Alector R&D Briefing:
A Review of Our Progranulin Franchise and Brain Carrier Programs

September 2025

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: our future financial condition, including the sufficiency of cash to fund operations into the second half of 2027; results of operations; business strategy and plans; the beneficial characteristics, safety, efficacy, and therapeutic effects of our product candidates; the properties of our Alector Brain Carrier platform; our plans, timelines and expectations related to our Alector Brain Carrier platform, research and preclinical programs, and product candidates , 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, preclinical and clinical development programs and the development and manufacturing of its product candidates and blood - brain barrier technology platform; 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, including the anticipated timing and detail regarding the release of data for INFRONT - 3 and PROGRESS - AD; 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 anticipated timing of enrollment 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.

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

01	**Opening Remarks: Advancing a Multi-Stage Pipeline in Neurodegeneration** *Sara Kenkare-Mitra, Ph.D., President and Head of Research and Development*	**9:00 - 9:05 am PT**
02	**PGRN-Elevating Franchise for FTD-*GRN* and Alzheimer's Disease** *Sara Kenkare-Mitra, Ph.D., President and Head of Research and Development*	**9:05 - 9:25 am PT**
03	**Progressing Our Wholly-Owned, Versatile Alector Brain Carrier Technology Platform** *Arnon Rosenthal, Ph.D., Chief Executive Officer*	**9:25 - 9:40 am PT**
04	**Alector Brain Carrier–Enabled Programs: Delivering Antibodies, Enzymes, and siRNA Across the BBB** *Arnon Rosenthal, Ph.D., Chief Executive Officer*	**9:40 - 10:00 am PT**
05	**Closing Remarks and Q&A** *Arnon Rosenthal, Ph.D., Chief Executive Officer*	**10:00 - 10:30 am PT**

Alector is Positioned to Drive Near- and Long- Term Value in Treating Brain Disorders

Clinical Programs:

- Pivotal Phase 3 data readout in FTD-*GRN* by mid-Q4 2025
- Phase 2 clinical trial in AD with enrollment completed in April 2025
- First-in-human clinical trial with Alector Brain Carrier expected in 2026

Innovative Science with 3R Strategy and Advanced Technologies:

- Selected lead candidates for brain-penetrant anti-Aβ antibody
- Selected lead candidate for brain-penetrant GCase ERT
- Advancing brain-penetrant siRNA programs targeting tau, α-Synuclein and NLRP3

Remove - Misfolded Proteins

Replace - Dysfunctional Proteins

Restore - Dysfunctional Immune Cells and Neurons

Well Resourced & Global Partnership:

- Experienced leadership
- Profit-sharing collaboration with commercial rights for multiple programs
- Over $300M in cash provides runway into 2H 2027

Key Programs

Latozinemab (AL001) Antibody: Pivotal Ph 3 in FTD-*GRN*; Breakthrough Therapy, Fast Track, Orphan Drug Designations; Data by Mid-Q4 2025

Nivisnebart (AL101/GSK4527226) Antibody: Phase 2 in Alzheimer's Disease; Enrollment Completed in April 2025

Anti-Aβ-Antibody-ABC: In Alzheimer's Disease; Targeting Initiation of First-in-Human Trial in 2026

GCase-ERT-ABC: In Parkinson's Disease; Targeting Initiation of First-in-Human Trial in 2027

Tau-siRNA-ABC: In Alzheimer's Disease

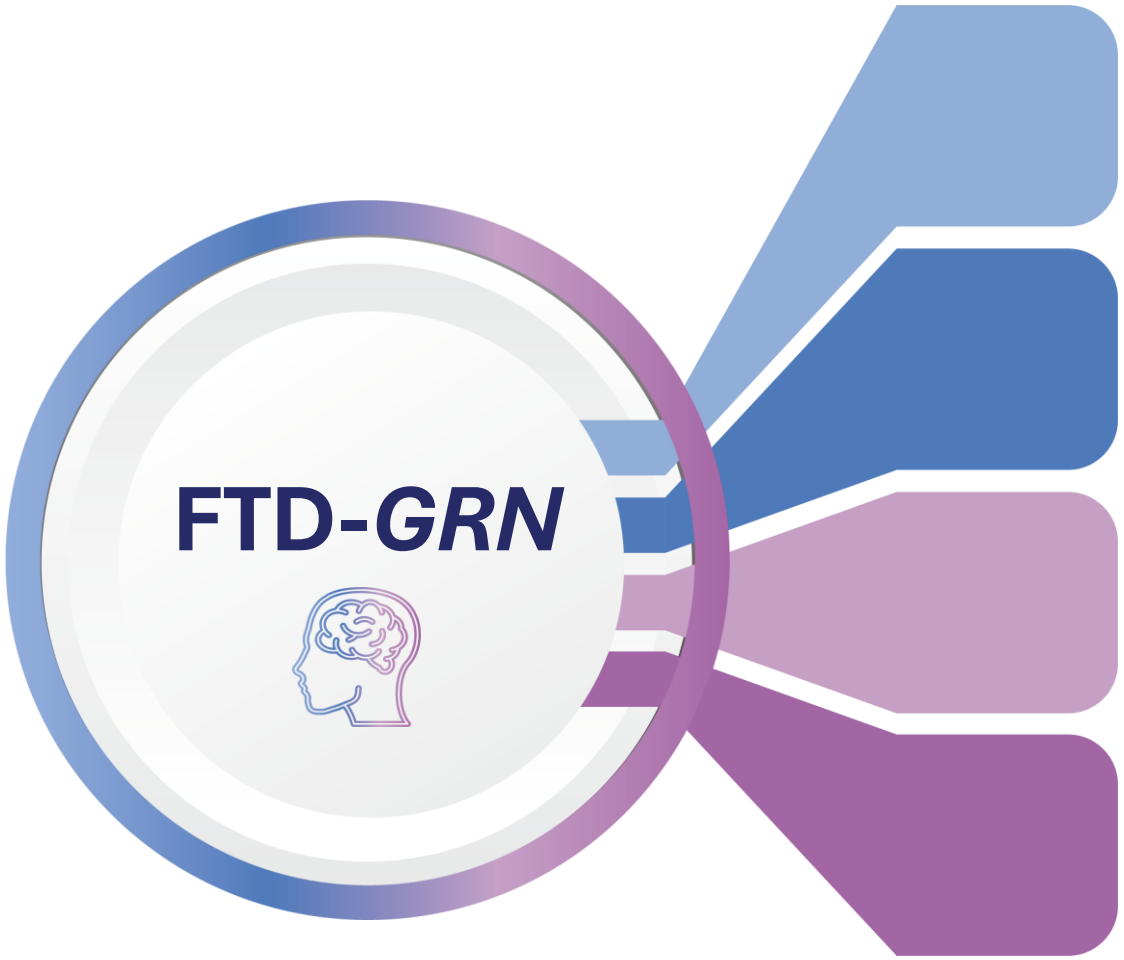
αSyn-siRNA-ABC: In Parkinson's Disease

NLRP3-siRNA-ABC: In Multiple Neurodegenerative Diseases

Partnered Portfolio:

Progranulin (PGRN)-Elevating Franchise for FTD-*GRN* and Alzheimer's Disease

FTD-*GRN*: Frontotemporal Dementia Caused by Mutations in the *GRN* Gene



The Disease:

- Aggressive, early-onset, dementia with compulsive behavior, lack of restraint, apathy, anxiety, aphasia, and life expectancy < 10 years since diagnosis

The Cause:

- Heterozygous loss-of-function mutations in the *GRN* gene reduce progranulin levels by ~50%

No Available Treatment:

- No approved symptomatic or disease modifying therapy

Our Therapeutic Hypothesis:

- Elevating PGRN back to physiological levels by blocking sortilin to prevent its degradation

UCSF Memory and Aging Center. Frontotemporal dementia. University of California, San Francisco. Taylor, R., & Finger, E. (2019, June). Frontotemporal dementias. Practical Neurology.
The Association for Frontotemporal Dementia. Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. Lancet Neurol. 2019 Dec 3;19(2):145–156. doi: 10.1016/S1474 - 4422(19)30394 - 1

Estimated Prevalence and Treatment Centers for FTD

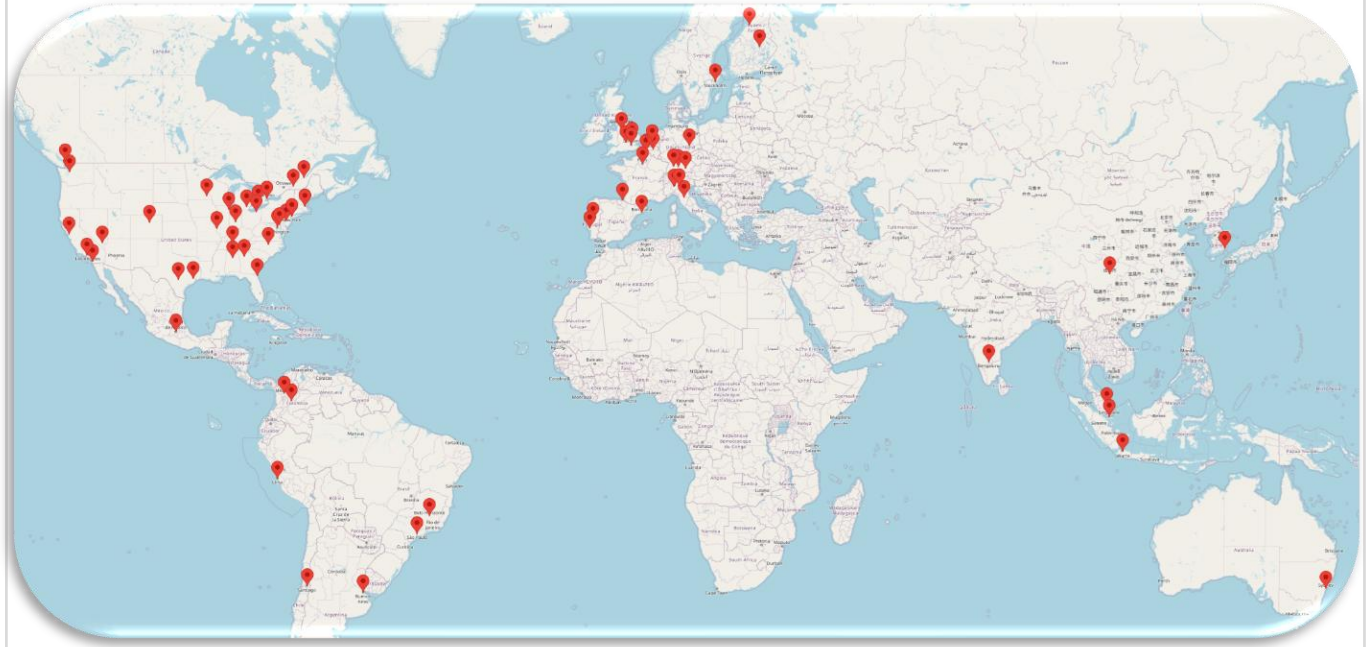
FTD is the most common cause of dementia under the age of 60, and most cases occur between the ages of 45 and 64.[1]

FTD affects ~50,000 to 60,000 individuals in the U.S. and ~110,000 in the EU.[2,3]

FTD-*GRN* accounts for 5 to 10% of FTD[4], representing ~8,000 to 17,000 symptomatic FTD-*GRN* across the U.S. and EU.[2,3,4]

The FTD disease burden is estimated to be nearly 2X that of Alzheimer's.[5]

FTD Treatment Centers Worldwide[6]



1.The Association for Frontotemporal Degeneration.
2. Patient estimates based on internal forecasting analysis using published literature sources.
3. E.U. estimates include EU5 countries only (Spain, Italy, France, U.K. and Germany).
4. FTD Disorders Registry.
5. Galvin JE, et al. The social and economic burden of frontotemporal degeneration. *Neurology*. 2017 Nov 14;89(20):2049 - 2056.
6. FPI | FTD Prevention Initiative

FTD-*GRN* Appears To Be Underdiagnosed: An Opportunity for Early, Genetically Based Improved Diagnosis

~30% of FTD-*GRN* is misdiagnosed as dementia not otherwise specified.

~8% of FTD-*GRN* is misdiagnosed as Alzheimer's disease.

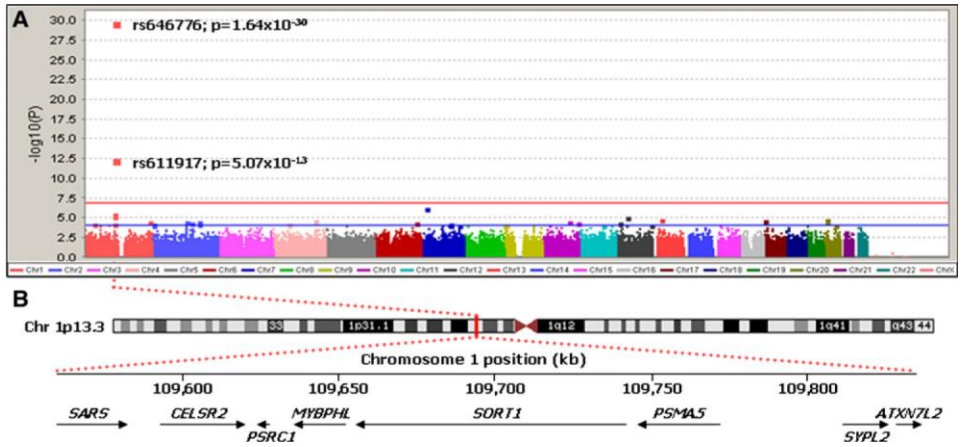
~2.5% of FTD-*GRN* is misdiagnosed as Parkinson's disease, dementia with Lewy Bodies, or vascular dementia.

Diagnosis of *GRN* Mutation Carriers	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%)

Moore et al., 2019 Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. *Lancet Neurol*. 3;19(2):145–156. doi: 10.1016/S1474 - 4422(19)30394 - 1

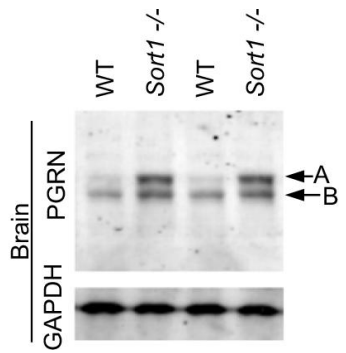
Latozinemab (AL001) and Nivisnebart (AL101): Designed to Increase PGRN Levels by Blocking Sortilin, a Degradation Receptor

PGRN levels inversely correlate with sortilin expression in human



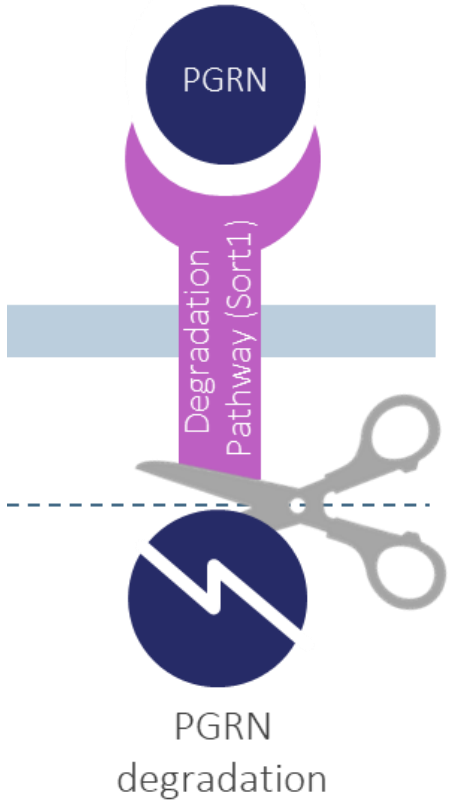
Carasquillo et al, AJHG 2010

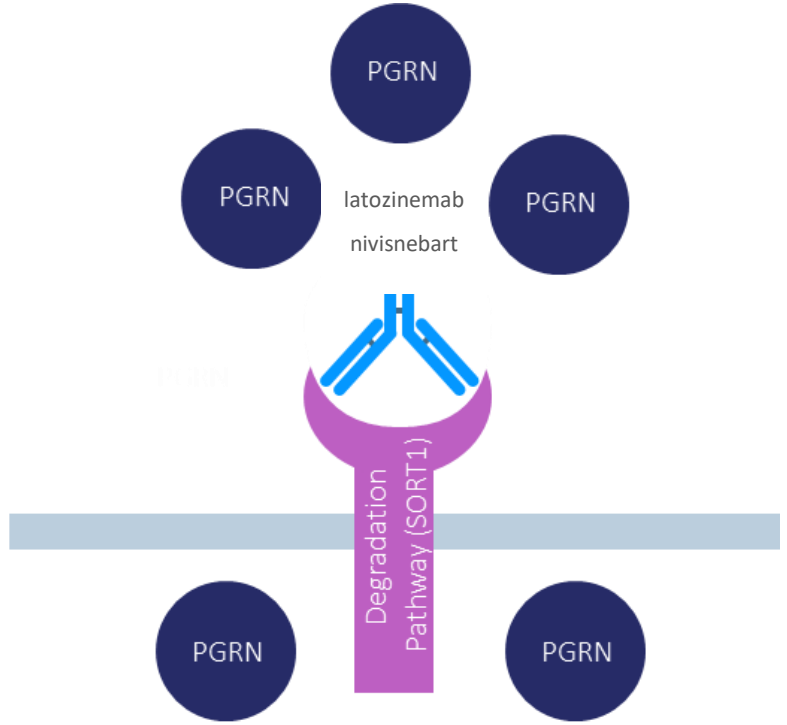
PGRN expression levels inversely correlate with sortilin levels in mice



Hu et al, Neuron 2010

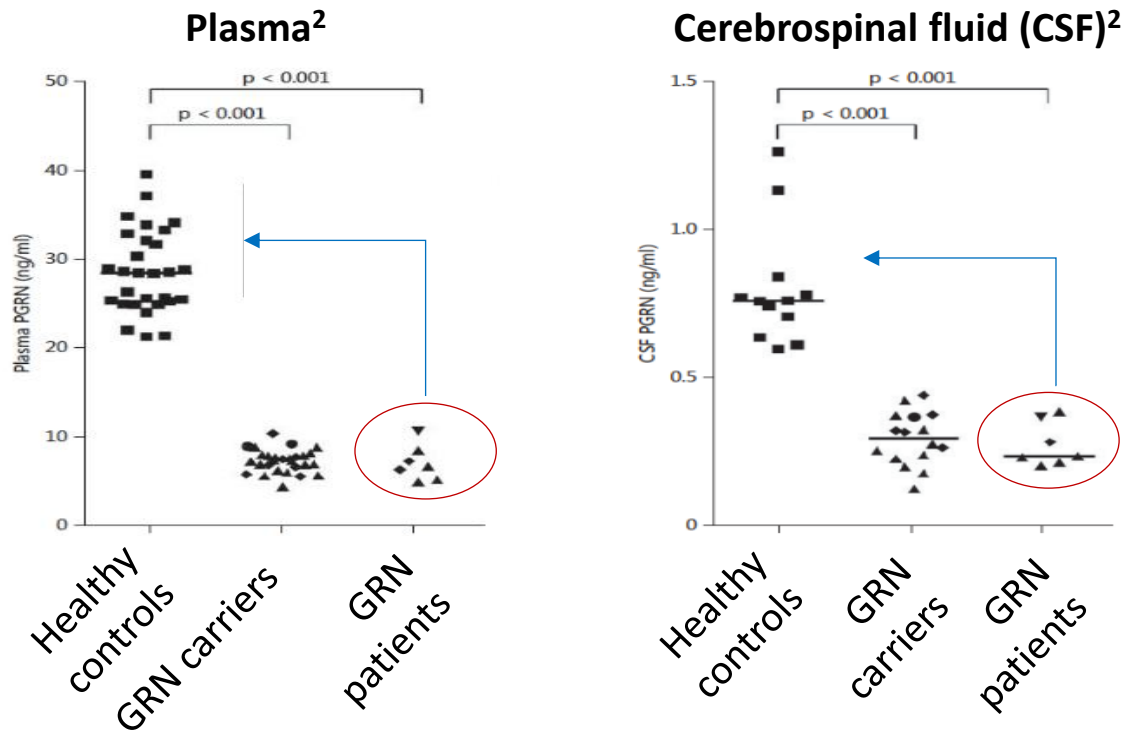
Latozinemab and nivisnebart are human monoclonal antibodies that are designed to increase the levels of PGRN by blocking sortilin



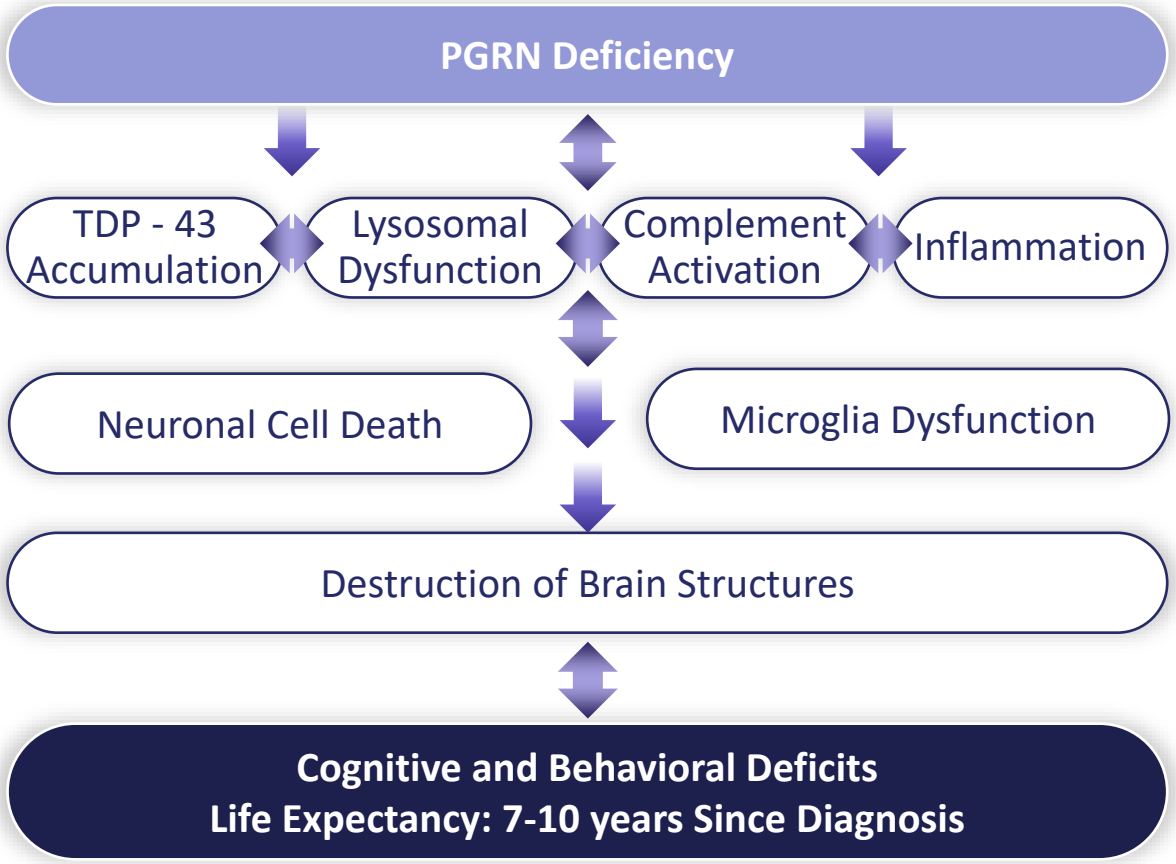


Latozinemab: Rationale for PGRN-Elevating Drugs in FTD

Heterozygous LOF Mutations in the *GRN* Gene Reduce PGRN and Directly Cause FTD



PGRN Deficiency Triggers a Multi-System Neurodegenerative Cascade

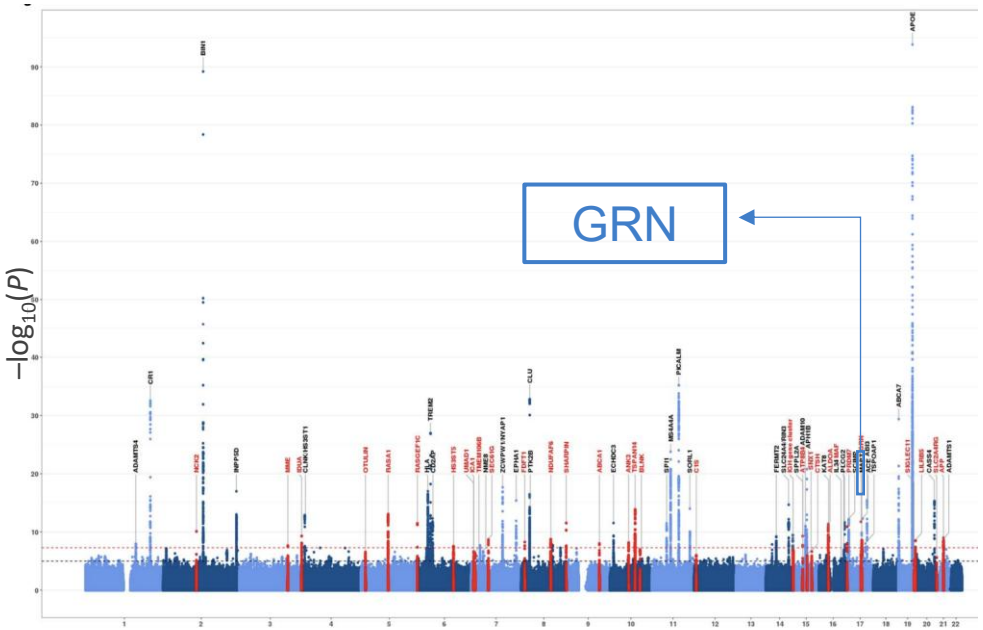


LOF = Loss - of - function

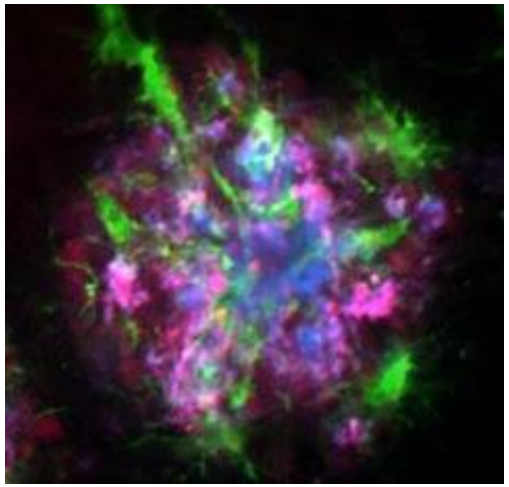
1. Sci Transl Med. 2017 Apr 12;9(385)
2. Dement Geriatr Cogn Disord Extra 2016;6:330 - 340;
3. Eur J Neurol. 2013 Dec;20(12):1571 - 3; Gene. 2014 Jun 1;542(2):141 - 5

Nivisnebart: Rationale for PGRN-Elevating Drugs in Alzheimer's Disease

PGRN is a Risk Gene for AD[1]

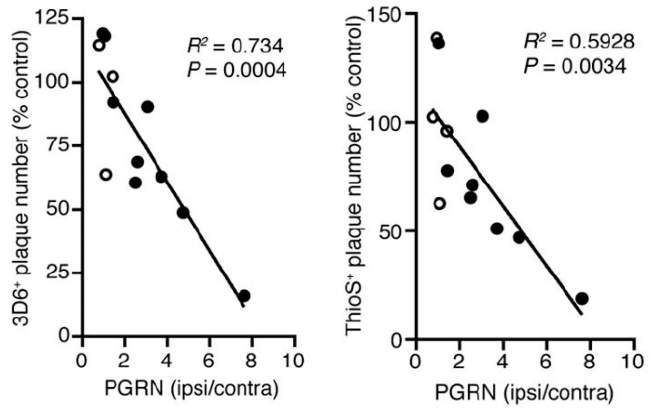


PGRN is Embedded in Aβ Plaques[2]



Microglia (green) surround amyloid plaques (blue), which also contain high levels of PGRN (purple)

PGRN is Protective in AD Model[2]

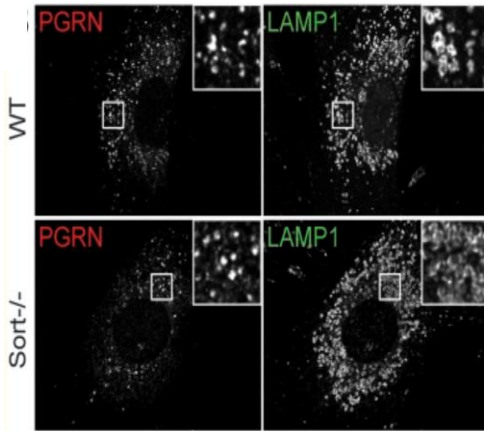


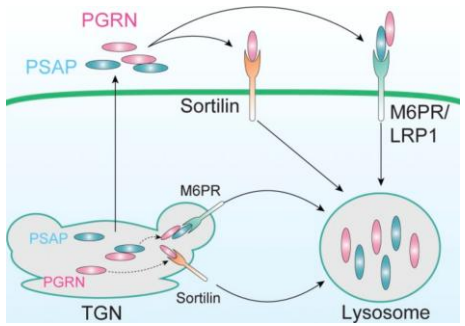
PGRN overexpression decreases Aβ plaque load in the dentate gyrus of AD mice

1. https://doi.org/10.1101/2020.10.01.20200659 (Left); ARTFL Diagnoses. The breakdown of clinical diagnoses among ARTFL FTD mutations carriers. [Courtesy of Adam Boxer.] https://www.alzforum.org/print - series/1093496 (Right). 2. Mendsaikhan A, et al. Characterization of lysosomal proteins Progranulin and Prosaposin and their interactions in Alzheimer's disease and aged brains: increased levels correlate with neuropathology. *Acta Neuropathol Commun*. 2019 Dec 21;7(1):215.

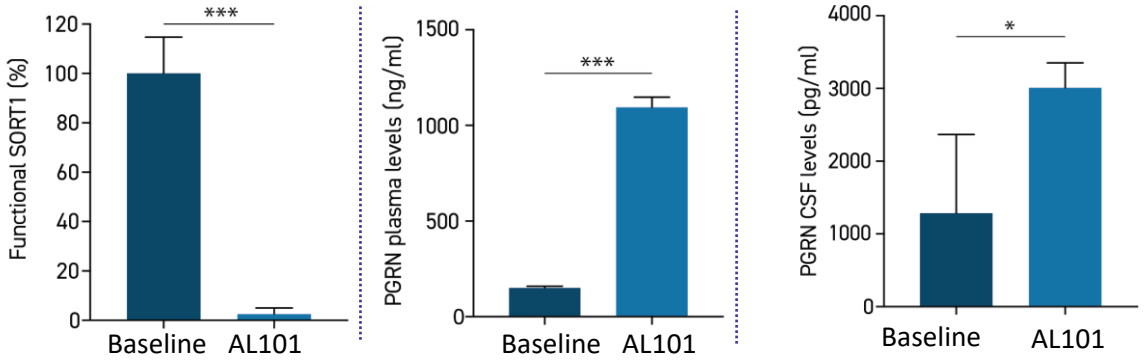
Genetic and Biological Rationale for Blocking Sortilin to Elevate PGRN

PGRN enters the lysosomes of *SORT1*-deficient cells through multiple alternative receptors





Blocking sortilin, encoded by *SORT1,* increases PGRN in FTD mice



Supporting evidence from genetics, biology, and experiments

Genetics: Loss-of-function mutations in *SORT1*

- Lead to chronic elevation of PGRN in humans and mice with minimal/no discernible adverse effects

Biology: PGRN that does not bind sortilin

- Enters lysosomes where it remains active
- Promotes neuronal survival
- Restores lysosomal function of PGRN-deficient neurons and microglia in mice
- Appears more potent than WT PGRN in rescuing microglial pathology, reducing NfL, and correcting lipid abnormalities in mice

Experiments: Sortilin-blocking antibodies

- Elevated PGRN and rescued phenotypes in an FTD- *GRN* mouse model
- Elevated PGRN with encouraging trends in clinical outcomes and biomarkers in FTD-GRN patients in our open-label INFRONT-2 Phase 2 trial

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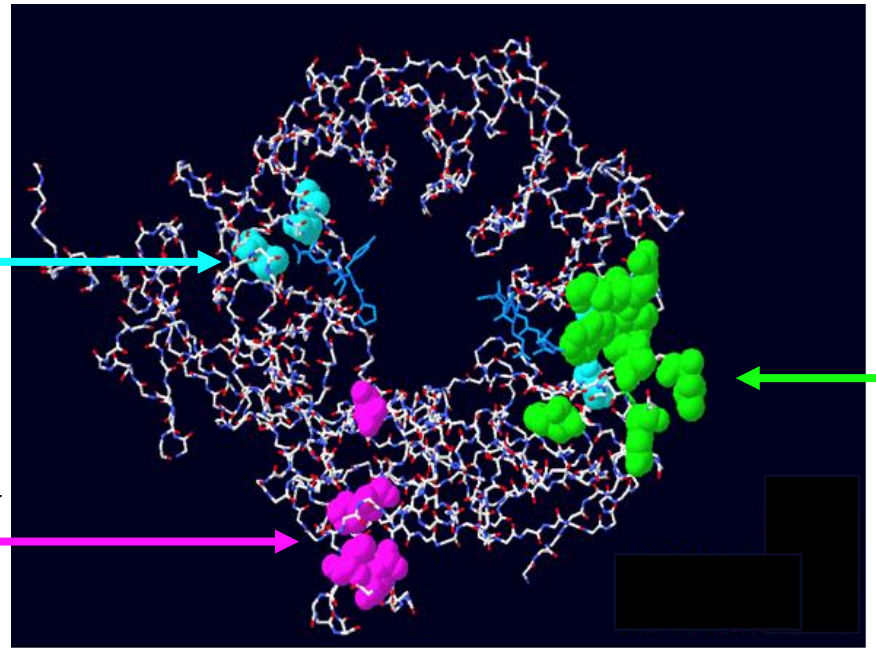
AL101 = Nivisnebart; Alz Res Therapy 4, 4 (2012); Sci Transl Med. 2017 Apr 12;9(385); Dement Geriatr Cogn Disord Extra 2016;6:330 - 34.; Eur J Neurol. 2013 Dec;20(12):1571 - 3; Gene. 2014 Jun 1;542(2):141 - 5.; Kashyap et al., *bioRxiv 2025,* https://www.biorxiv.org/content/10.1101/2024.09.15.613118v1

Differentiating Alector's PGRN-Elevating Antibodies: Latozinemab and Nivisnebart

Latozinemab and Nivisnebart Have a Distinct Binding Epitope on SORT1

3D CRYSTALLOGRAPHY STRUCTURE OF SORT1



Drug Candidate Profiles

- Latozinemab and nivisnebart are human **anti-SORT1** antibodies.
- **PK/PD profile** distinguishes nivisnebart from latozinemab.
- Nivisnebart is designed for more prevalent neurodegenerative diseases, including **AD** and **PD**.
- Latozinemab and nivisnebart have demonstrated a 2- to 3-fold increase in **PGRN levels** and have been generally **well-tolerated** in clinical trial results to date.

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Alector data on file

INFRONT-2 Open-Label Phase 2 Trial with Latozinemab

Symptomatic FTD-*GRN* (N=12), Latozinemab 60 mg/kg q4w for 49 weeks

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

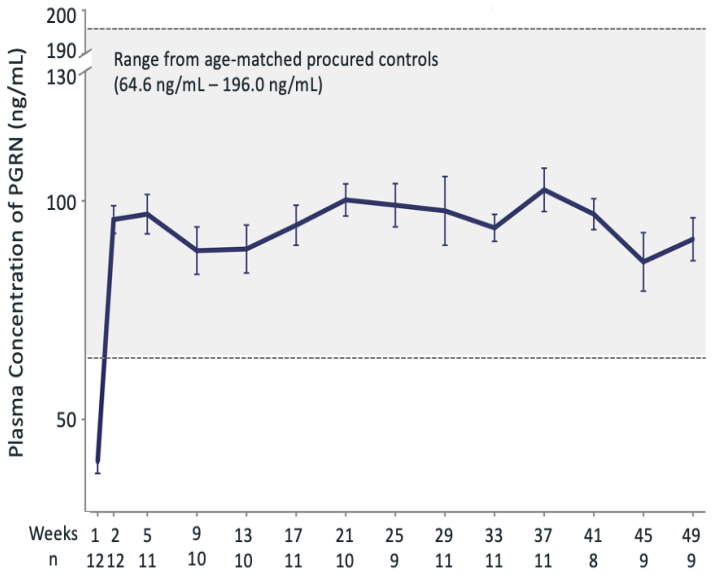
TARGET ENGAGEMENT	BIOMARKERS				CLINICAL BENEFIT
PGRN (Plasma and CSF)	Lysosomal Dysfunction	Inflammation	Astrogliosis	Brain Atrophy	Clinical Outcome Assessments
PGRN CSF and plasma PGRN levels	**e.g. CTSD, LAMP1** Dysfunctional lysosomes are hallmarks of FTD-*GRN*	**e.g. C1QB** Elevation of complement proteins occurs in FTD-*GRN*	**GFAP** Elevation of GFAP is a hallmark of FTD-*GRN* correlates with cognitive decline	**MRI** Accelerated brain tissue loss is a hallmark of FTD-*GRN* and correlates with cognitive decline	**CDR® plus NACC FTLD-SB** A measure of clinical progression in FTD agreed upon by the FDA and EMA

CTSD = cathepsin D; LAMP1 = lysosomal associated membrane protein 1; C1QB = complement C1q B chain; GFAP = glial fibrillary acidic protein
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)

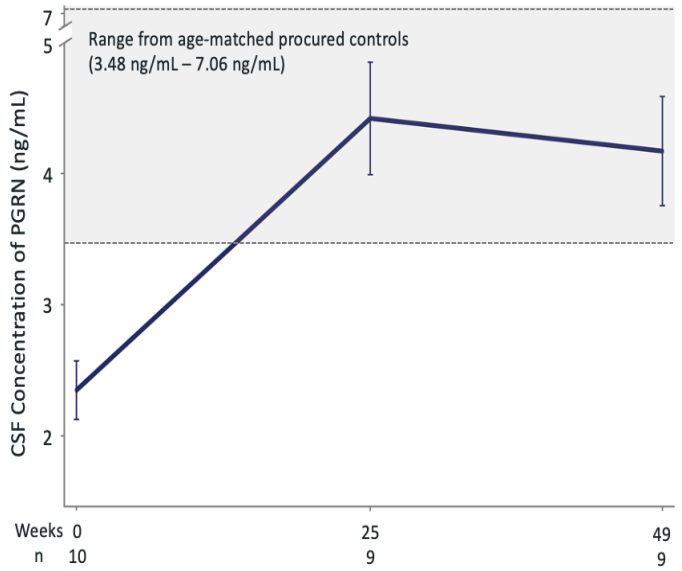
INFRONT-2: Latozinemab Restores PGRN in Plasma and CSF to Levels Seen in Healthy Volunteer Age - Matched Controls

ACHIEVED PGRN RESTORATION IN FTD-*GRN* PARTICIPANTS

PGRN Plasma Concentration

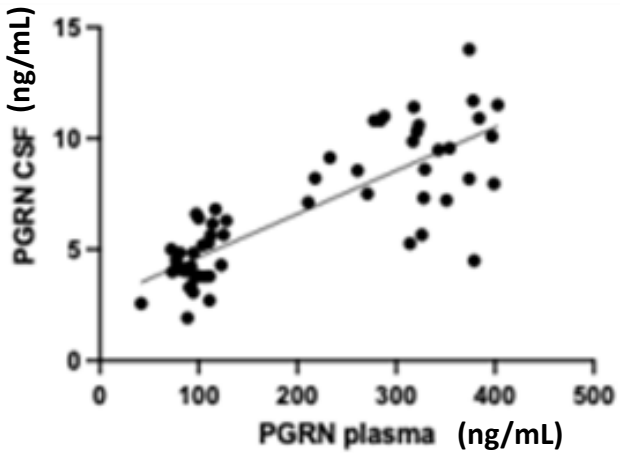


PGRN CSF Concentration



Correlation of PGRN CSF vs. Plasma

Pearson R=0.79, p<0.0001
Samples collected post-treatment
Concentrations in ng/mL

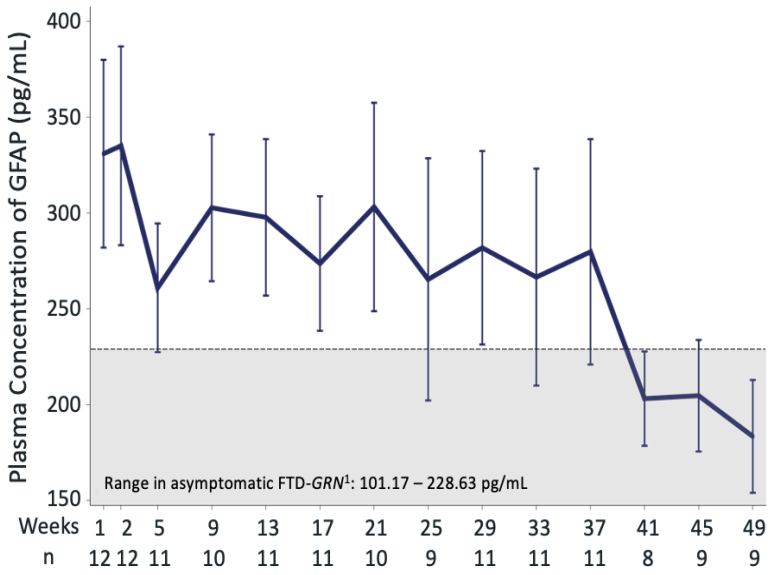


Data cut - off June 15, 2021
Mean +/ - SEM
Source: AAIC 2021.

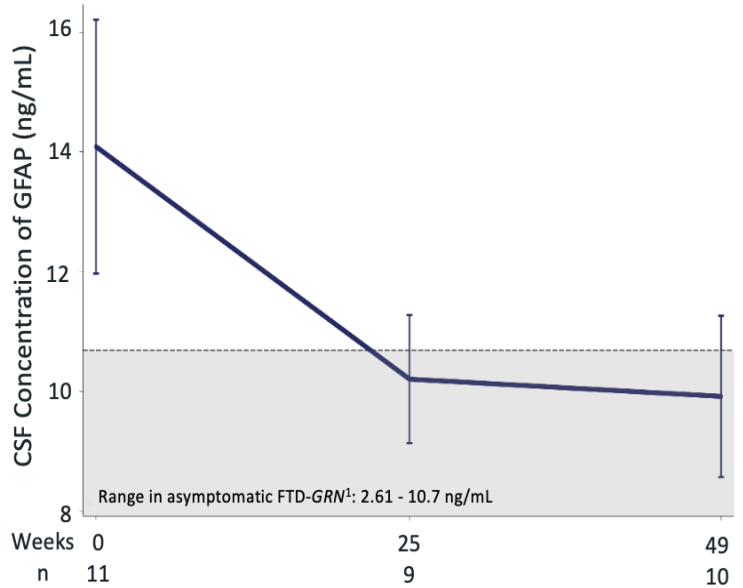
INFRONT-2: Latozinemab Treatment Decreases Glial Fibrillary Acidic Protein (GFAP) Levels Towards Range Seen in Asymptomatic Carriers of FTD-*GRN* Mutation

BIOMARKERS OF DISEASE ACTIVITY – ASTROGLIOSIS

GFAP Plasma Concentration



GFAP CSF Concentration



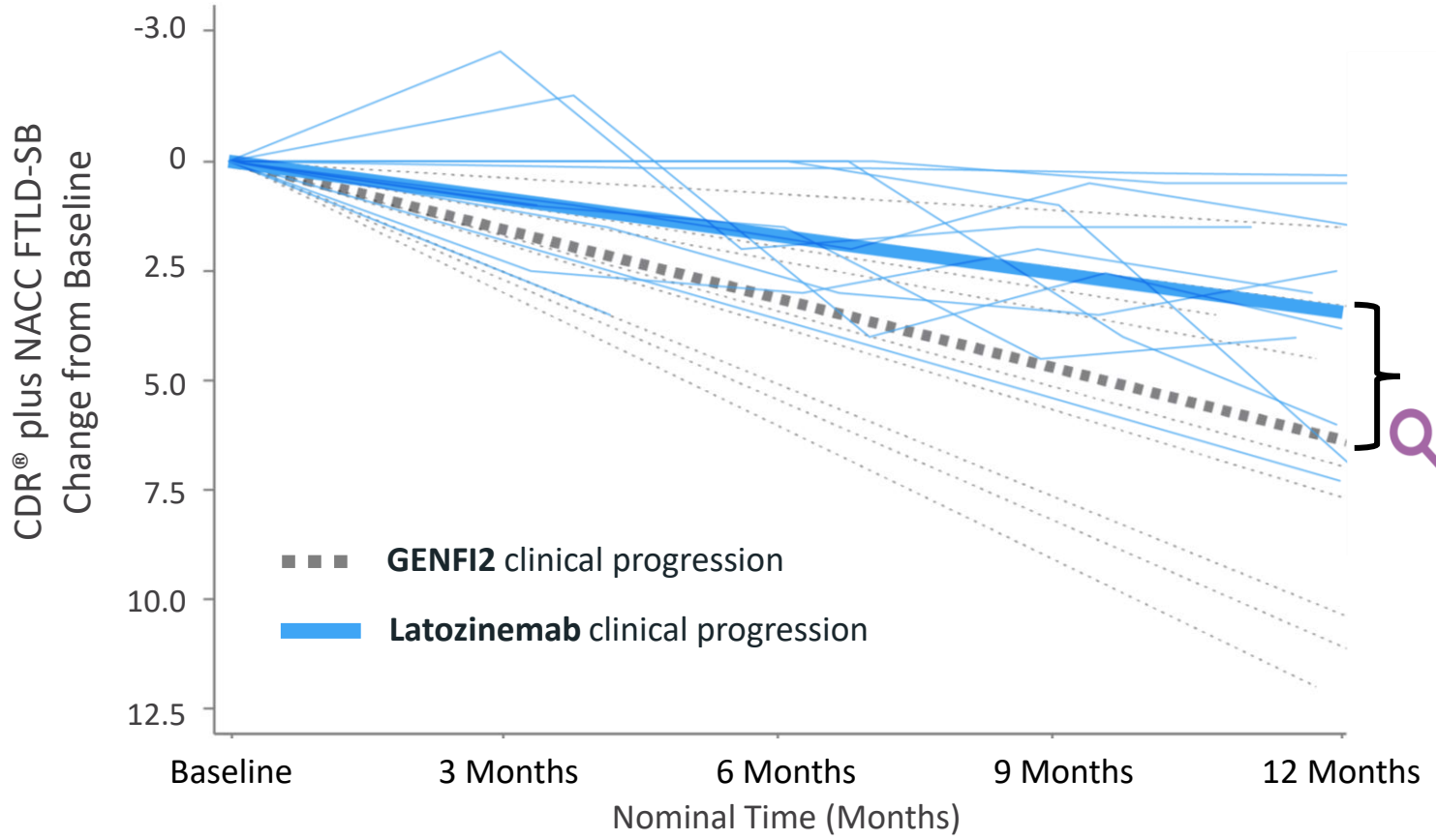
Symptomatic *GRN* mutation carriers were injected with AL001 60 mg/kg q4w for 49 weeks, and the levels of their PGRN in the Plasma and CSF was measured.

Data cut - off June 15, 2021, Mean +/ - SEM,. 1. Range is of baseline GFAP levels in asymptomatic FTD - GRN patients enrolled in INFRONT – 2, Source: AAIC 2021.

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

CLINICAL OUTCOME ASSESSMENT

CDR® plus NACC FTLD-SB[2]



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]**

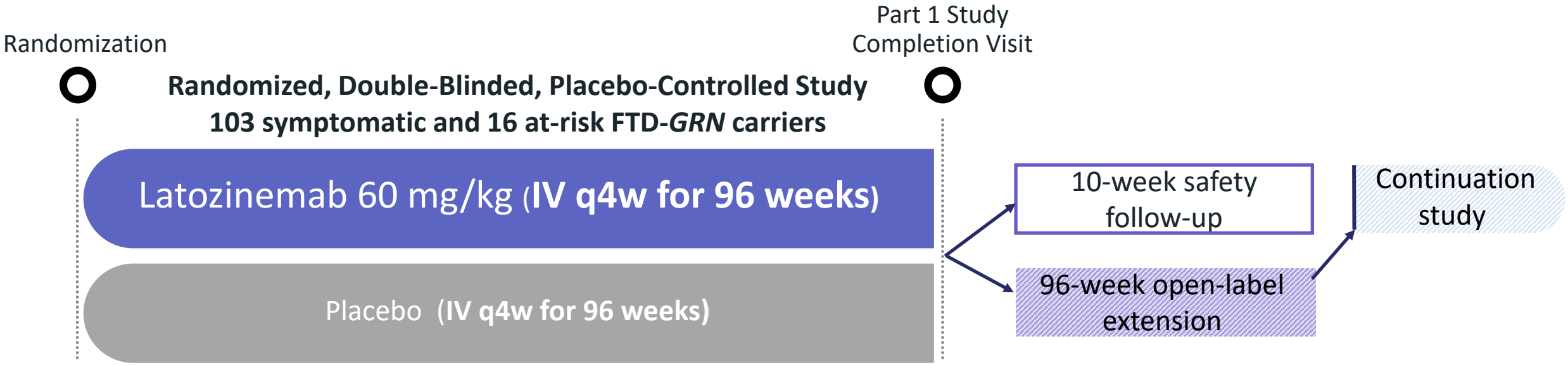
Estimated to slow annual disease progression by ~48% (3.1-point change)

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

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

Latozinemab: Pivotal Phase 3 INFRONT-3 Study Design

LATOZINEMAB IS THE MOST ADVANCED CANDIDATE IN DEVELOPMENT FOR FTD-*GRN*[1], WITH PIVOTAL DATA EXPECTED BY MID-Q4 2025



CO - PRIMARY ENDPOINTS	SECONDARY CLINICAL OUTCOMES ASSESSMENTS:	EXPLORATORY ENDPOINTS
CDR® plus NACC FTLD-SB Plasma Progranulin*	CGI-S, CGI-I, FRS, RBANS	e.g., NfL, GFAP, vMRI

"At risk" = GRN carriers who are pre - symptomatic and meet a pre - specified NfL threshold for enrollment in the Phase 3 trial;
CDR® plus NACC FTLD - 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

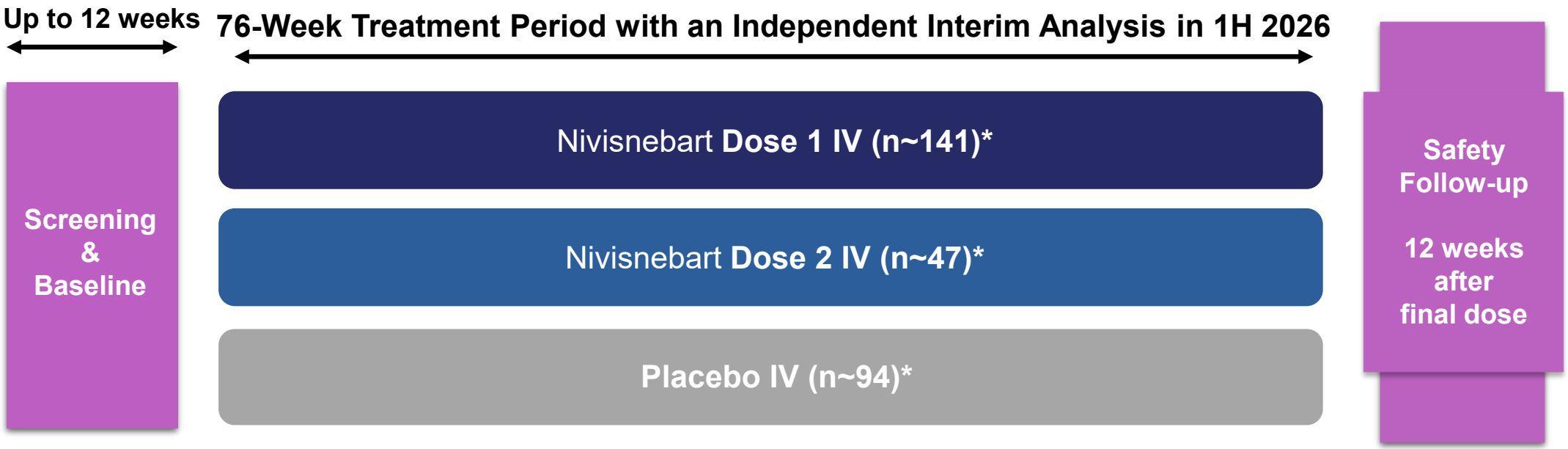
1. Alector is not aware of any other candidates in a Phase 3 trial for FTD as of August 2025.

*Plasma progranulin is a co-primary endpoint in the U.S. only and does not apply to the EU.

Nivisnebart: Phase 2 PROGRESS-AD Study Design

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY NIVISNEBART IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE

Completed Enrollment in April 2025



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

alector *Planned sample size

Latozinemab and Nivisnebart: Currently Partnered in a Collaboration Agreement

GSK

$700M upfront (2021 and 2022)	$1.5B in potential milestone payments	U.S. 50/50 profit share and co - commercialization	Tiered double - digit royalties (ex U.S.)	$160M for first commercial sale in U.S.	$90M for first commercial sale in at least two of the following countries: France, Germany, Italy, Spain or U.K.

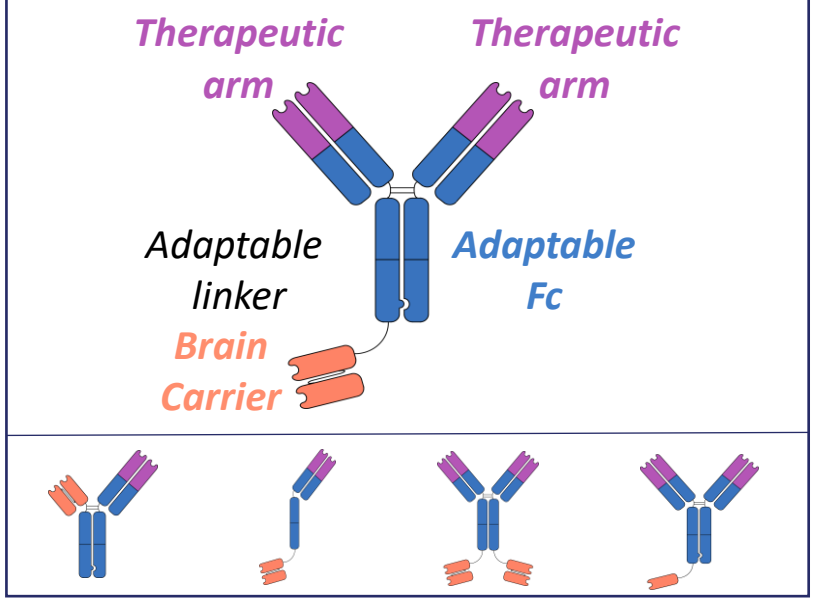
Latozinemab Pivotal Phase 3 INFRONT-3 data anticipated by mid-Q4 2025.
Nivisnebart Phase 2 PROGRESS-AD enrollment completed in April 2025.

Alector Brain Carrier (ABC) Platform

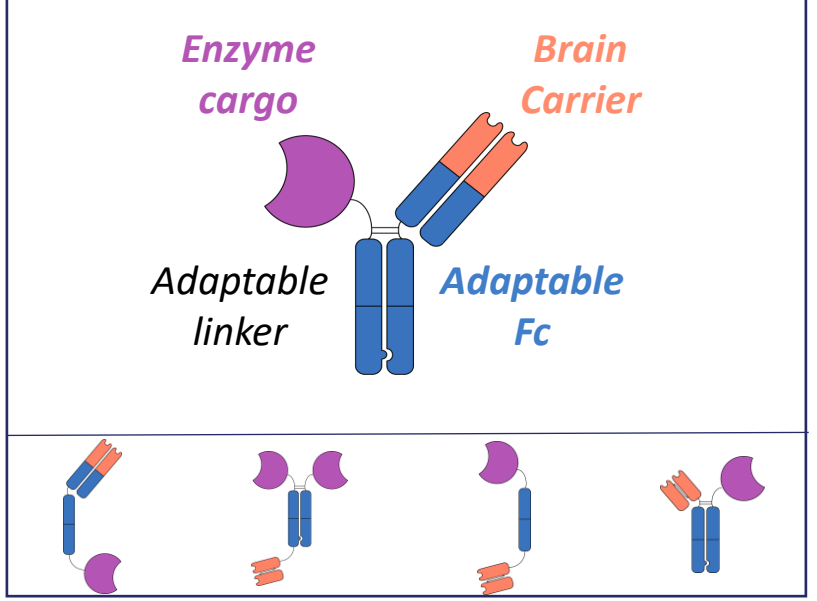
Alector's Versatile Drug Configurations Are Tailored to the Cargo

Versatile Configurations, Orientations and Size of Linkers That Are Optimal for the Cargo

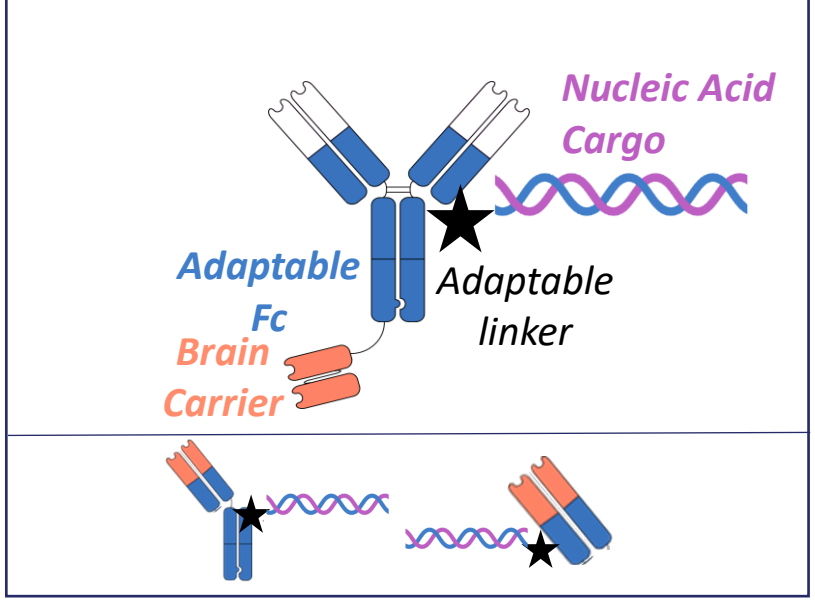
Antibody Cargo



Enzyme Cargo



Nucleic Acid Cargo



ABC Designed to Optimize Configuration, Orientation, Linker Size, Valency and Effector Function

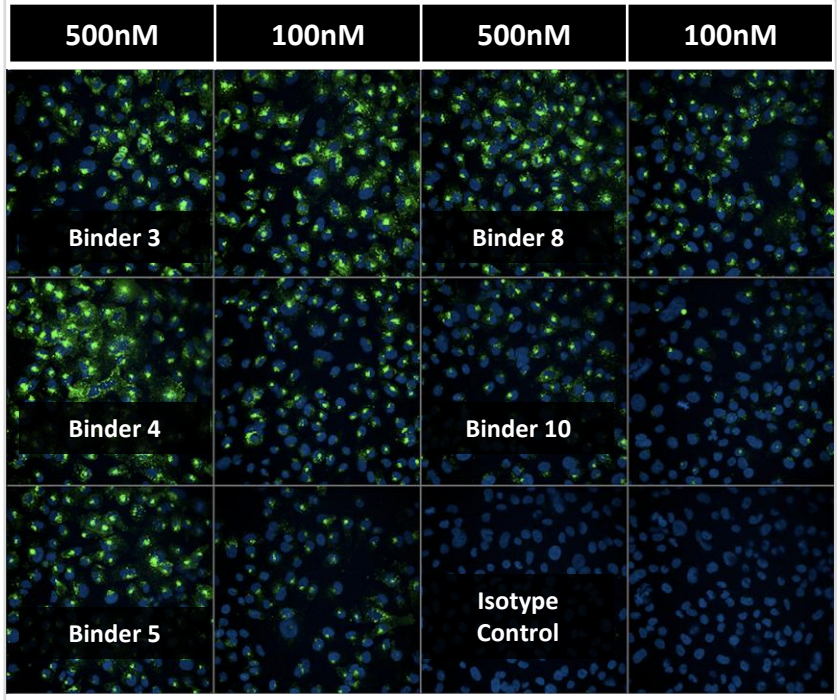
- Designed to enable optimal brain penetration, drug activity, stability and manufacturability
- Serum half-life compatible with monthly IV/SubQ dosing
- Adaptable to cargos whose mechanism of action requires effector function
- Ability to deliver into brain parenchyma and/or brain cells

Adaptable TfR Binding Affinities and Effector Functions for a Variety of Cargos

500-Fold Affinity Range Tailored to Antibodies, Enzymes, and siRNA

TfR Binder	KD (nM)
Binder 1	5
Binder 2	19
Binder 3	126
Binder 4	127
Binder 5	176
Binder 6	182
Binder 7	274
Binder 8	390
Binder 9	639
Binder 10	1040
Binder 11	1210
Binder 12	4720

ABC Displays Affinity-Dependent Internalization Into Human Brain Endothelial Cells



Anti-TfR binders at multiple affinities were incubated on hCMEC/D3, cells for 2 *hours. Internalized antibodies detected with anti-huIgG in green; nuclei labeled in blue with DAPI.*

TfR Binding Affinities Tailored to Drug Modalities and Antibody Effector Function

- Facilitates transcytosis of drugs through the BBB
- Tailored to enter cell types of interest
- Designed to reduce effect on drug half-life
- Reduces concurrent binding to TfR and FcγR

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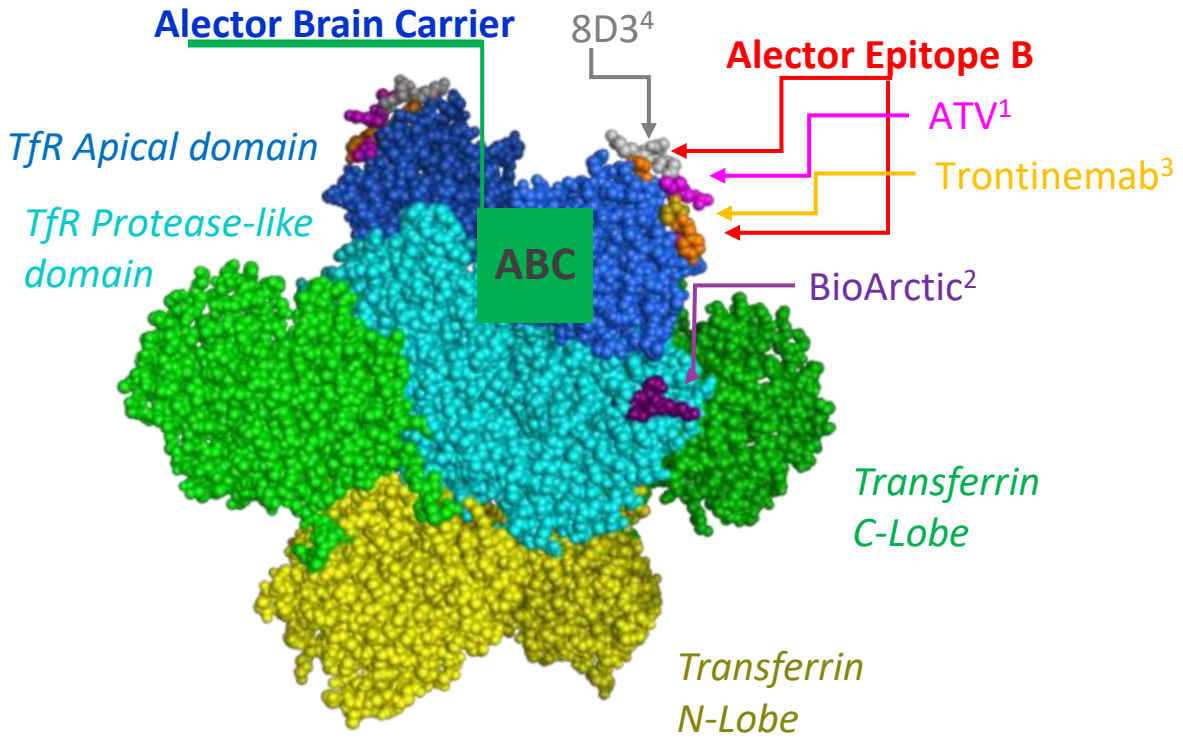
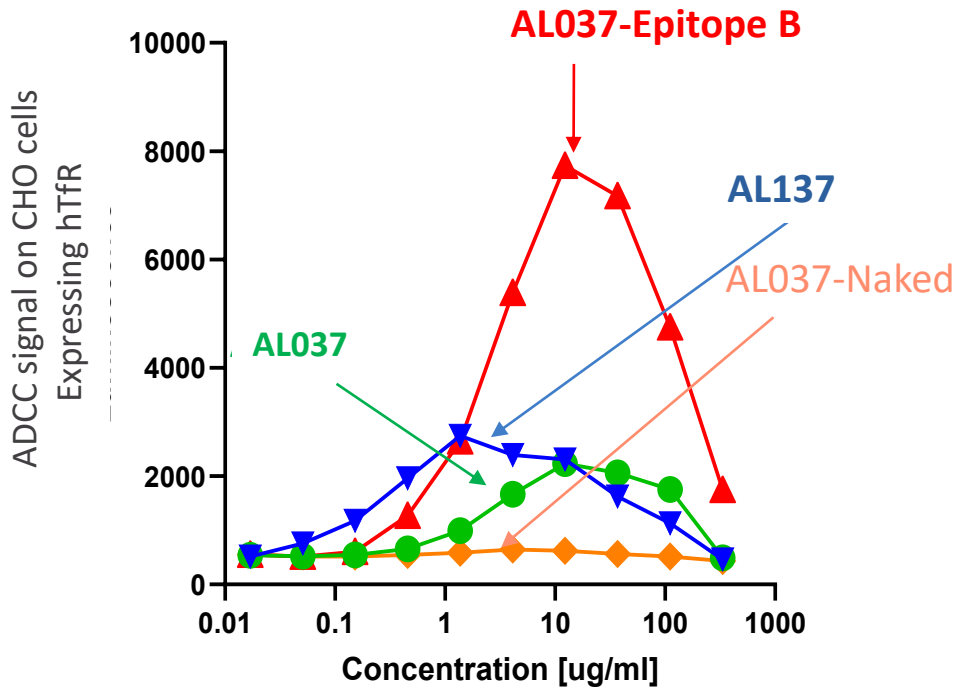
Alector data on file

Alector's TfR ABC Reduces TfR-Mediated ADCC: A Measure for Reticulocytes Depletion

Structure of The Human Transferrin Receptor Bound to TfR and Binding Epitopes of Distinct BBB Approaches



TfR and Antibody-Dependent Cell Cytotoxicity (ADCC) Are Determined by the TfR Binding Epitope and Affinity



AL037 = Alector ABC-enabled anti-Aβ-antibody. AL137 = second Alector ABC-enabled anti-Aβ antibody. AL037-Naked = AL037 without ABC platform. *RBC = Red Blood Cells. Structure of human transferrin receptor-transferrin complex from 1SUV. (1) ATV epitope (Kariolis et al., 2000); (2) BioArctic epitope (International Patent Pub. No. WO2024200271); (3) Trontinemab epitope (Alector internal data) (4) 8D3 epitope (de la Rosa et al., 2025). Epitope B binds TfR at the same region as Denali's ATV and Roche's Trontinemab. ADCC activity, used here as a surrogate for TfR-dependent hematologic adverse effects, was assayed using Promega ADCC Reporter Bioassay kit with huTfR overexpressing Chinese Hamster Ovary (CHO) cells.*

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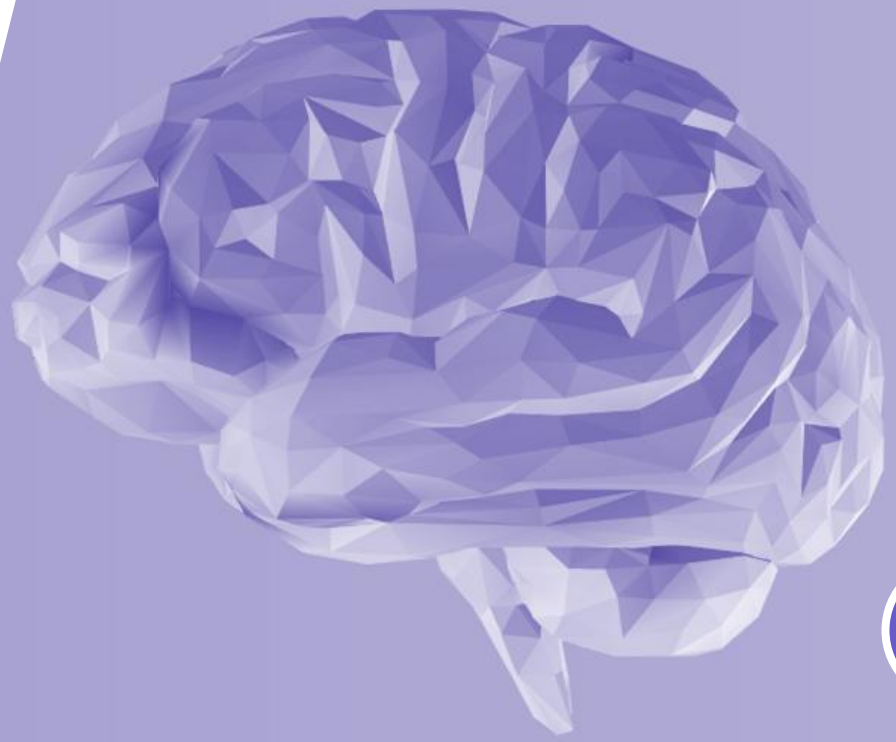
Alector data on file

Research and Preclinical Programs:
Remove toxic proteins and **Replace** deficient proteins using advanced technology



Establish Alector Brain Carrier (ABC) Technology Across Modalities

Antibodies + ABC
- Removing Aβ
- Removing Tau

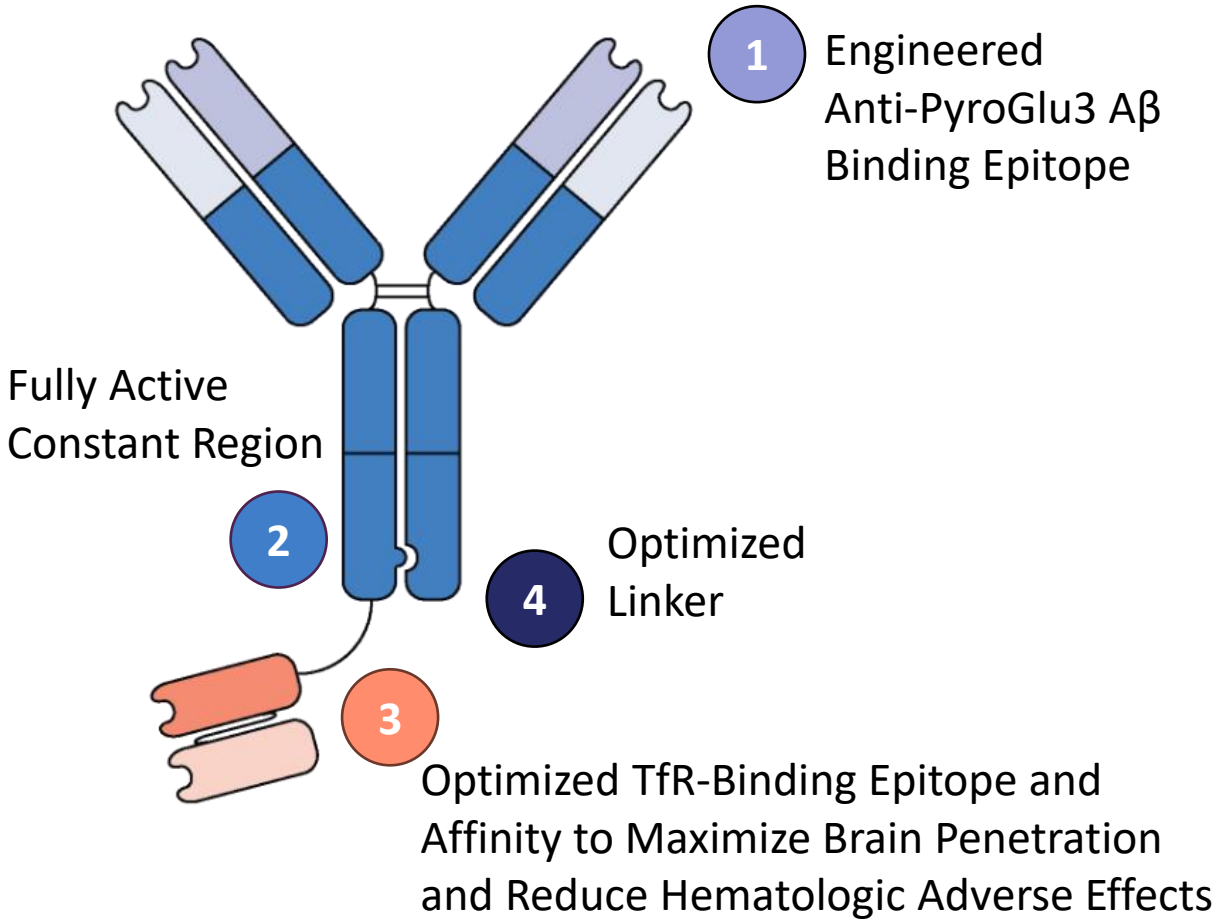
Enzymes + ABC
- Replacing GCase

siRNAs + ABC
- Removing Tau
- Removing α-Synuclein
- Removing NLRP3

Applying our versatile ABC platform toward multiple drug modalities
Targeting AD and PD with research and preclinical programs against validated drug targets

AL037: Alector Brain Carrier (ABC)—Enabled Anti-Aβ Antibody for Alzheimer's Disease

Design of AL037: ABC-Enabled Anti-Aβ Antibody



Targeted Design Features

Selectivity

- Engineered high-affinity, fully human antibody that selectively binds toxic Aβ plaques

Potency

- Fully active constant region enabling effective recruitment of myeloid cells to remove Aβ plaques

Safety

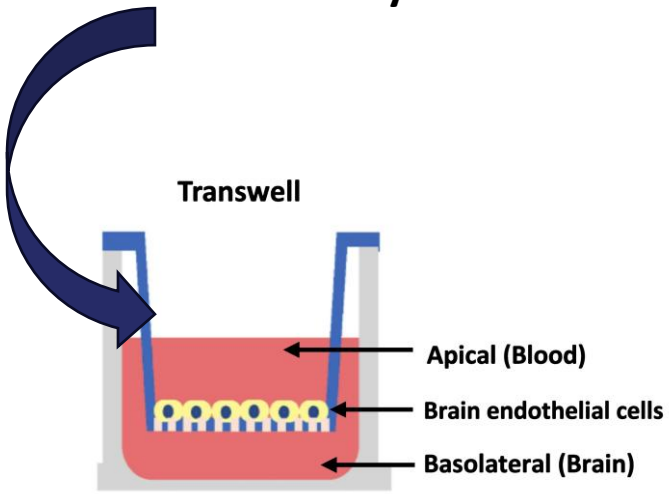
- Proprietary ABC with tuned affinity and binding epitope seeks to facilitate effective brain penetration and plaque removal while minimizing hematologic adverse effects

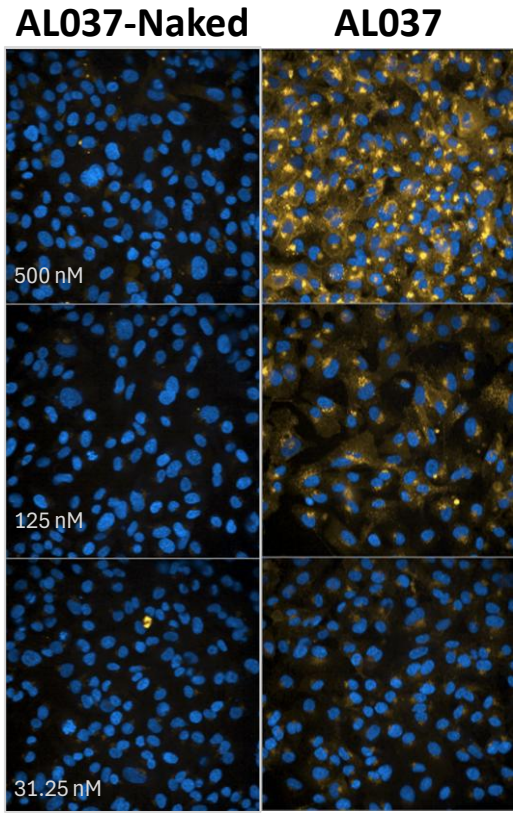
Convenience

- ABC enables potential for low dosing regimen and subcutaneous delivery

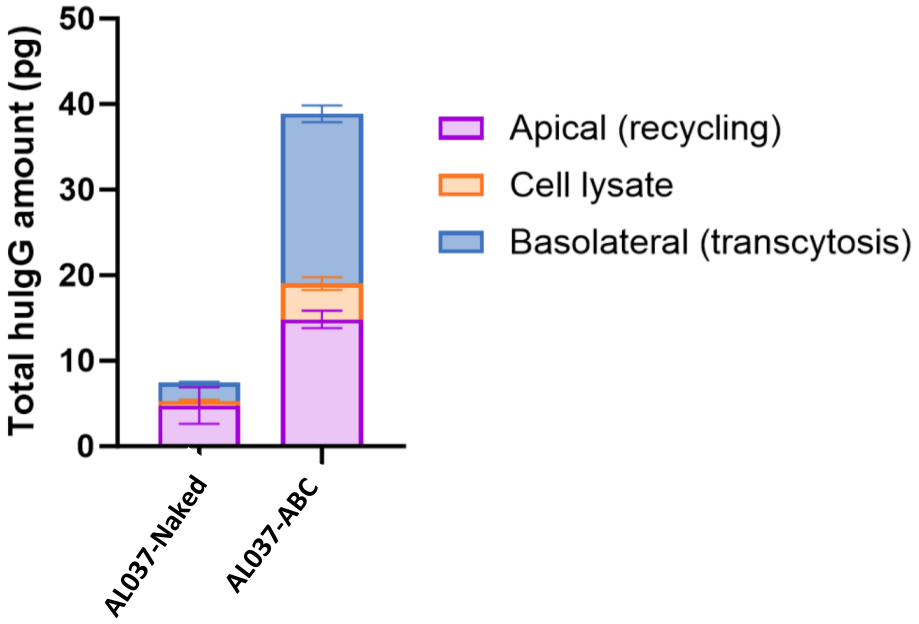
ABC-Dependent Transcytosis of AL037 in Human Brain Endothelial Cells

2 Hour Pulse with Antibody





4 Hour Chase and Assessment of Antibody Levels

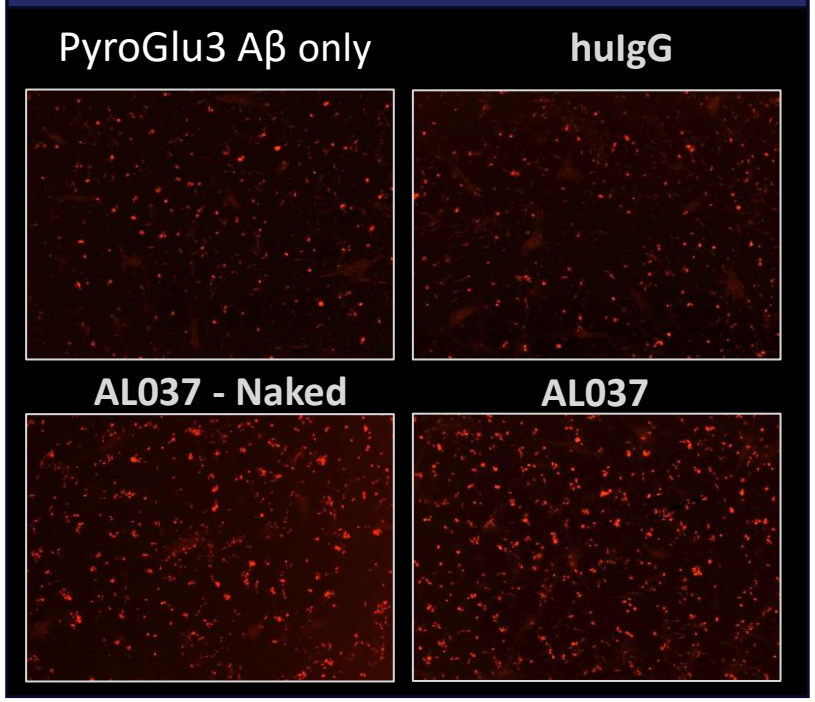


AL037-Naked (without the ABC platform) or AL037 at various concentrations were incubated on hCMEC/D3 cells for 2 hours. Internalized antibodies detected with anti-hulgG in yellow; nuclei labeled in blue with DAPI. Levels of internalized, recycled or transcytosed antibody were assessed by MSD.

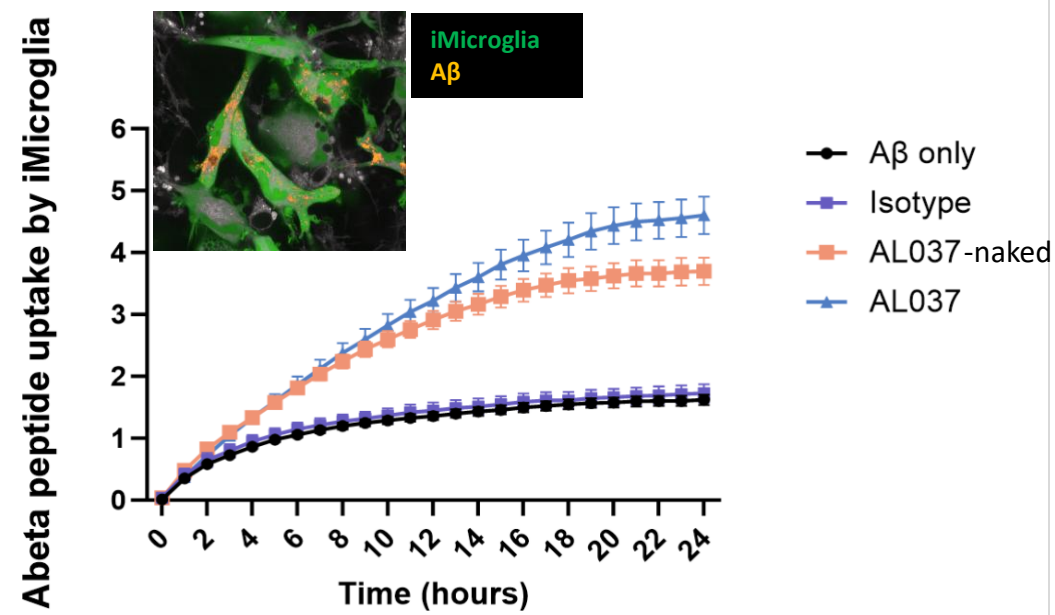
Alector ABC facilitated robust uptake and transport of AL037.

AL037 Facilitates Phagocytosis of PyroGlu3 Aβ by Human Microglia

Fluorescent Imaging (red) of PyroGlu3 Aβ Phagocytosed by Microglia in 24h



AL037-Dependent Phagocytosis of PyroGlu3 Aβ by Human IPSC Microglia in Culture

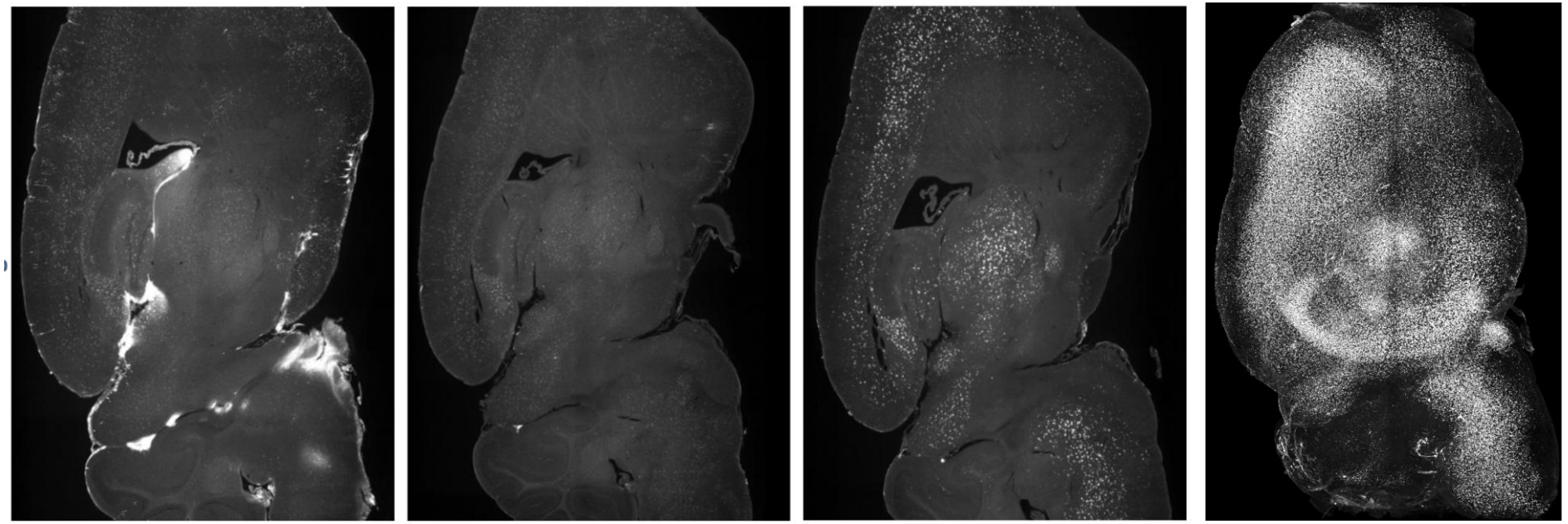


AL037-Naked (without the ABC platform), Isotype huIgG, or AL037 and pyroGlu3 Aβ were incubated with IPSC-derived CNS triple cultures (containing iMicroglia, iNeurons, human fetal astrocytes) for 24h and imaged hourly for uptake of pHrodo-labeled pyroGlu3 Aβ in GFP-iMicroglia.
(inset, iMicroglia in green, Aβ in orange)

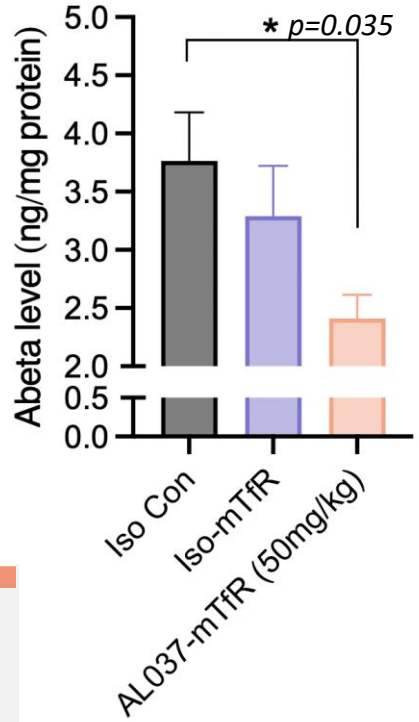
AL037 Surrogate Binds To and Reduces Amyloid Plaque in the Mouse Brain

MOUSE

Iso Control 50 mg/kg	Iso mTfR 5 mg/kg	AL037-mTfR 5 mg/kg	AL037-mTfR 3D Reconstruction



Reduction in Brain Aβ42 in AL037 Surrogate-dosed Mice



Light sheet microscopy on 9-month-old 5xFAD mice dosed 3 times weekly at levels indicated. Aβ42 levels were assessed in total brain lysates by ELISA; means +/-SEM, n=16-17 per group; 24-168h post last dose. Naked antibody primarily labels the vasculature and ventricles while AL037 Surrogate with mouse TfR binding domain is on amyloid plaques distributed throughout the brain.

One way ANOVA with Dunnett's multiple comparisons test

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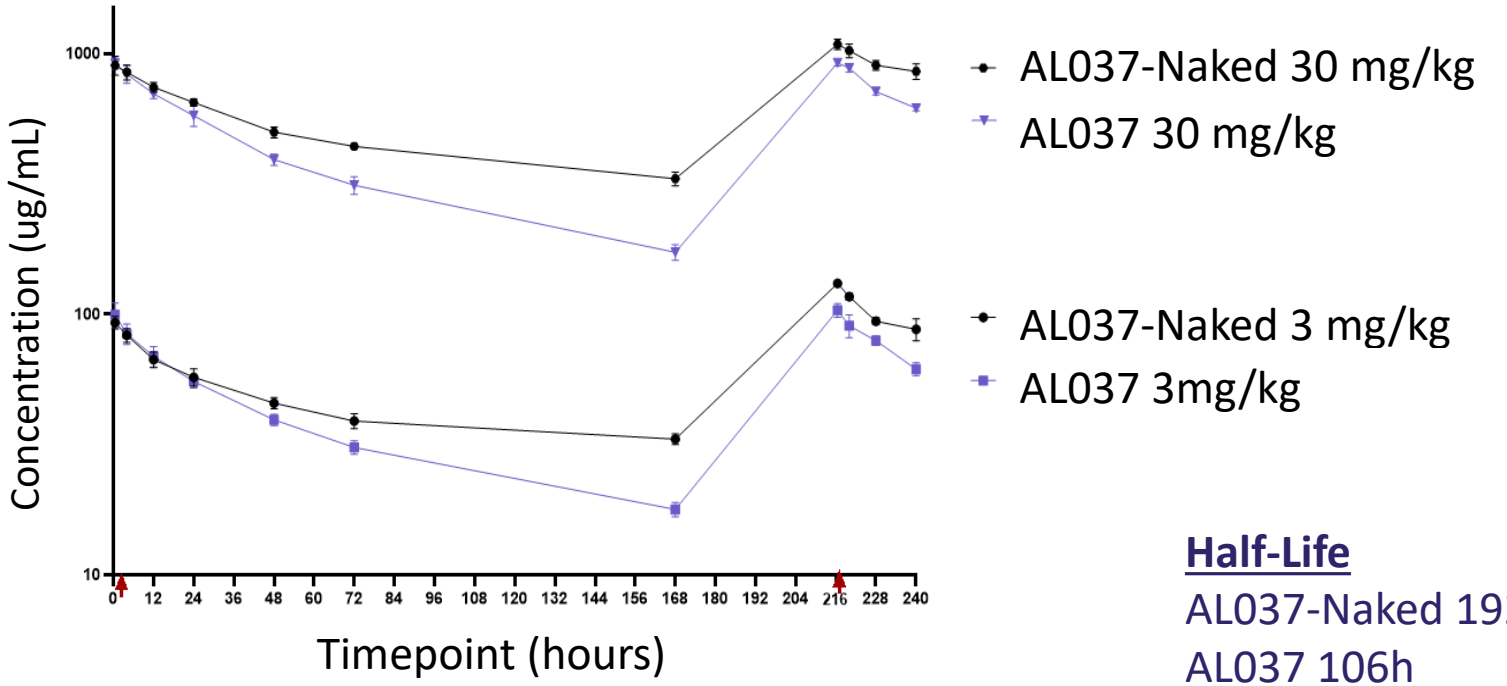
AL037 Displays Favorable Serum Pharmacokinetics in NHP

NHP

AL037 Displays an Estimated Serum Half-life of 106h



Half-Life

AL037-Naked 192h

AL037 106h

Treatment Regimen (Cynomolgus monkeys, N=3/group)

Two-Dose PK study with termination 24 hrs post 2nd dose

Three NHP per group were injected on days 1 and 9. Serum samples were analyzed for the levels of AL037-Naked (without the ABC platform) and AL037.

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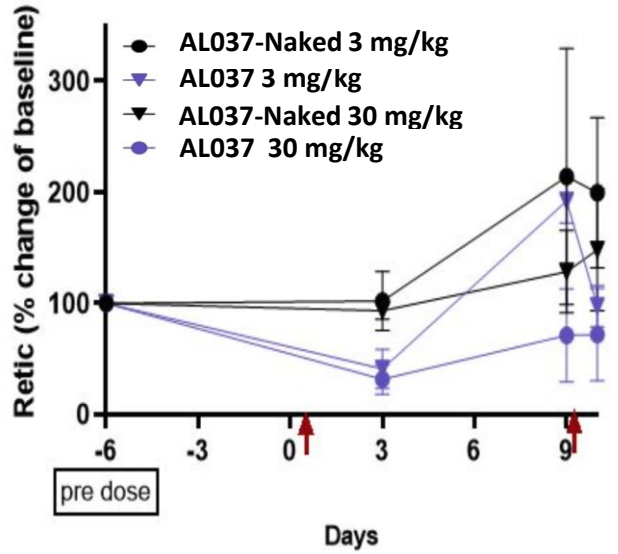
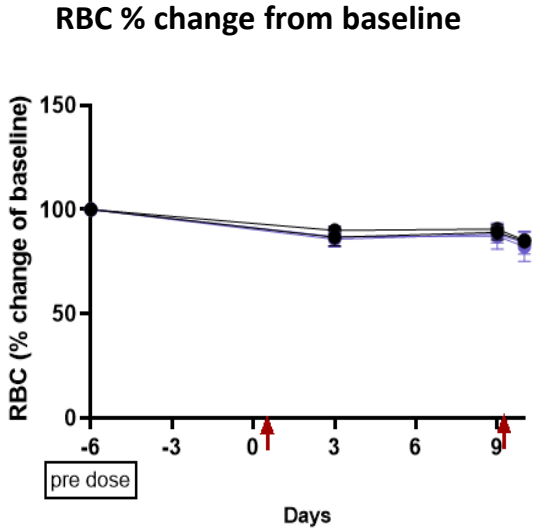
AL037 Impact on Reticulocytes RBC and Hemoglobin

NHP

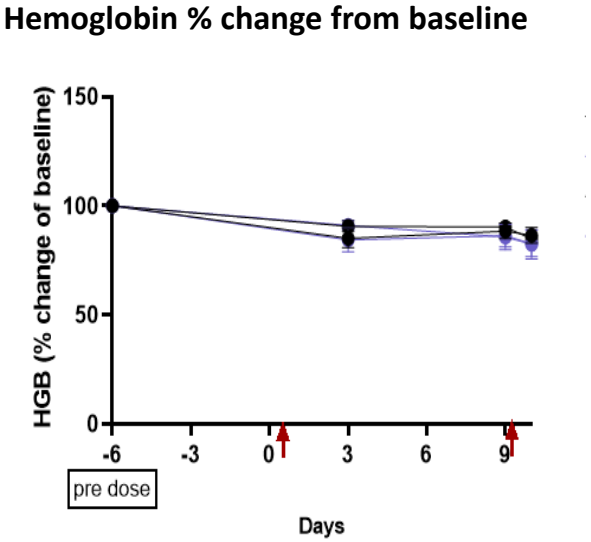
Reticulocyte Counts Quickly Recover



Red Blood Cell Counts Were Not Affected



Hemoglobin Levels Were Not Affected

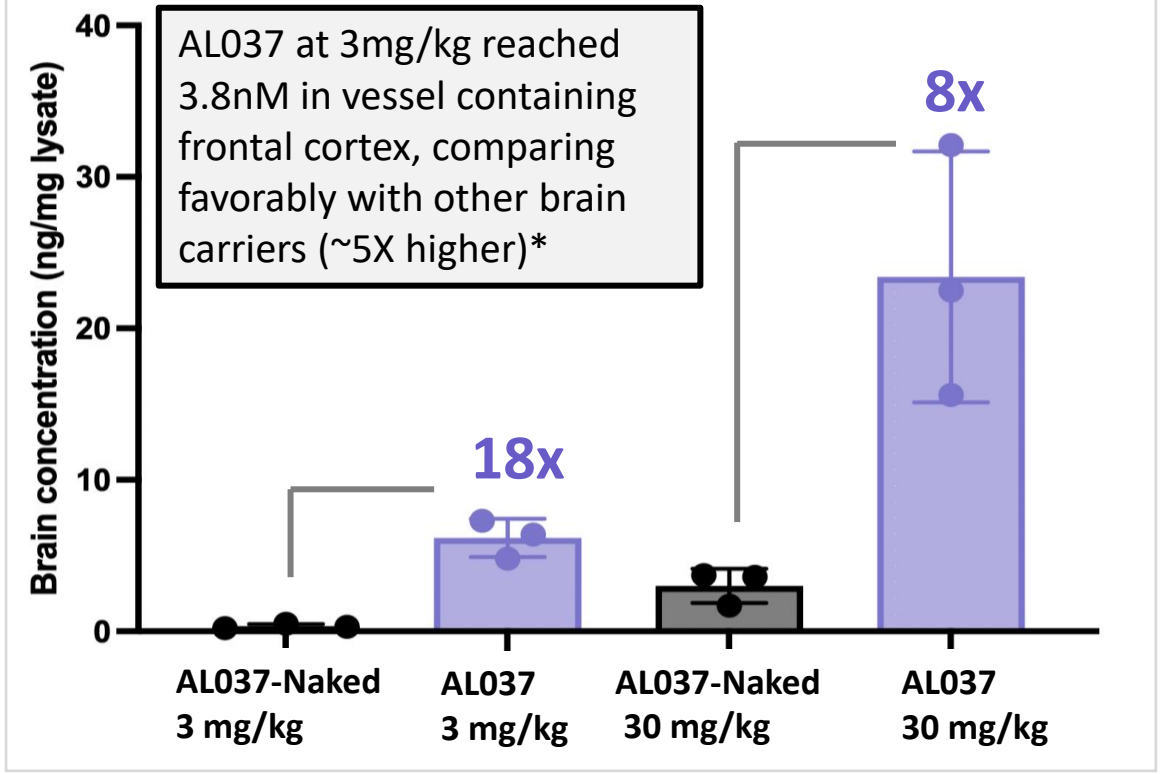


Three NHP per group were injected on days 1 and 9 (red arrows). Blood samples were analyzed for reticulocytes, red blood cell counts and hemoglobin levels at the indicated times. AL037 caused a transient decrease in reticulocytes but did not negatively impact red blood cell count. AL037-Naked = AL037 without ABC platform.

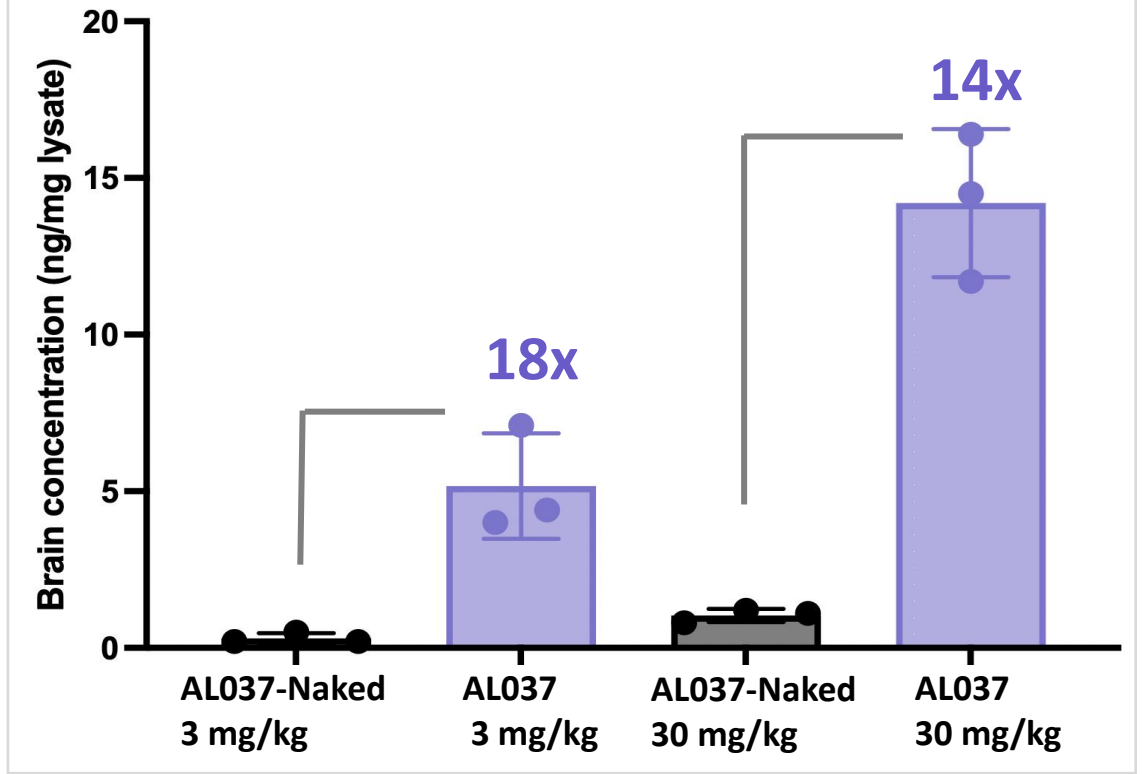
ABC Enhances Brain Uptake of AL037

NHP

Frontal Cortex



Hippocampus



*Three NHP per group were dosed on days 1 and 9. Brain tissues were collected 24 hours after the second injection and drug levels were measured in the vessel-depleted fraction. *E.g. According to our calculations, trontinemab is reaching 2.1nM in the NHP vessel-containing cortex 24h following a single injection of 10mg/kg (Grimm et al., MABS, 2023). AL037-Naked = AL037 without ABC platform.*

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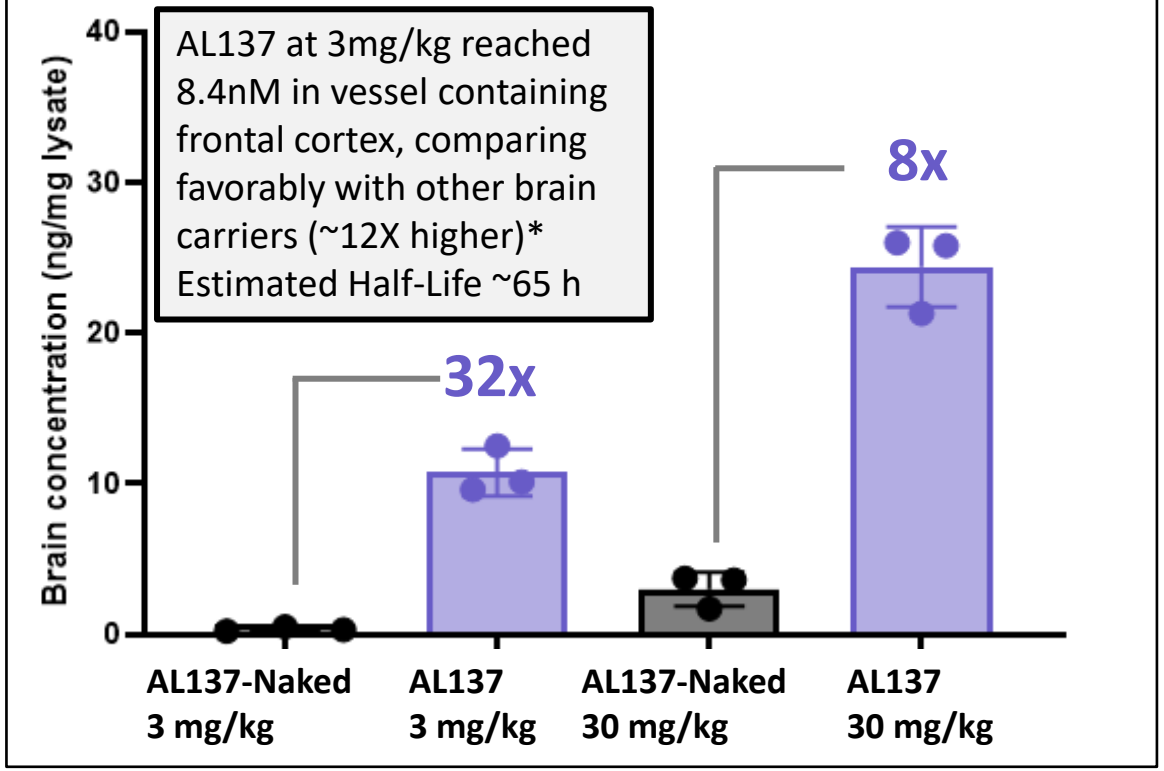
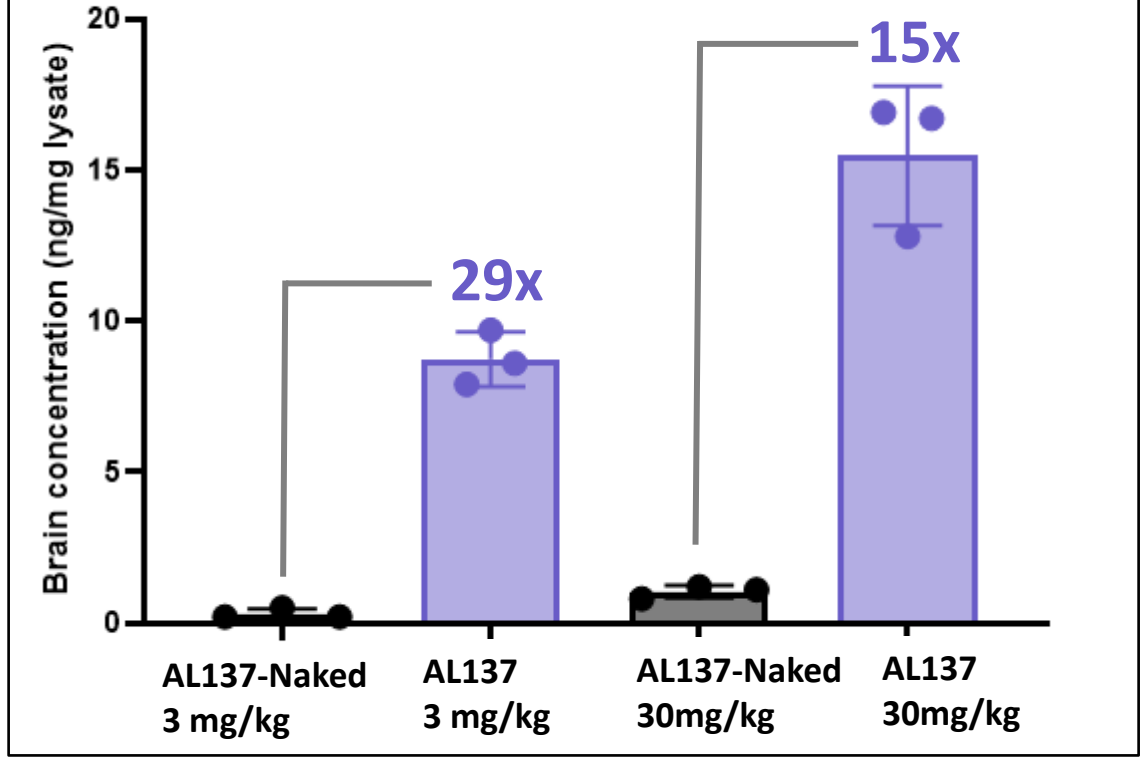
ABC Enhances Brain Uptake of AL137: A Second Anti-Aβ Antibody Lead

NHP

Frontal Cortex



Hippocampus



*Three NHP per group were dosed on days 1 and 9. Brain tissues were collected 24 hours after the second injection and drug levels were measured in the vessel-depleted fraction. AL137 is associated with a reduction in reticulocytes and different PK than AL037 (Data not Shown) *E.g. According to our calculations trontinemab reaches levels of 2.1nM in the NHP vessel-containing cortex 24h following a single injection of 10mg/kg (Grimm et al., MABS, 2023) and estimated half-life of 31h. AL137-Naked = AL037 without ABC platform.*

Summary and Conclusion

Alzheimer's Disease Impact:

- Approximately 24 million people worldwide affected by Alzheimer's disease[1]
- Aβ pathology remains a key driver of disease progression
- Significant unmet need for safe, effective, and convenient anti-amyloid therapies enabled by BBB tech

Design:

- AL037/AL137 were designed to treat Alzheimer's disease by delivering an ABC-enabled anti-Aβ antibody that targets PyroGlu3 Aβ with a fully active Fc region, to optimize for brain penetration safety and efficacy.

Demonstrated:

- Robust brain penetration (18-32-fold representing 3.8-8.4 nM with 3 mg/kg)
- Plaque engagement, microglial activation, and reduction of amyloid burden in preclinical models
- Adequate PK , transient effect on Reticulocytes and no apparent findings on RBC to date

Clinic Target:

- Targeting first-in-human trial in 2026

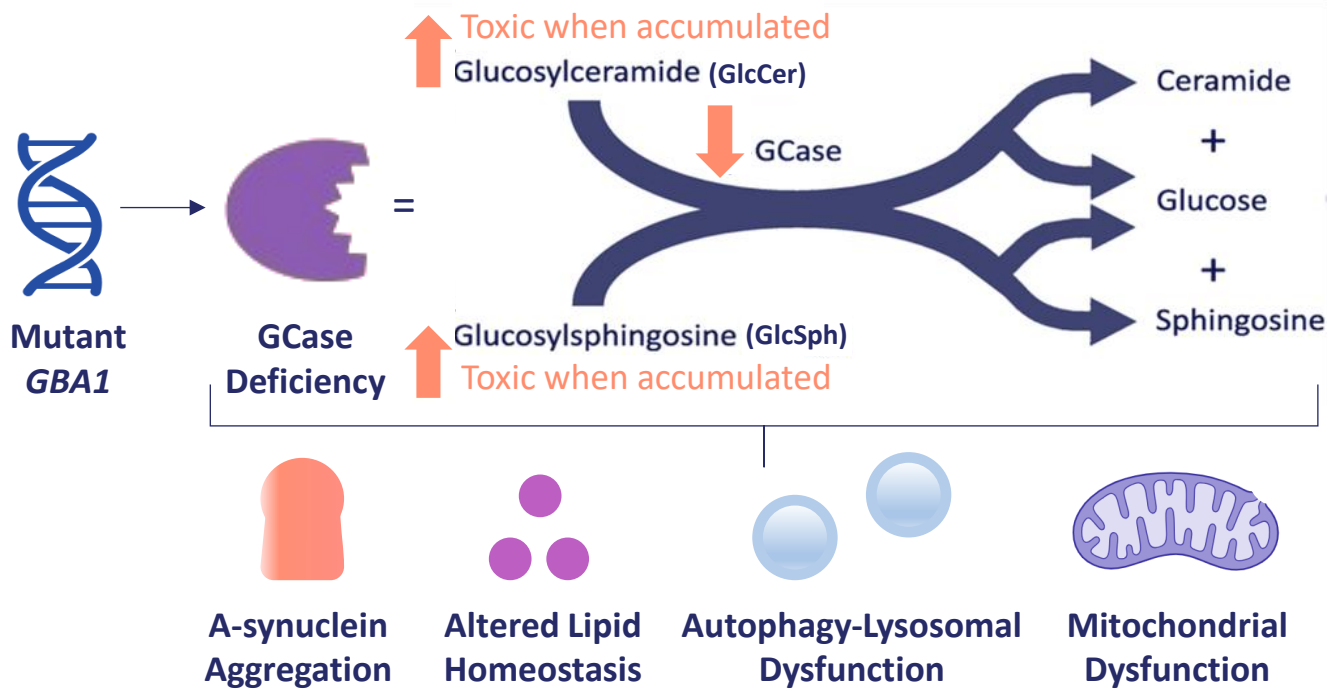
1. Mayeux R, Stern Y. Epidemiology of Alzheimer disease. Cold Spring Harb Perspect Med. 2012 Aug 1;2(8):a006239.

AL050: Alector Brain Carrier (ABC)—Enabled GCase ERT for Parkinson's Disease

GBA1 Gene Mutations Are a Major Risk Factor for Neurodegenerative Diseases

GBA1 mutations lead to reduced **GCase enzyme activity** and toxic substrate accumulation (GlcCer and GlcSph) in the brain.

No therapy has effectively restored GCase activity in the brain: Current GCase enzyme replacement therapy does not enter the brain

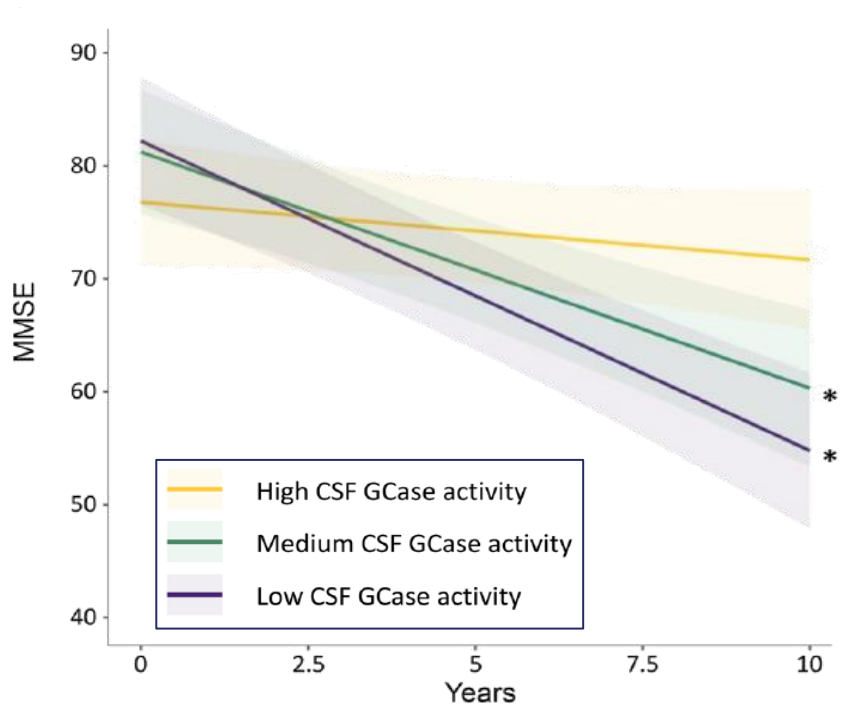


- **Parkinson's Disease (PD)**
  - ~10 million patients worldwide[1]
  - 0.5-1.5 millions are GBA1 mutation carriers[2]
  - Activity is reduced in non-carriers[2]
- **Gaucher's Disease (GD)**
  - ~125,000 patients with GBA1 mutation worldwide[5]
  - GD type 1 have increased risk of PD[6]
  - GD type 2 and 3 are neuronopathic[7]
- **Lewy Body Dementia (LBD)**
  - ~5-8 million patients worldwide[3]
  - 0.15--2.4 millions are GBA1 mutation carriers[4]
  - Activity is reduced in non-carriers[4]

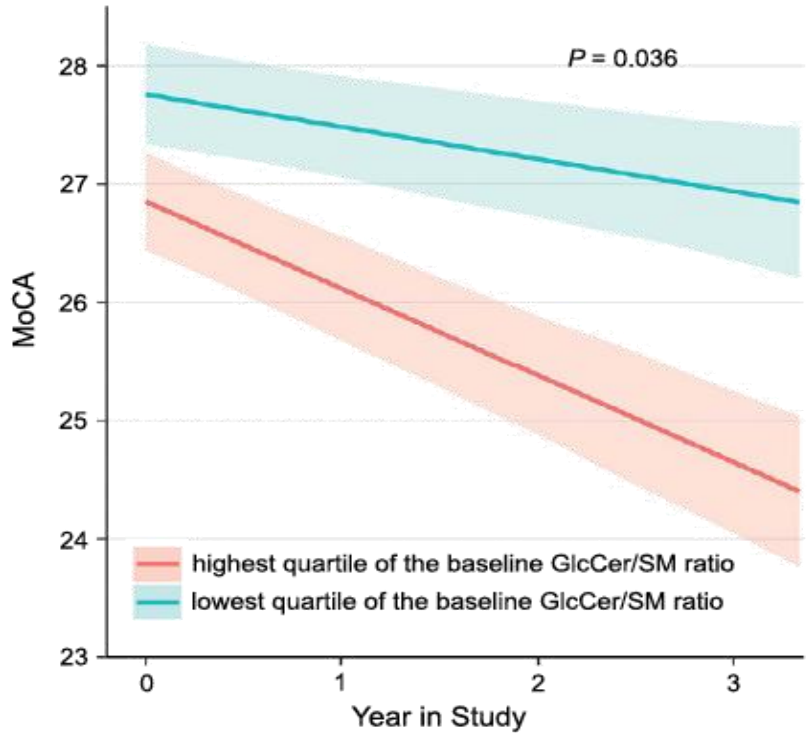
1. Parkinson's Foundation Statistics
2. Smith L, Schapira AHV. GBA Variants and Parkinson Disease: Mechanisms and Treatments. *Cells*. 2022 Apr 8;11(8):1261.
3. Alzheimer's Disease International, Dementia with Lewy Bodies
4. Nalls MA, et al. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. *JAMA Neurol*. 2013 Jun;70(6):727 - 35.
5. Meikle PJ, et al. Prevalence of lysosomal storage disorders. JAMA. 1999 Jan 20;281(3):249 - 54.
6. Bultron G, et al. The risk of Parkinson's disease in type 1 Gaucher disease. *J Inherit Metab Dis*. 2010 Apr;33(2):167 - 73.
7. National Gaucher Foundation, Gaucher Disease Types 2 and 3

Rationale for GCase ERT in Parkinson's Disease

Parkinson's Disease Patients with Lower CSF GCase Activity at Diagnosis Progress Faster



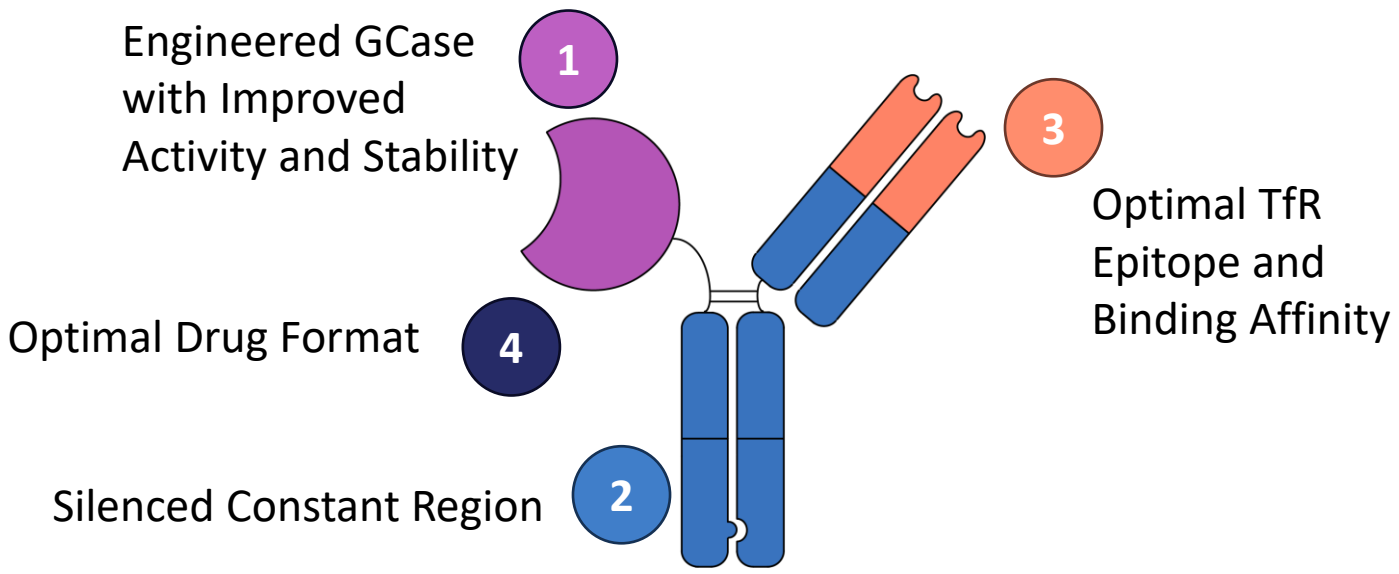
Parkinson's Disease Patients with Higher CSF Toxic Substrate Levels at Diagnosis Progress Faster



These Findings Support the Hypothesis that Brain Penetrant GCase ERT Could Slow Parkinson's Disease Progression

2021 Huh et al. *NPJPD* Glucosylceramide in cerebrospinal fluid of patients with GBA - associated and idiopathic Parkinson's disease enrolled in PPMI
2023 Oftedal et al. *Translational Neurodegeneration* Early GCase activity is a predictor of long-term cognitive decline in Parkinson's disease

Optimized Design of AL050: ABC-Enabled GCase Enzyme Replacement Therapy (ERT)



Targeted Design Features

Potency

- Engineered enzyme that is more active and stable than the WT enzyme and effectively enters the brain

Safety

- ABC with tuned affinity and binding epitope and a silenced FcgR binding domain seeks to minimize hematologic adverse effects

Convenience

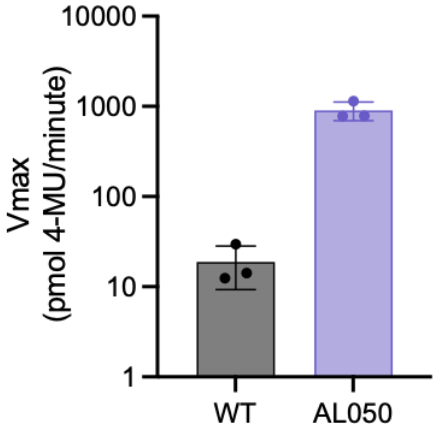
- ABC enables potential for low-dose regimen and monthly dosing

AL050 Stability

Enzyme	Mutations	Tm ℃	Half-life at 37℃
Wild-type	n/a	57.5	~ 6.0 hrs
AL050	<5 AA	64.9	> 7-days

Determined in monovalent - Fc format

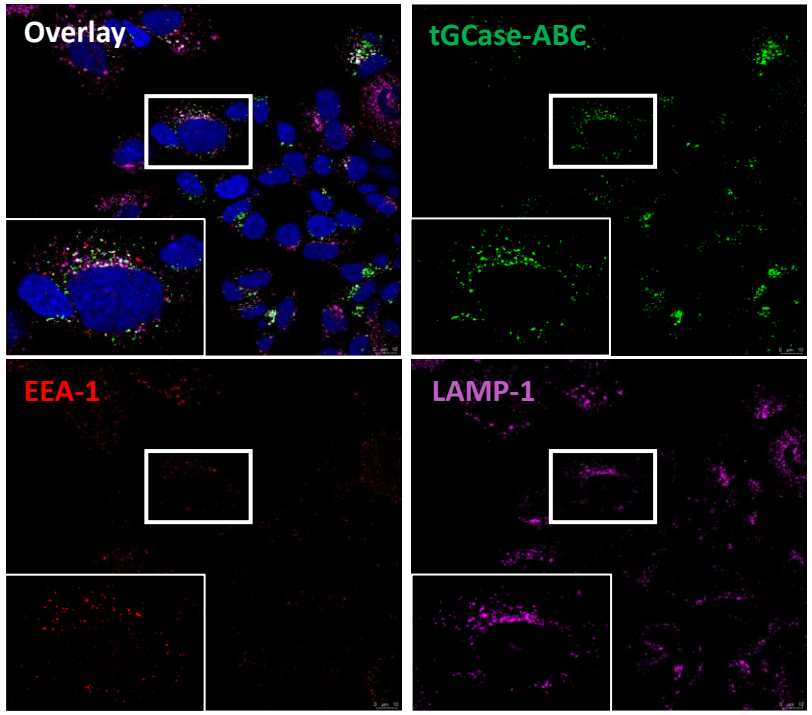
AL050 Activity



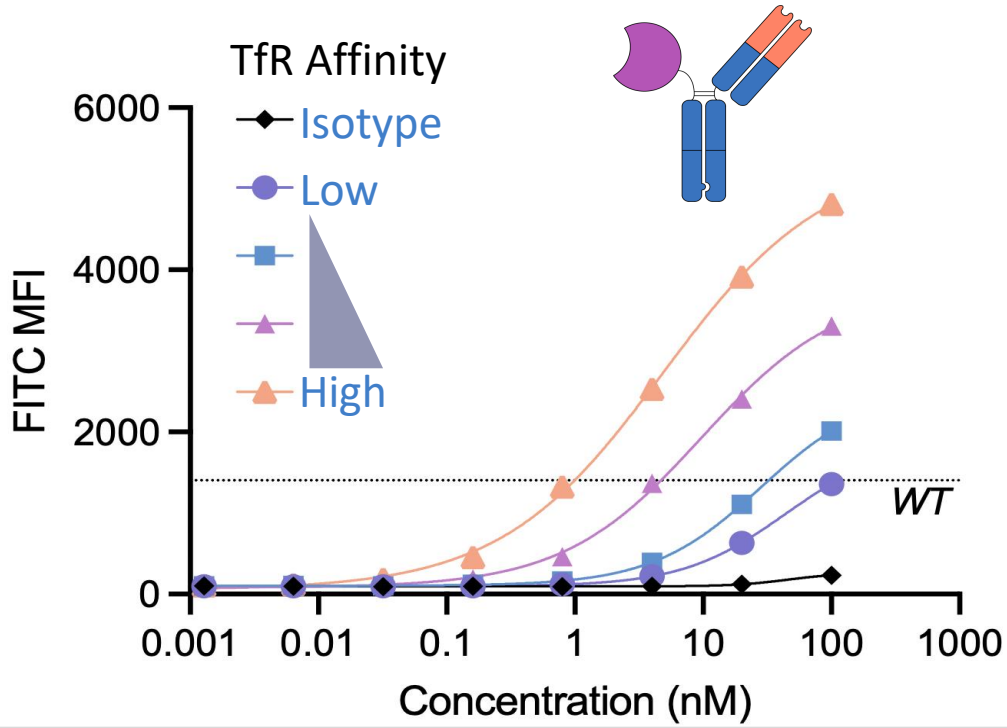
alector™ Alector data on file

AL050 Affinity Was Optimized for Cell Rescue and Lysosomal Uptake

GCase-ABC Is Delivered to the Lysosomes of GBA1$^{-/-}$ Neuroblastoma Cells



Ability of AL050 to Rescue GCase Activity in GBA1$^{-/-}$ Neuroblastoma Cells Is TfR-Affinity-Dependent



Left: GBA1$^{-/-}$ SH-SY5Y cells were incubated with 100nM toolGCase-TfR for 2h. Cell uptake was determined by confocal microscopy with antibodies against EEA-1 (early endosomes), LAMP-1 (lysosomes), and anti-human Fc (tGCase-TfR). Nuclei: DAPI (blue).
Right: GBA1$^{-/-}$ SH-SY5Y cells were incubated with increasing concentrations of AL050-ABC at different anti-TfR affinities for 2 hours. GCase activity was measured by flow cytometry using the GCase fluorescent substrate PFB-FDGlu (1h incubation).

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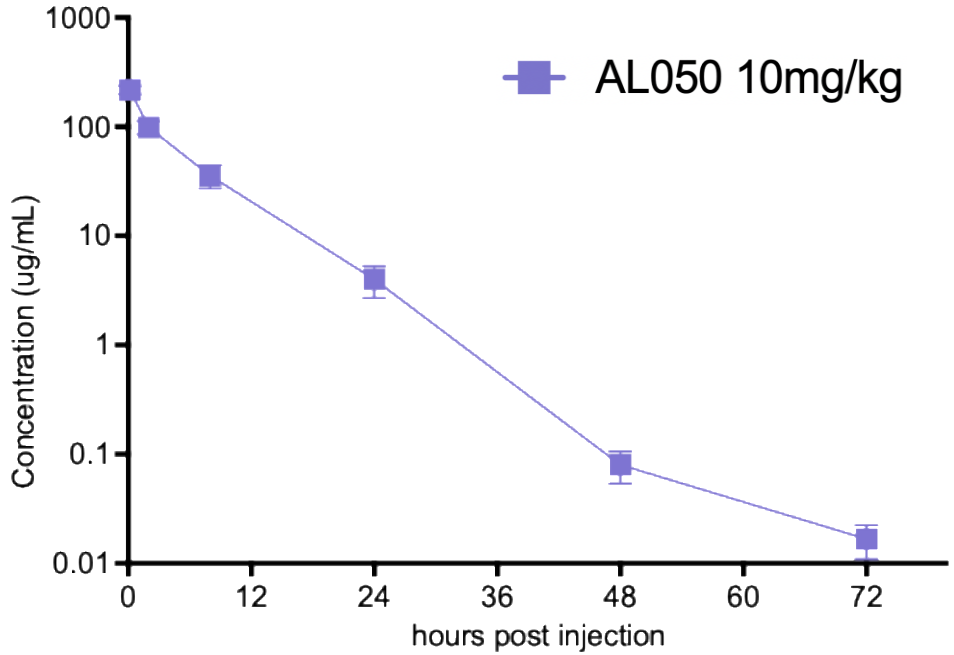
AL050 Displays ~10 Fold Longer Half-Life in NHP Plasma Compared to Current GCase ERTs

NHP

AL050 Displays Plasma Half-Life of ~5 hours in NHPs



Treatment Regimen (Cynomolgus monkeys, N=3/group)

Two-Dose PK study with termination 24 hrs post 2nd dose

Current GCase ERTs Display Protein Half-Life of 5 to 30 Minutes in Plasma

Imiglucerase:

Displays terminal t½ up to for ~20–30 min **in human patients**

Taliglucerase alfa:

Displays terminal t½ of ~25min **in human patients**

Velaglucerase alfa:

Displays terminal t½ of 5-12 min **in NHP**

- European Medicines Agency (EMA), **Cerezyme EPAR – Scientific discussion**. European Medicines Agency (EMA)
- Therapeutic Goods Administration (TGA, Australia), **AusPAR: Velaglucerase alfa (VPRIV)**. Therapeutic Goods Administration (TGA)
- EMA, **VPRIV EPAR – Public assessment report** European Medicines Agency (EMA)
- TGA, **AusPAR:** Taliglucerase alfa (Elelyso)

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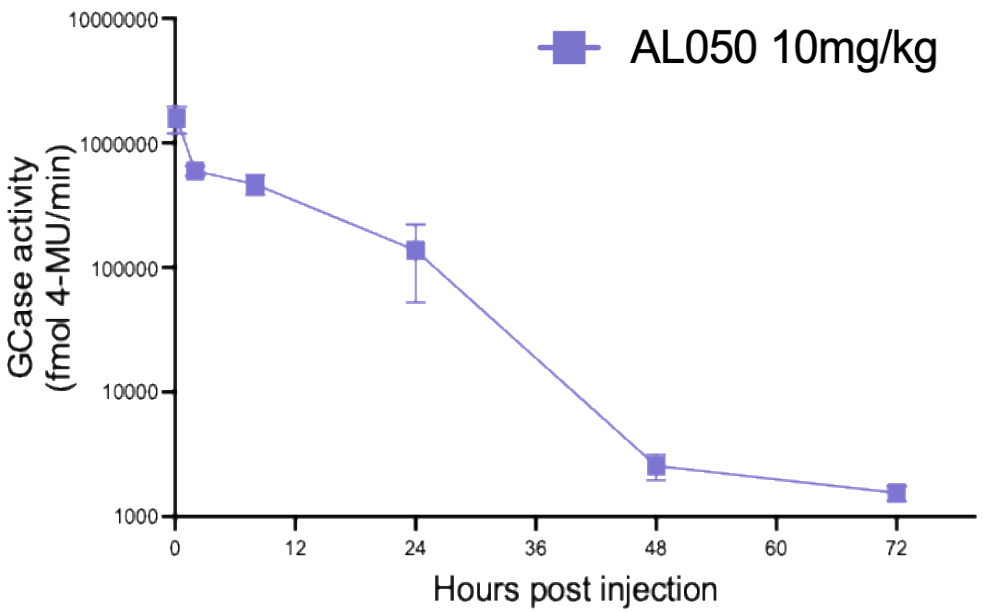
AL050 Displays ~40 Fold Longer Enzymatic Activity in NHP Plasma Compared to Current GCase ERTs

NHP

AL050 Displays GCase Enzymatic Activity Half-Life of ~6.6 hours in NHP Plasma



Treatment Regimen (Cynomolgus monkeys, N=3/group)

Two-Dose PK study with termination 24 hrs post 2nd dose

Current GCase ERTs Display Enzymatic Activity Half-Life of 4 to 10 Minutes in Plasma

Imiglucerase:

T½ Enzymatic Activity 3.6 – 10.4 min. in **human patients**

Velaglucerase alfa:

T½ Enzymatic Activity 4.0 – 4.7min. in **NHP**

- European Medicines Agency (EMA), **Cerezyme EPAR – Scientific discussion**. European Medicines Agency (EMA)
- Therapeutic Goods Administration (TGA, Australia), **AusPAR: Velaglucerase alfa (VPRIV)**. Therapeutic Goods Administration (TGA)
- EMA, **VPRIV EPAR – Public assessment report** European Medicines Agency (EMA)

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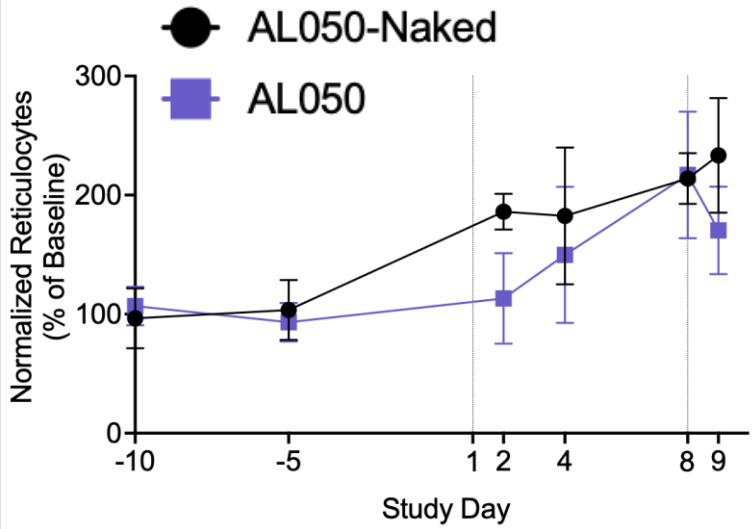
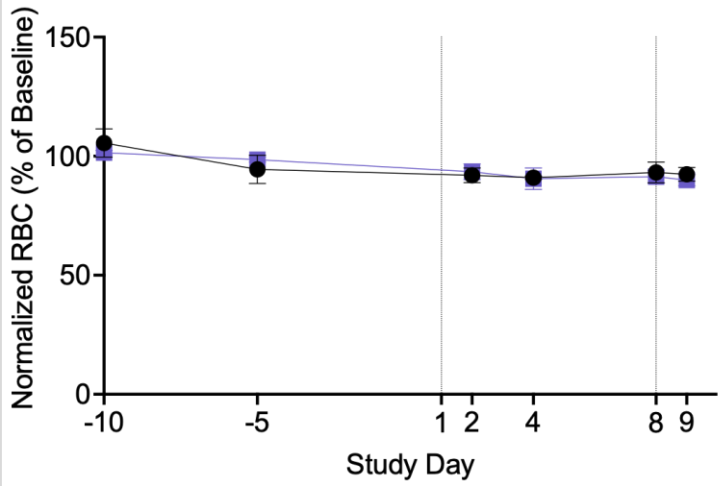
AL050 Did Not Negatively Impact Reticulocytes, RBC Count or Hemoglobin Levels

NHP

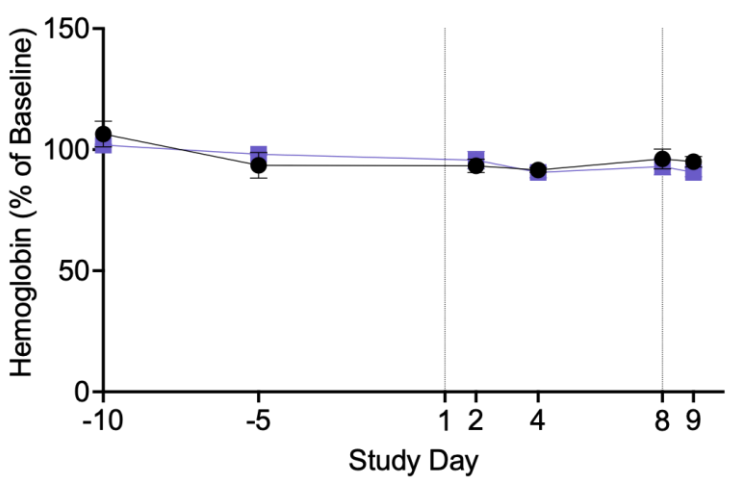
Reticulocyte Counts in Normal Range



Red Blood Cell Counts Were Not Affected



Hemoglobin Levels Were Not Affected



Three NHP per group were injected on days 1 and 8 (vertical lines). Blood samples were analyzed for reticulocytes, red blood cell counts and hemoglobin levels at the indicated times. Increase in reticulocytes was observed in all groups due to frequent blood collections.
AL050-Naked = AL050 without ABC platform.

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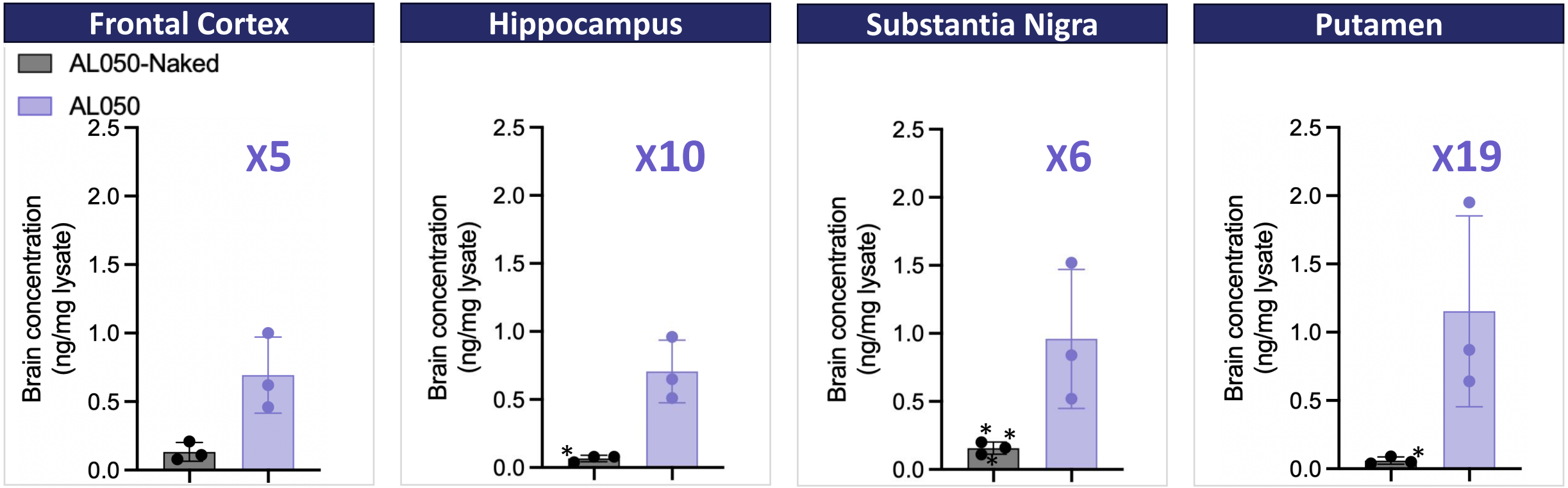
NHP

ABC Enhances Brain Delivery of Engineered GCase Cargo by 5- to 19-Fold



Three NHP per group were injected on days 1 and 8. Brain tissues were collected 24 hours after the second injection and drug levels were measured in the vessel-depleted fraction.
AL050-Naked = AL050 without ABC platform.

*Samples below lower limit of detection graphed at LLOD.

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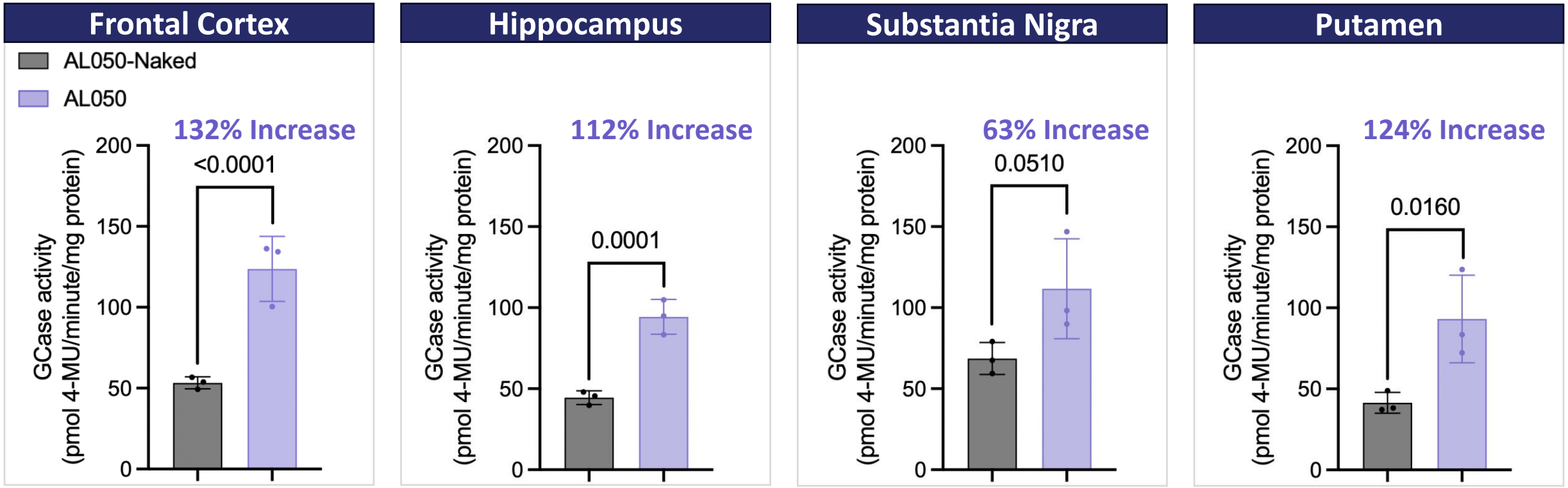
AL050 Increases GCase Activity in the Brain of NHPs by >2-Fold



Three NHP per group were injected on days 1 and 8 and brain tissues were collected 24 hours after the second injections. GCase enzymatic activity was determined using a 4-MUG kinetic assay (graphs represent the combination of endogenous NHP GCase and AL050. AL050-Naked = AL050 without ABC platform.

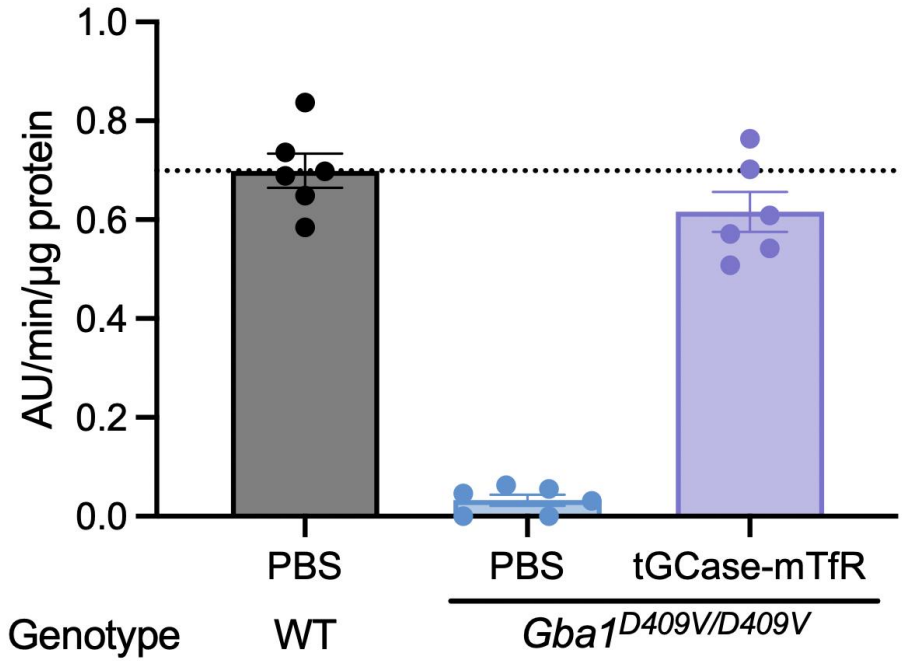
Alector data on file

One way ANOVA with Dunnett's multiple comparison test

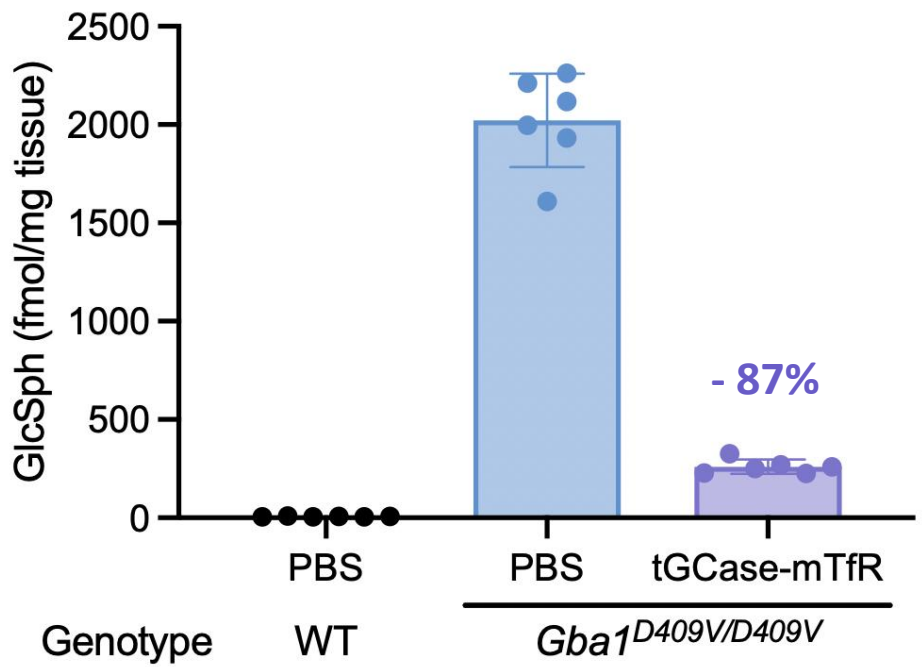
AL050 Surrogate Rescues GCase Activity and Reduces Toxic Substrate Accumulation in Peripheral Tissues of *Gba1*-Mutant Mice

MOUSE

Liver GCase Activity is Rescued 24h After Injection



Liver GlcSph Levels are Reduced by 87% 24h After a Single Dose of AL050-TfR-Surrogate

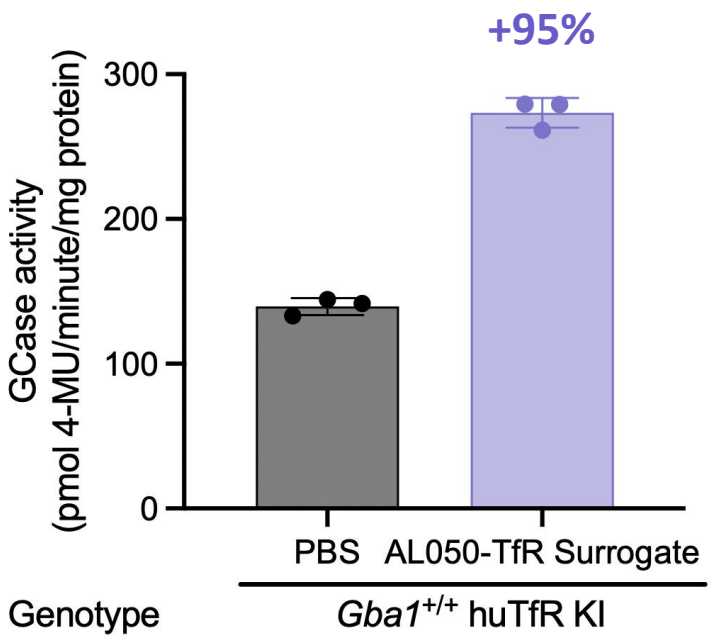


Wild-type or Gba1-mutant mice were injected once with PBS or 10mg/kg toolGCase-anti-mouse-TfR. Liver samples were collected 24h after injection. GCase activity was determined using a 4-MUG kinetic assay on liver lysates and GlcSph was quantified by LC-MS/MS.

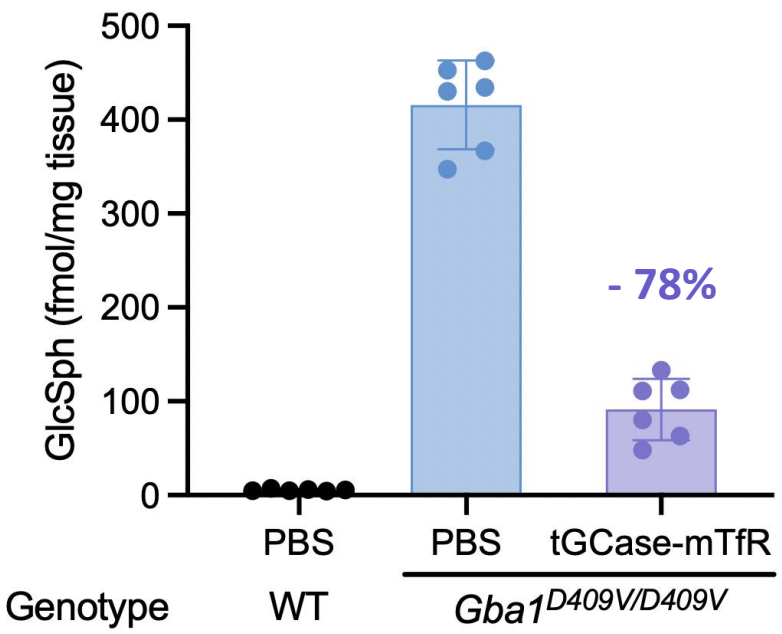
AL050 Surrogate Rescues Brain GCase Activity and Reduces Toxic Substrate Accumulation in the Brain of *Gba1*-Mutant Mice

MOUSE

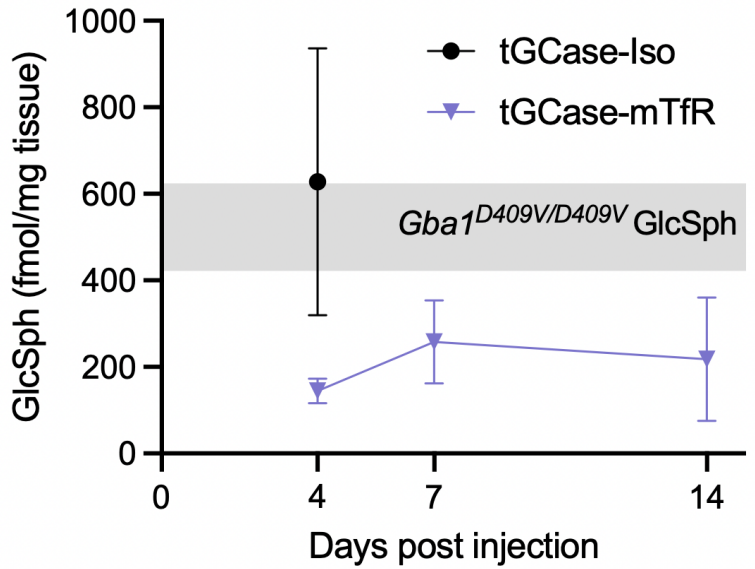
GCase-ABC Increases Brain GCase



GCase-ABC Reduces GlcSph by ~80% 8dpi



Durable Reduction in Brain GlcSph



Wild-type or Gba1-mutant mice were injected once (left, right) or twice (middle) with PBS, or 10mg/kg toolGCase-Iso, AL050-TfR Surrogate *(left), or toolGCase-anti-mouse-TfR (middle, right). GCase activity (left) was determined by 4-MUG kinetic assay in vessel-depleted brain lysates. Brain GlcSph concentration (middle, right) was determined by LC-MS/MS.*

Summary and Conclusion

GBA1 Gene Mutation Impact:

- Up to 1 million Parkinson's disease (PD) cases are associated with *GBA1* gene mutations
- Up to 2.4 million Lewy body dementia (LBD) cases are associated with *GBA1* gene mutations
- Approximately 125,000 Gaucher disease (GD) cases are caused by *GBA1* gene mutations

AL050 Design:

- AL050 was designed to address GCase deficiencies in PD, LBD, and GD by enhancing GCase, encoded by the *GBA1* gene, delivery to the brain

AL050 Demonstrated:

- Superior activity and stability in vitro and in NHP compared to current GCase ERT
- Superior PK in the NHP plasma compared to current GCase ERT
- Good brain penetration and doubling of enzymatic activity in the NHP

Clinic Target:

- Targeting first-in-human trial in 2027

Alector Brain Carrier (ABC)—Enabled siRNA Programs

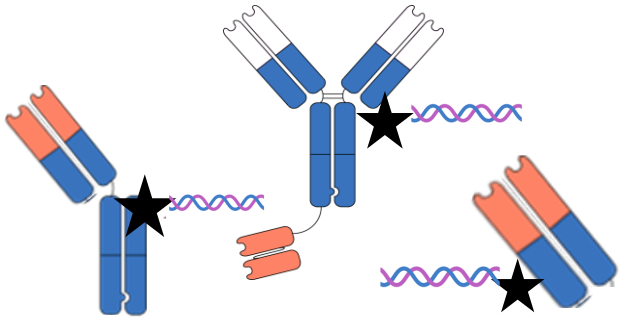
SiRNA-ABC: Designed to Support Effective Brain Distribution with Peripheral Delivery

POTENTIAL ADVANTAGES

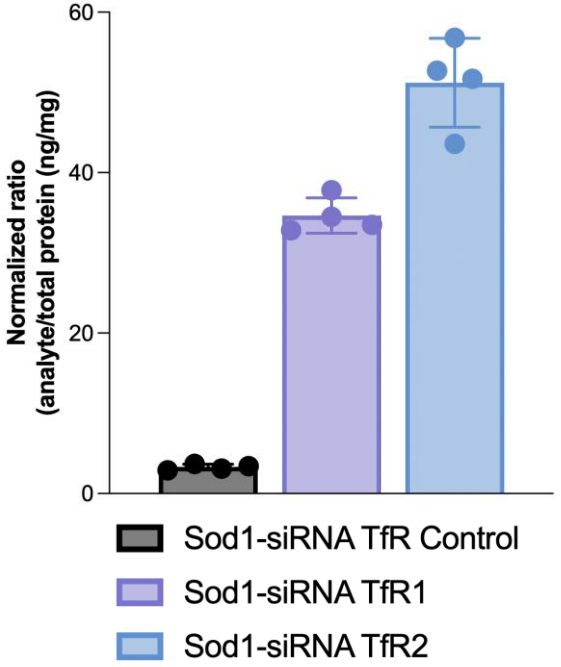
- Safer than IT, ICV delivery
- Better efficacy due to homogeneous brain distribution
- Ease and convenience of use
- Scalable to a large patient population
- Applicable for brain and peripheral tissue delivery

PARAMETERS TESTED

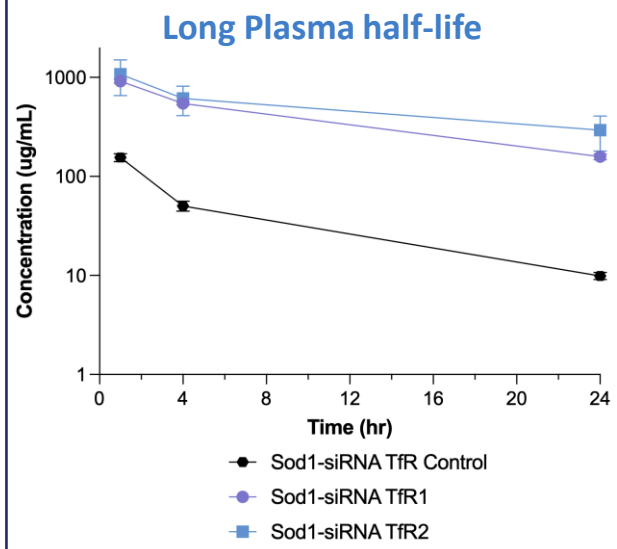
- ~1,000-fold range of TfR affinities
- Multiple drug configurations
- Multiple siRNA linkers *(cleavable, e.g., Val-Cit and non-cleavable, e.g., SMCC)*
- Multiple siRNA modifications (*e.g., 2'-OMe, PS, etc)*



FOLD BRAIN PENETRATION

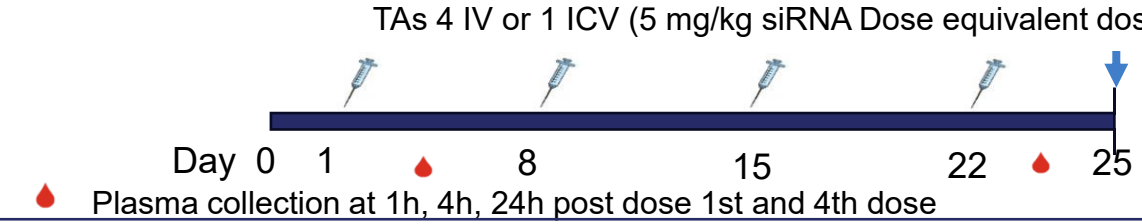


PHARMACOKINETICS



**The control represents a less effective drug configuration*

EXPERIMENTAL PROTOCOL



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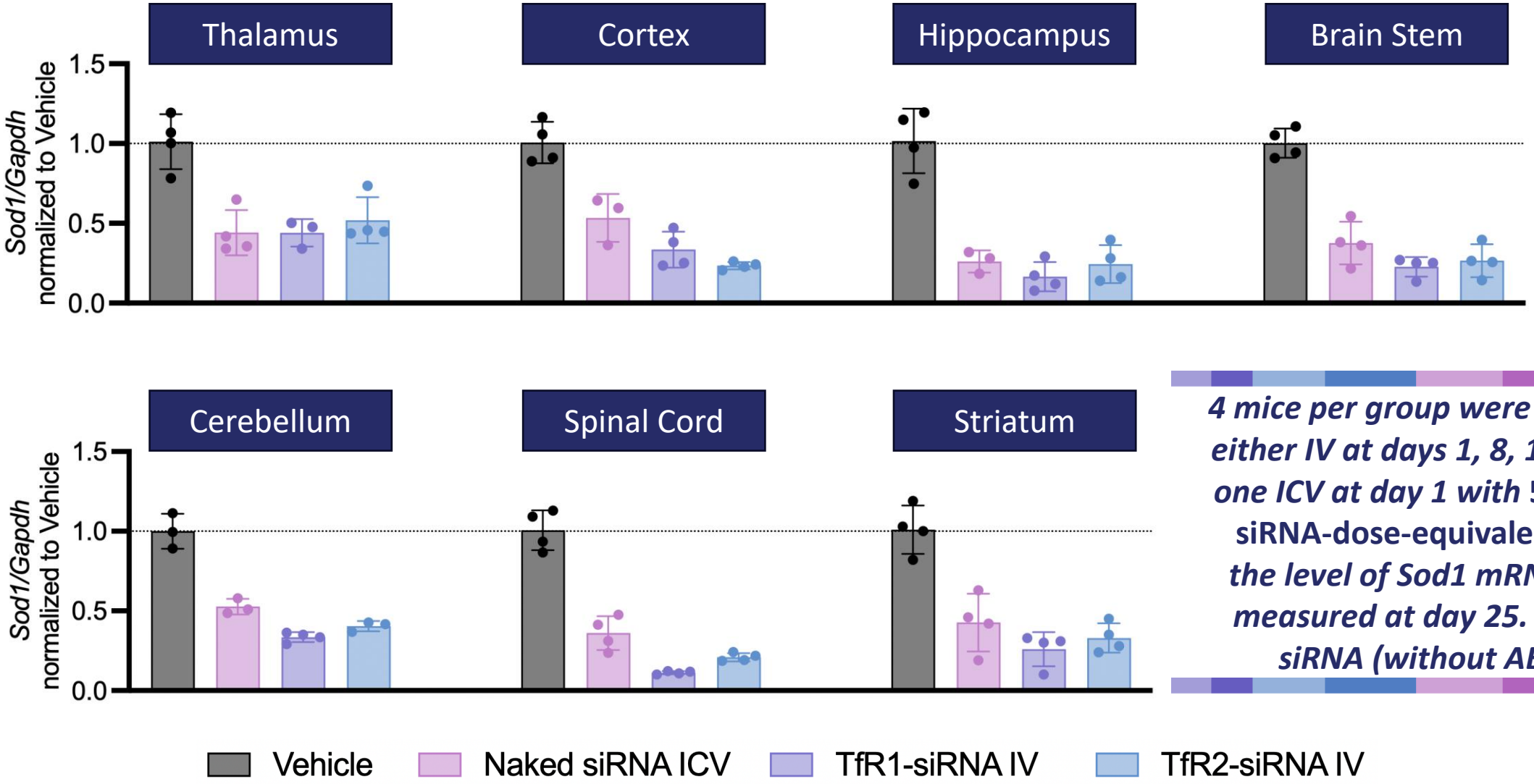
SOD1- Superoxide dismutase

Peripheral Delivery of SOD1 siRNA-ABC: 50-80% Knockdown Across Multiple Brain Structures



4 mice per group were injected either IV at days 1, 8, 15, 22 or one ICV at day 1 with* 5 mg/kg siRNA-dose-equivalent *and the level of Sod1 mRNA was measured at day 25. Naked siRNA (without ABC).

Developing a Platform of siRNA-ABC Drugs

Tau-siRNA-ABC: For Alzheimer's Disease and Frontotemporal Dementia

Syn-siRNA-ABC: For Parkinson's Disease and Lewy Body Dementia

NLRP3-siRNA-ABC: For Multiple Neurodegenerative Diseases

Alector is Focused on Opportunities to Drive Near- and Long- Term Value

Alector's Current Focus & Priority Goals

DELIVER LATE - STAGE CLINICAL PROGRAMS

- **Latozinemab** Ph 3 data in FTD-*GRN* by mid-Q4 2025
- **AL101** Ph 2 study in AD, with enrollment completed in April 2025

ADVANCE PROGRAMS TO CLINIC

Alector Brain Carrier applied to:

- **Antibodies:** Anti-Aβ-ABC For AD
- **Enzymes:** GCase-ABC For PD, LBD, GD
- **siRNA: Tau-siRNA-ABC** for AD, FTD; **a-Syn-siRNA-ABC** for PD, LBD; **NLRP3-siRNA-ABC** for AD, PD, ALS, MS, HD

FUTURE POTENTIAL TO EXPAND PORTFOLIO

- Novel 3R (Replace, Remove, Restore) drugs for degenerative brain disorders
- Well-resourced to continue advancement of our ABC pipeline
- Clear, value-creating catalysts through 2026–2027

Thank You