & Dement, 2018
Ph2a trial of HDACi for GRN haploinsufficiency
Plasma and CSF progranulin: pharmacodynamic biomarkers

Latozinemab (anti-sortilin)

**PGRN Plasma Concentration**

Range from age-matched procured controls (64.6 ng/mL – 196.0 ng/mL)

**PGRN CSF Concentration**

Range from age-matched procured controls (3.48 ng/mL – 7.06 ng/mL)
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)

Staffaroni et al., *Nature Medicine*, 2022
DPM’s to identify best clinical trial endpoints

Estimated disease age (years to clinical onset)
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
Progranulin is associated with Aβ plaques, but not tangles in AD.

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

Pathological aggregates consist of amyloids (cryo-EM)

- Beta amyloid (Aβ₁₋₄₂)
- WT & mutant α-synuclein
- Tau
- TDP-₄₃ (Type A & B)
- FTLD-TDP (type A)
- TMEM103b
- FUS (fused in sarcoma)
Impaired protein clearance may be a common ND mechanism

Root et al, Neurobiol Dis, 2021
TDP-43 pathology and hippocampal atrophy in AD

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

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

<table>
<thead>
<tr>
<th>Latozinemab Milestone</th>
<th>AL101 Milestone</th>
<th>Expansion to Other Indications</th>
<th>Commercial Rights</th>
<th>Potential GSK Milestone Payment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>Patient screening underway and anticipate dosing first participant with early Alzheimer’s disease in PROGRESS-AD Phase 2 clinical trial in Q4 2023.</td>
<td>Potential to expand into other indications including amyotrophic lateral sclerosis (ALS), Parkinson’s disease, and other neurodegenerative diseases.</td>
<td>U.S. 50-50 profit share with GSK co-promote and tiered double-digit royalties ex-U.S.</td>
<td>$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.</td>
</tr>
</tbody>
</table>
Thank you