Enhancing Alector's pipeline with Alector Brain Carrier (ABC) Platform

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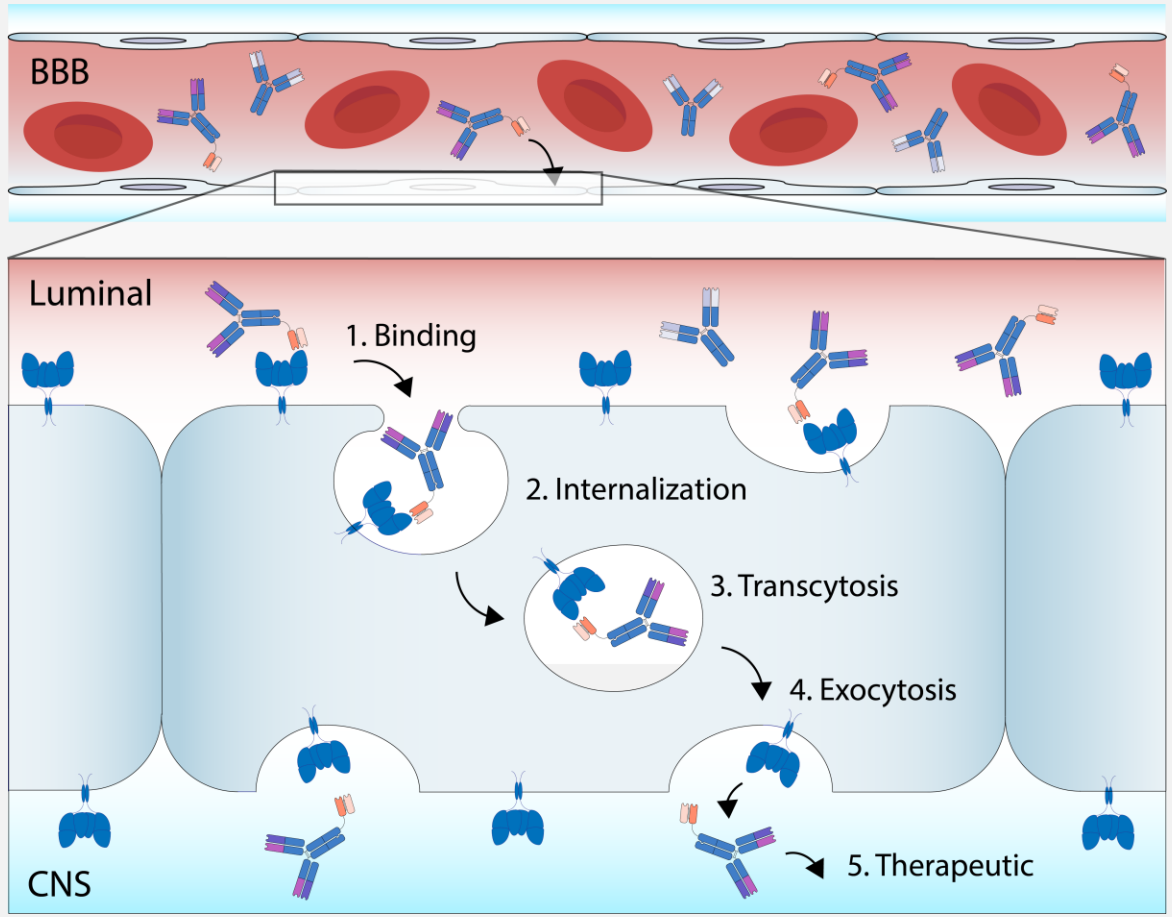
Alector Brain Carrier (ABC) is Designed for Effective Brain Delivery

Alector Brain Carrier (ABC)

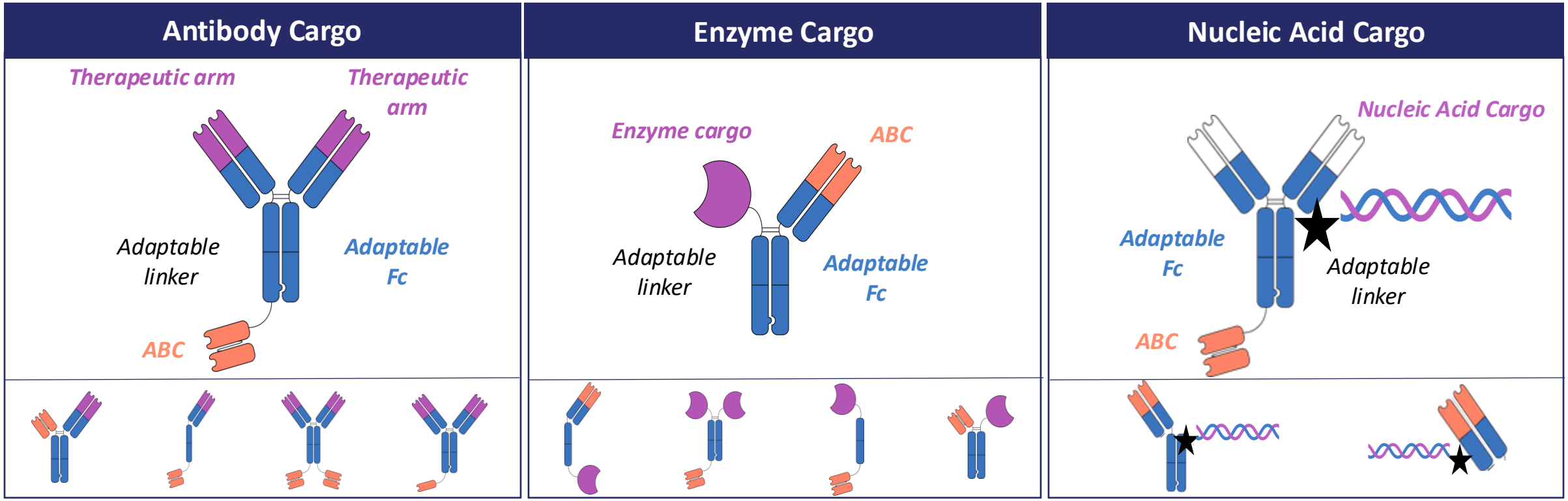
- BBB technology that enables **non-invasive peripheral delivery** of therapeutics to the brain
- **Versatile** and **tunable** design seeks to optimize **efficacy** and **safety**
- Validated for brain uptake with **multiple therapeutic cargos**
- Enables the potential to **widen the therapeutic window** while **lowering the costs of goods** and facilitating **convenient delivery** options

Receptor-Mediated Transcytosis



alector™ Alector Brain Carrier is herein abbreviated as ABC

Alector's Versatile Drug Configurations are Tailored to the Cargo



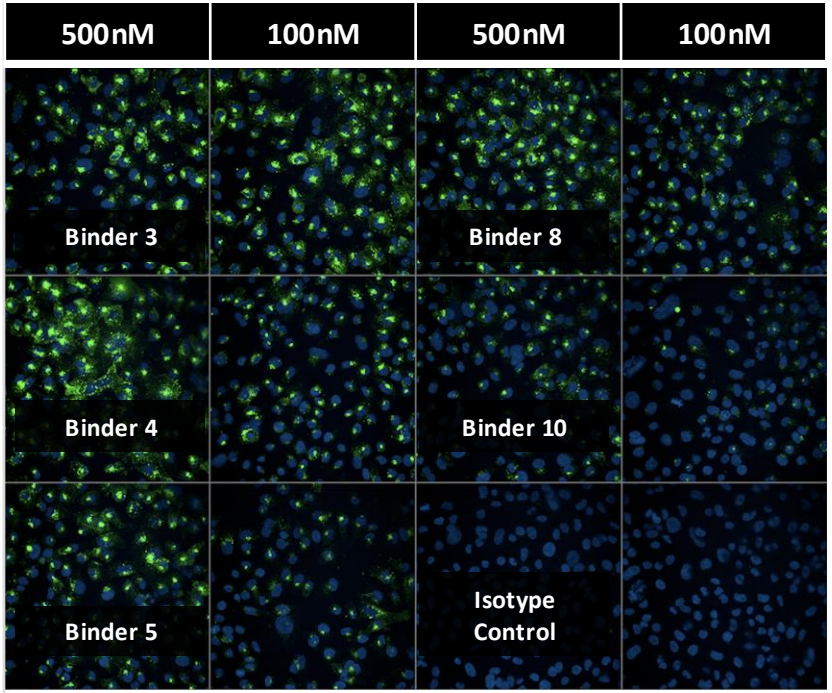
Versatile Configurations, Orientations and Linkers that are Optimal for Different Cargo

Adaptable TfR Binding Affinities for a Variety of Cargos

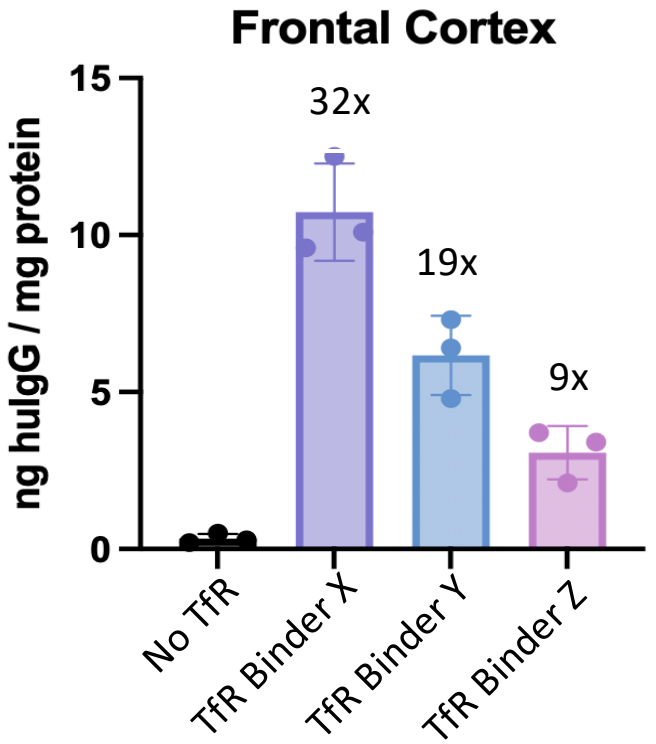
1000-Fold Affinity Range Tailored to Antibodies, Enzymes, and siRNA

TfR Binder	K_D (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



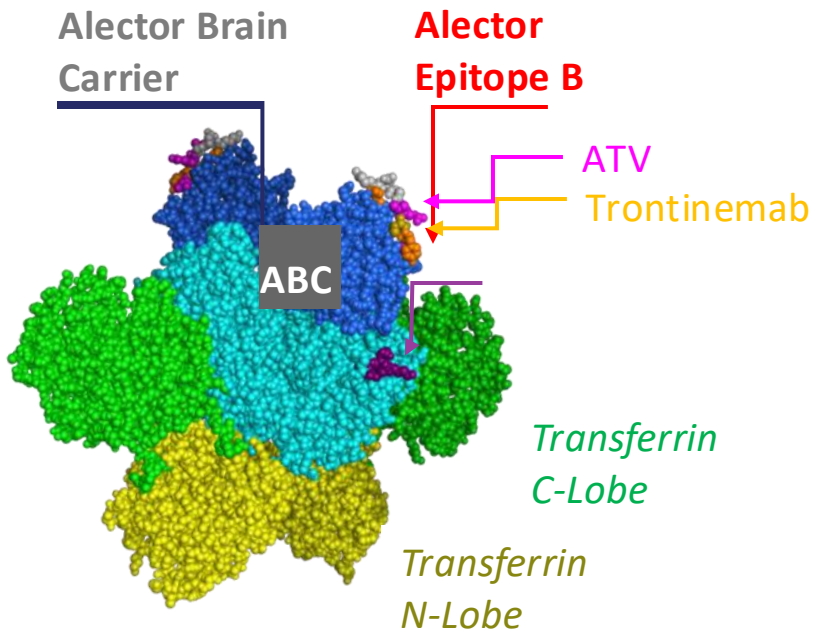
TfR Affinity-Dependent Entry to the Frontal Cortex of NHP



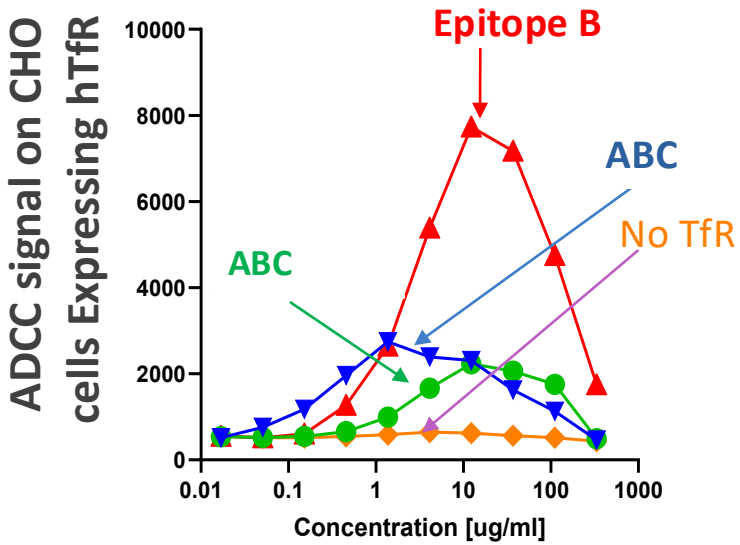
ABC Epitope is Associated with Reduced ADCC and Lower Reticulocyte Loss

For antibody cargo that requires Fc effector function

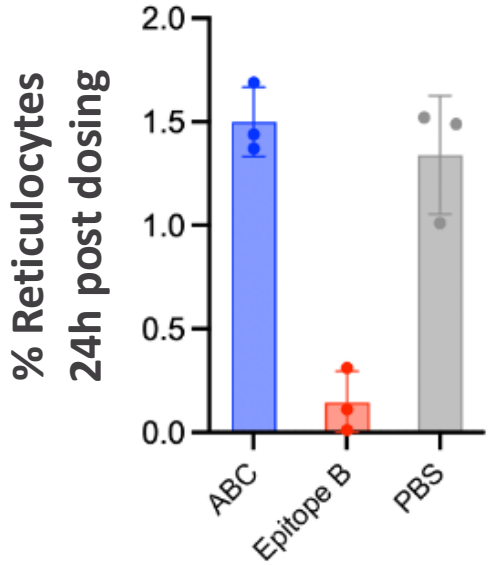
Structure of the Human Transferrin Receptor Bound to TfR and Binding Epitopes of Distinct BBB Approaches



TfR Dependent ADCC is Determined by the TfR Binding Epitope

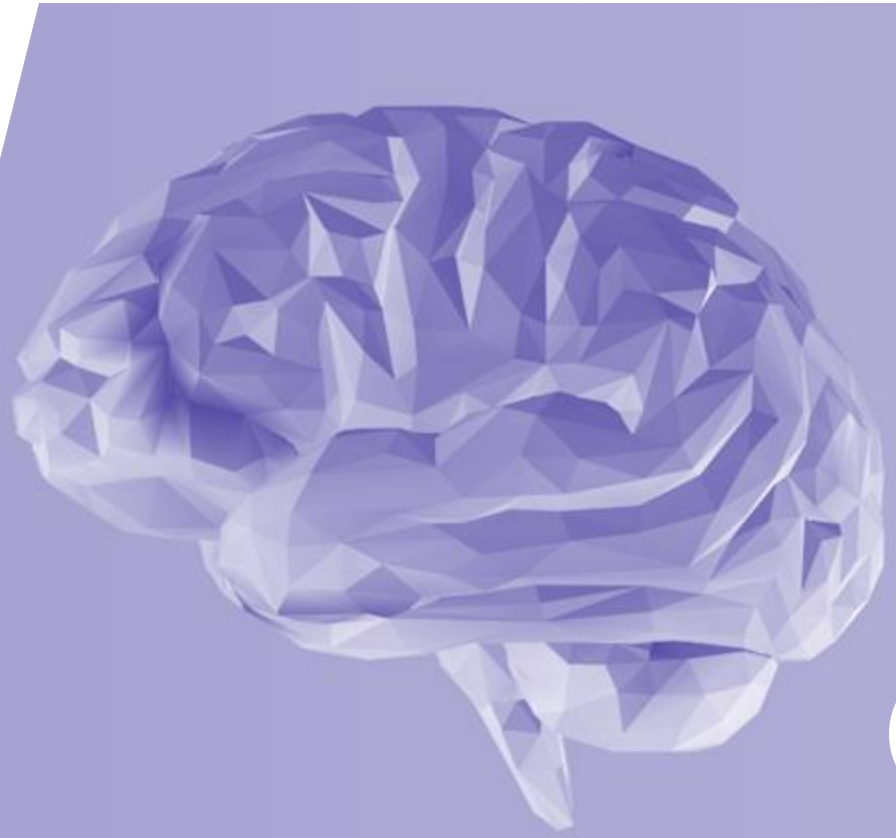


Alector's TfR ABC Epitope is Associated with Lower Reticulocyte Loss in Mice



ABC and Epitope B bind hTfR with the same affinity

ABC Applied Toward Multiple Drug Modalities to Enhance Alector's Pipeline



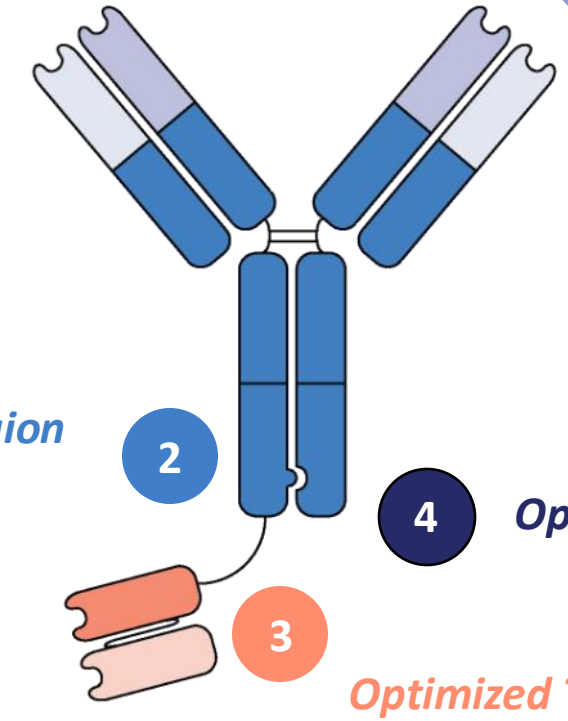
Antibodies + ABC
Removing Aβ
Removing Tau

Enzymes + ABC
Replacing GCase

siRNAs + ABC
Removing Tau
Removing α-Synuclein
Removing NLRP3

AL137: Alector Brain Carrier (ABC)—Enabled Anti-Aβ Antibody for Alzheimer's Disease

Design of AL137: ABC-Enabled Anti-Aβ Antibody with Distinct Safety and Efficacy Features



1 *Engineered Anti-PyroGlu3 Aβ Binding Epitope*

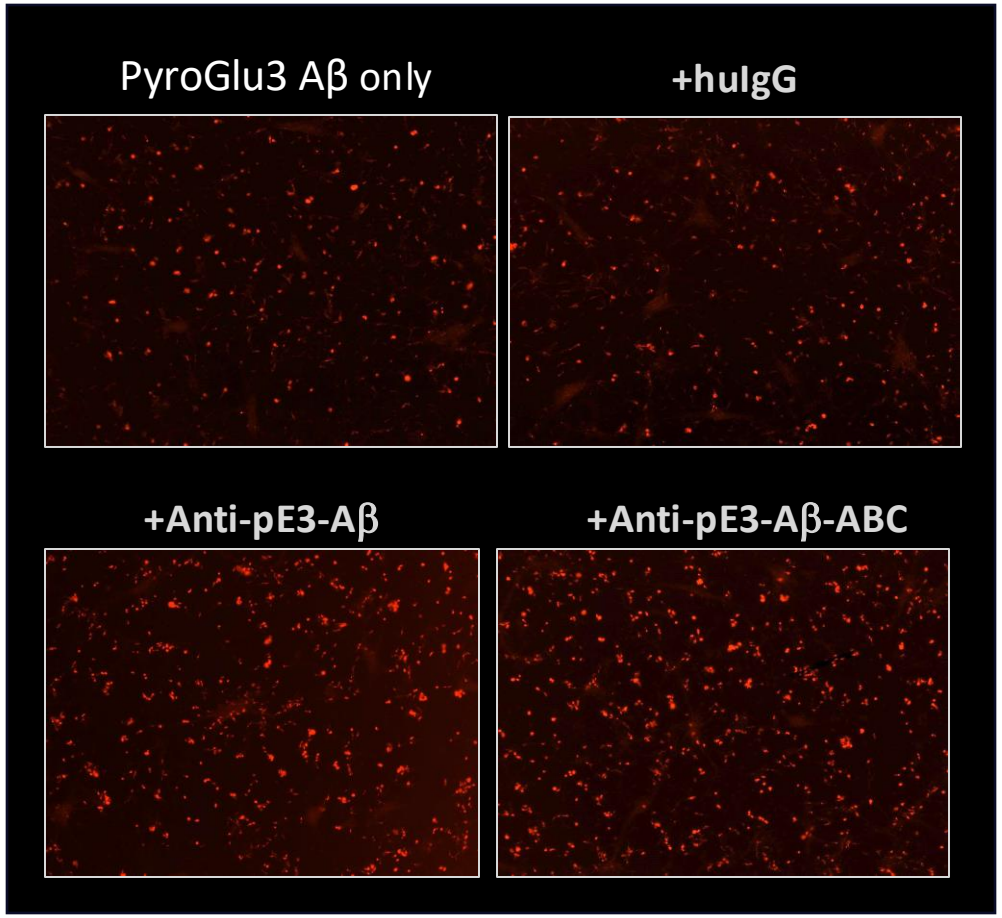
Fully Active Constant Region 2

4 ***Optimized Linker***

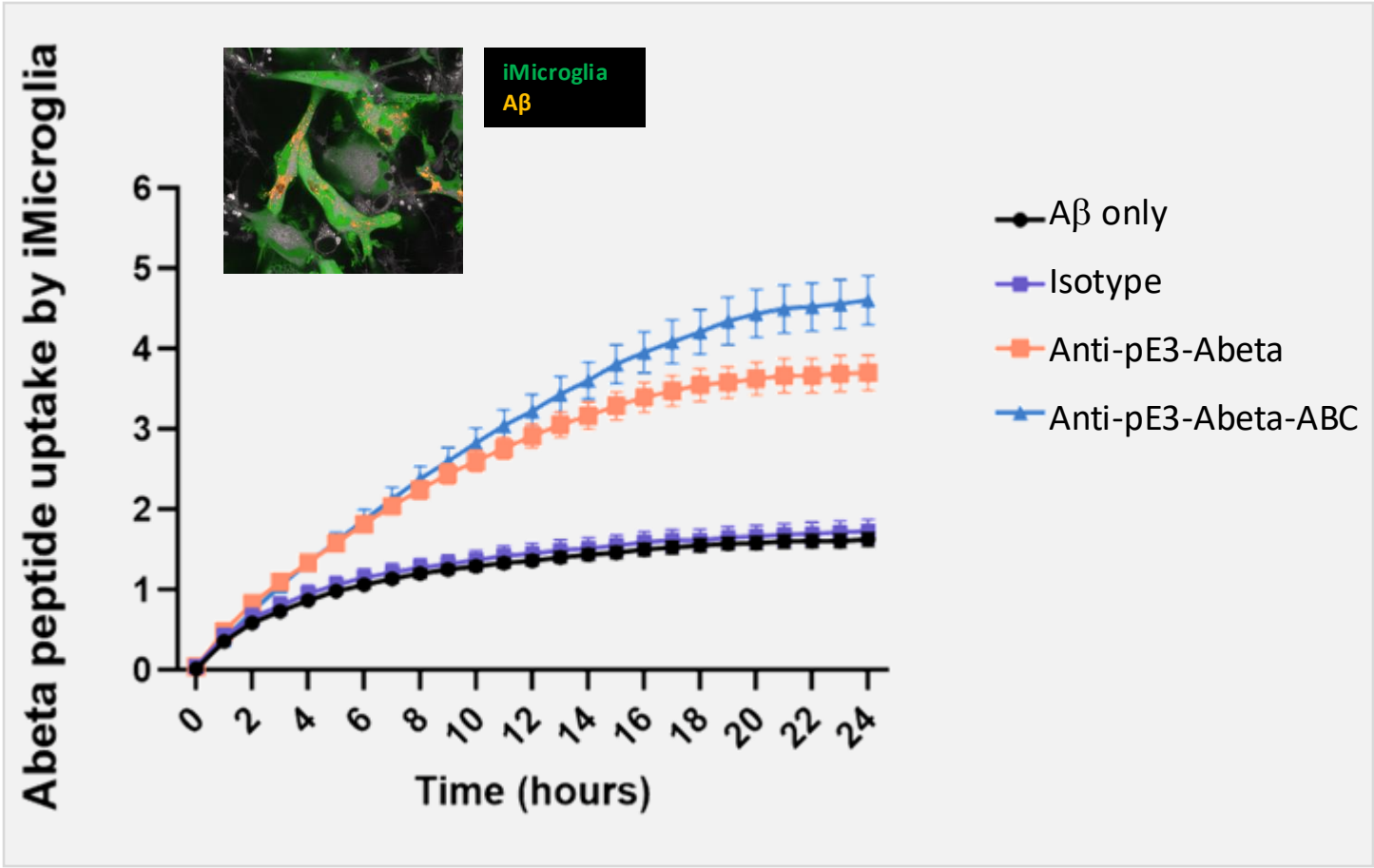
3 *Optimized TfR-Binding Epitope and Affinity to Maximize Brain Penetration and Reduce Hematologic Adverse Effects*

Anti-Aβ-ABC Facilitates Phagocytosis of PyroGlu3 Aβ by Human Microglia

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

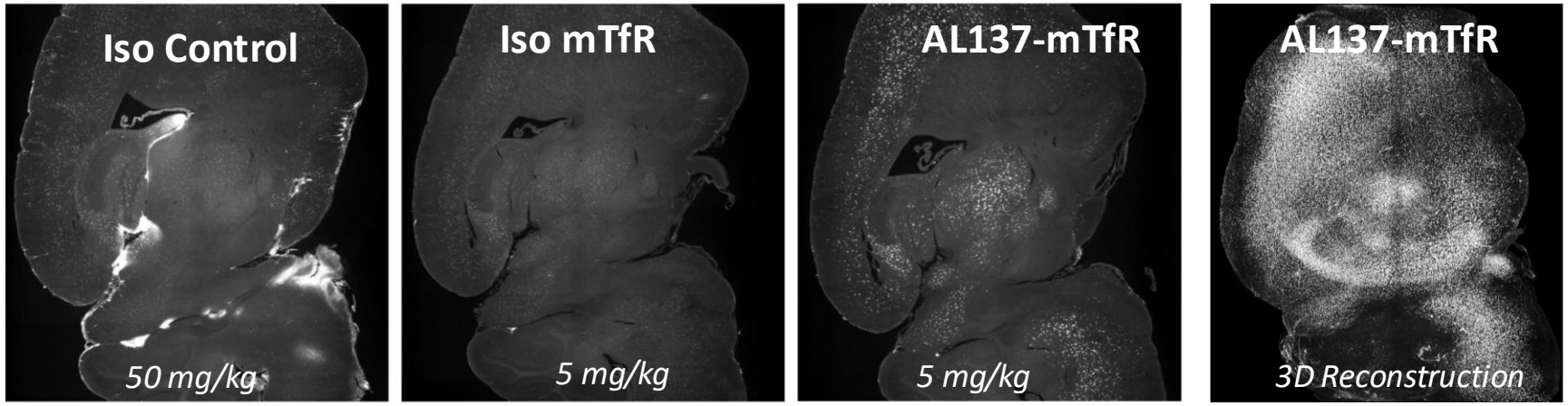


Anti-pE3-Aβ□Dependent Phagocytosis of PyroGlu3 Aβ by Human IPSC Microglia in Culture

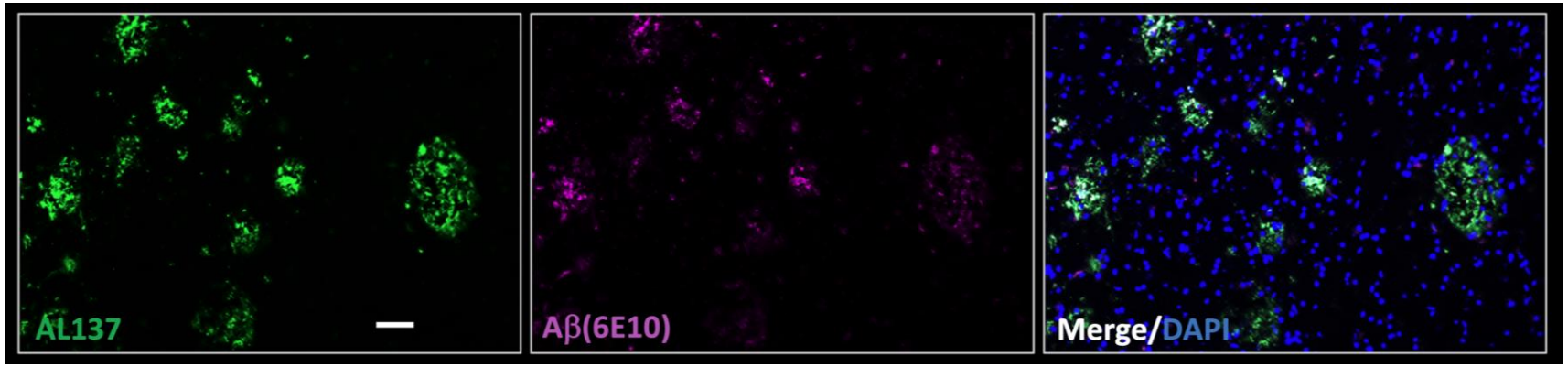


AL137 Binds to Amyloid Plaque in Human and Mouse AD Brains

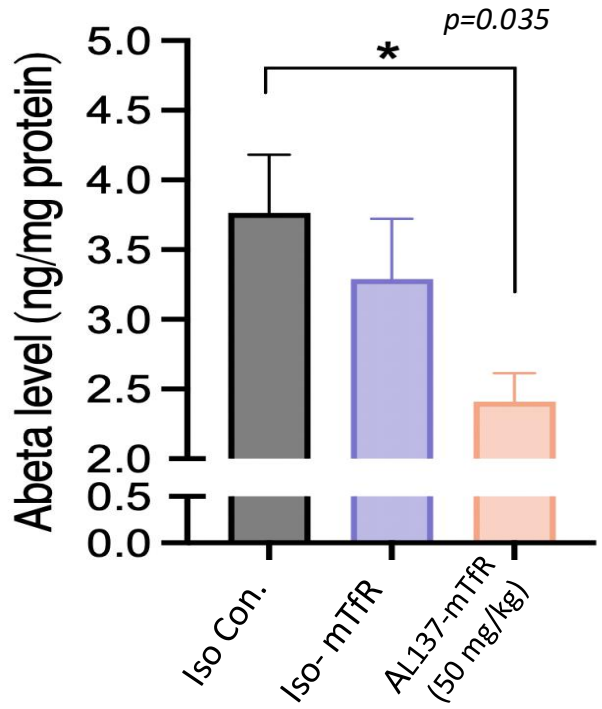
AL137-mTfR Colocalizes with Aβ Plaques in the 5XFAD AD Mouse



AL137 Colocalizes with Aβ Plaques on Human AD Brain Sections



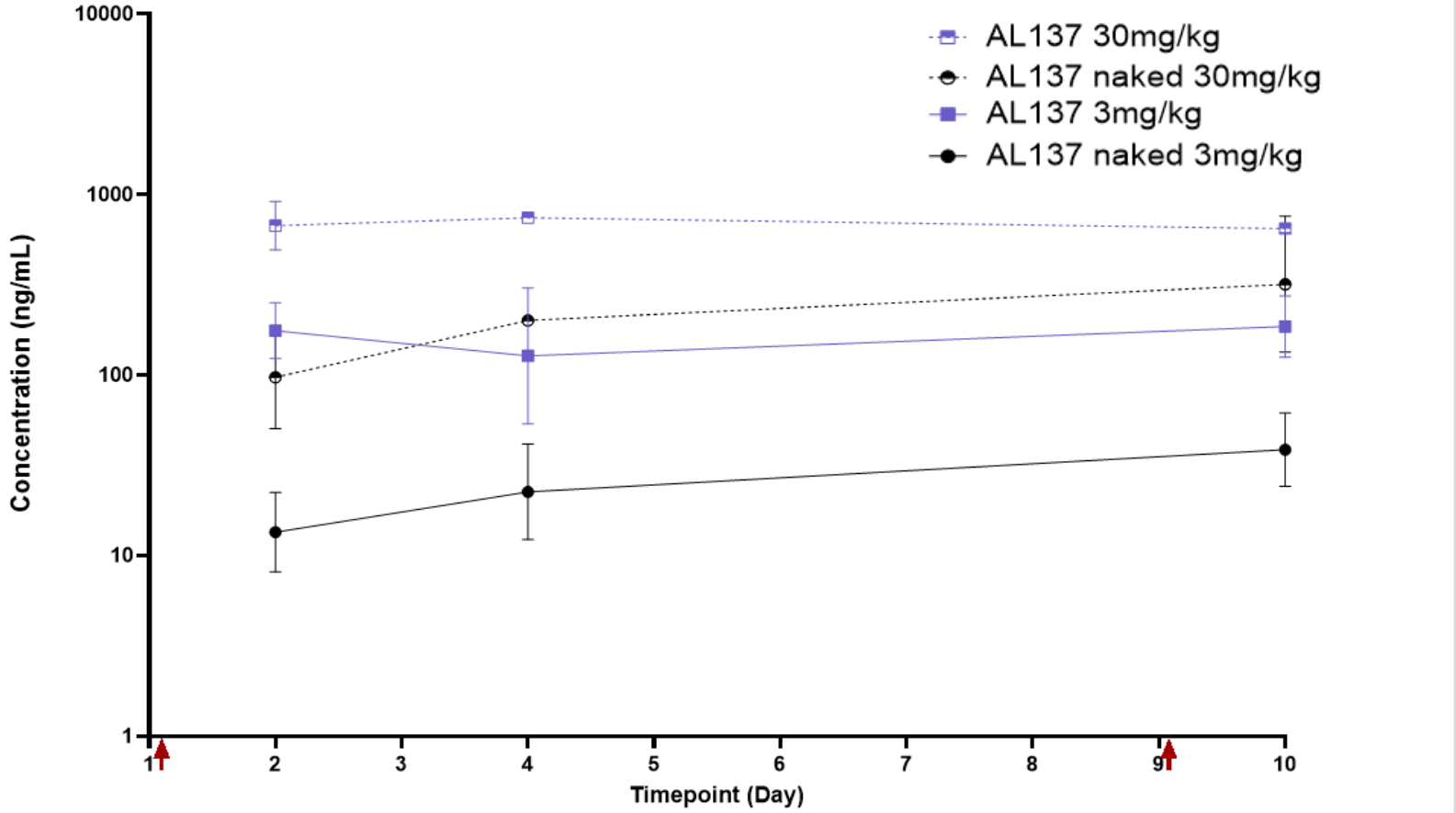
Reduction in Brain Aβ42 in AL137 mTfR-Dosed Mice



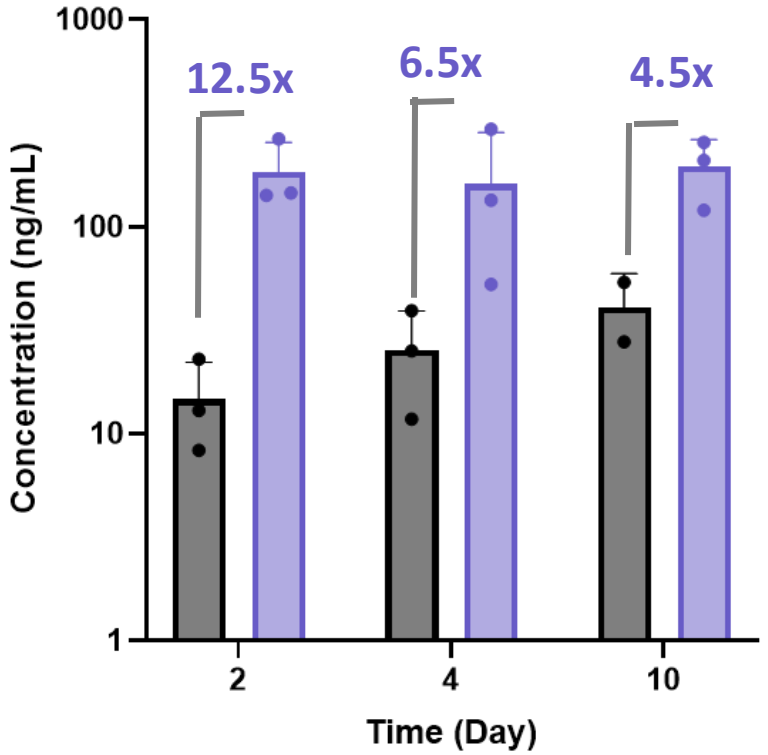
AL137-mTfR is the murine surrogate TfR with the AL137 Fab and mIgG2a Fc

AL137 Demonstrates Enhanced CSF Uptake Over Time

CSF Concentration Following 1st and 2nd Administration



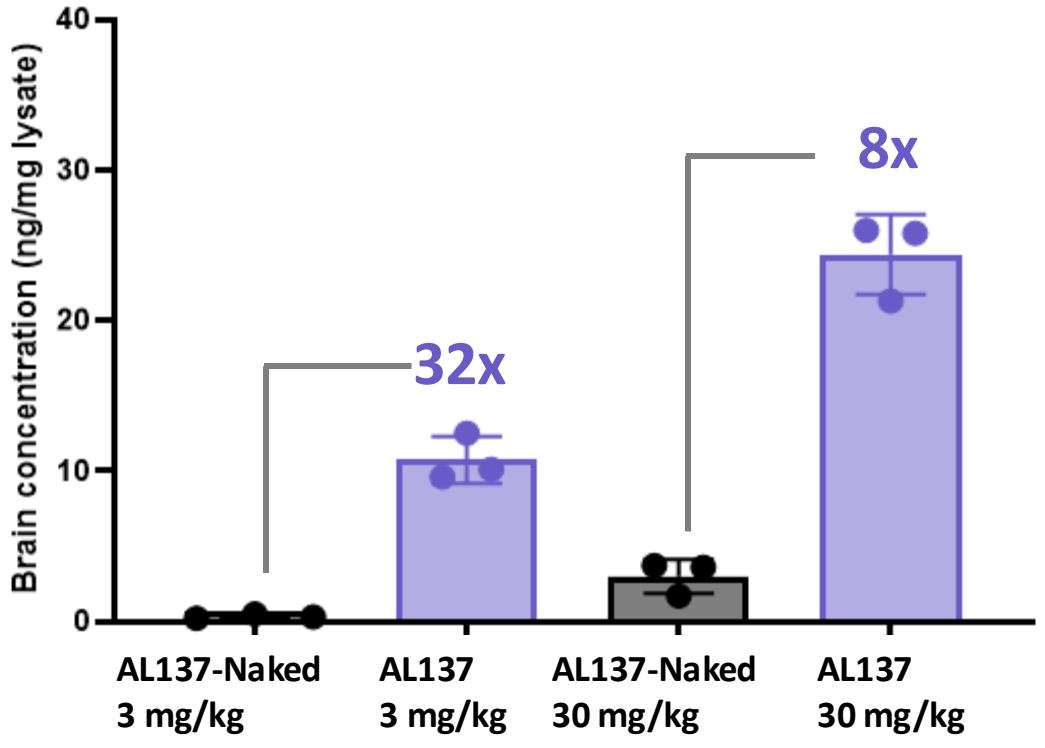
CSF AL137 naked vs AL137 3mg/kg



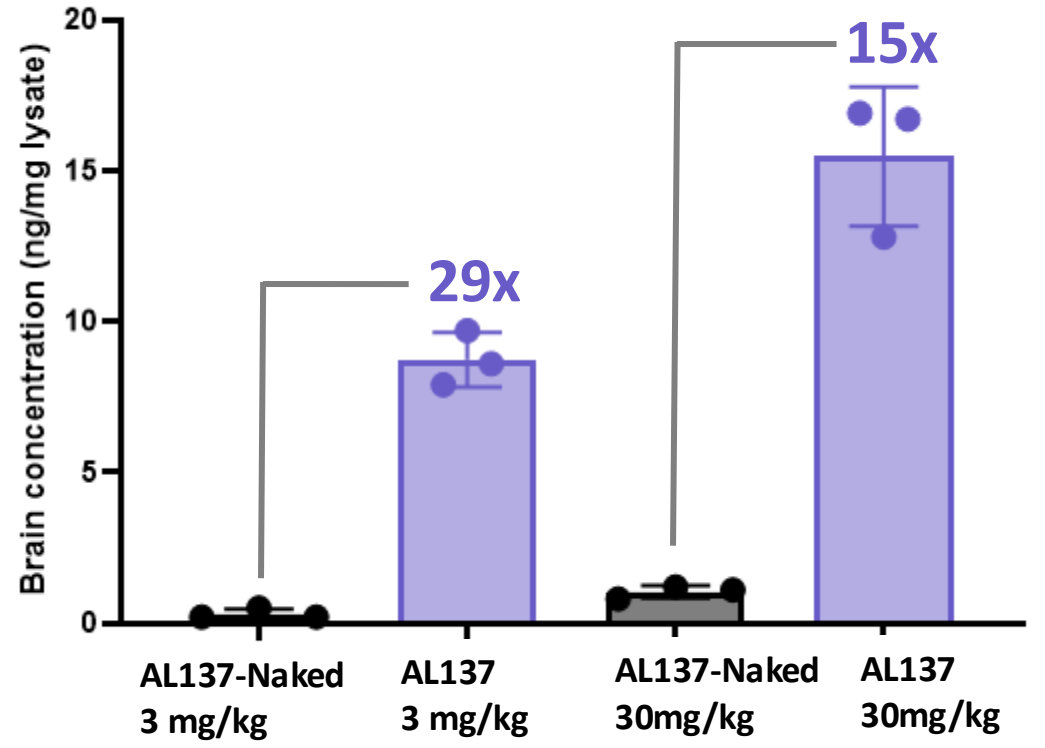
Three monkeys per group were injected on days 1 and 9 (red arrows).

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

Frontal Cortex



Hippocampus



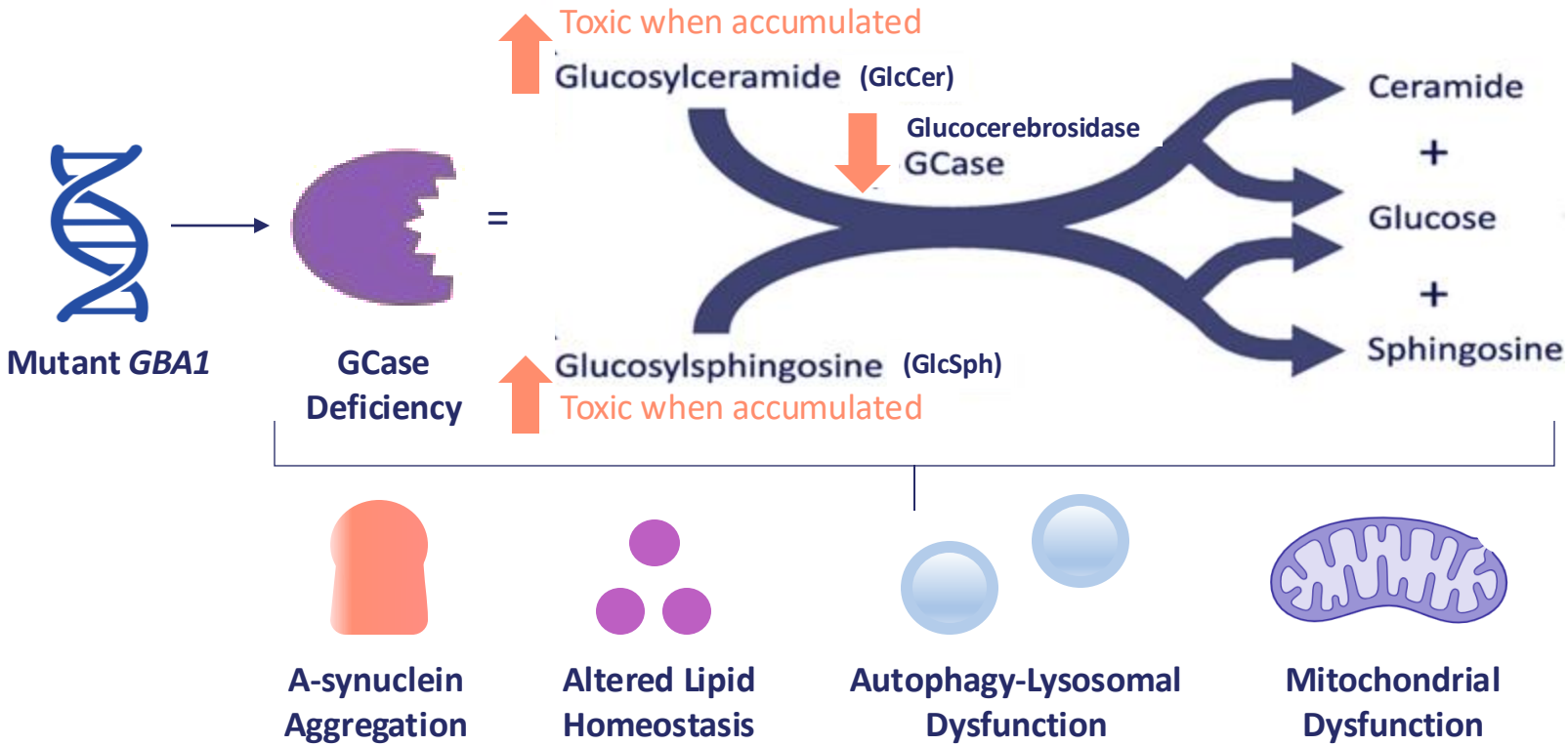
Three monkeys per group were i.v. dosed on days 1 and 9.
Brain tissues were collected 24 hours after the second injection and drug levels were measured in the vessel-depleted fraction.
For whole brain tissues, brain uptake reaches 8.4 nM for AL137 3 mg/kg group.

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

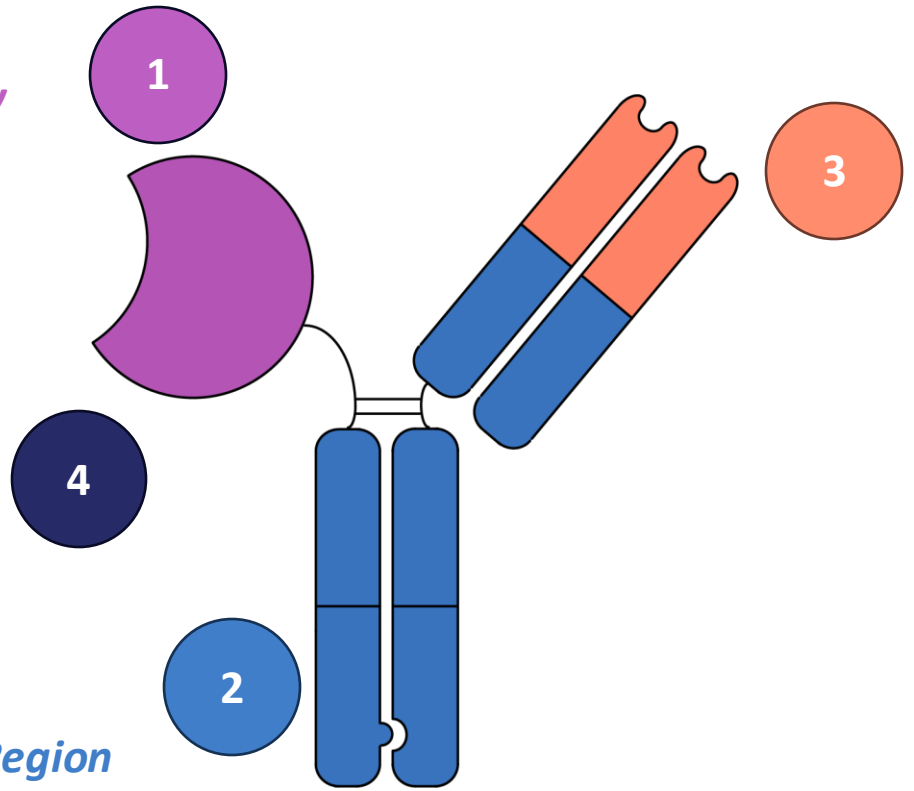
No therapy has effectively restored GCase activity in the brain: Current GCase enzyme replacement therapy does not enter the brain



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

Engineered GCase with Improved Activity and Stability

Optimal TfR Epitope and Binding Affinity

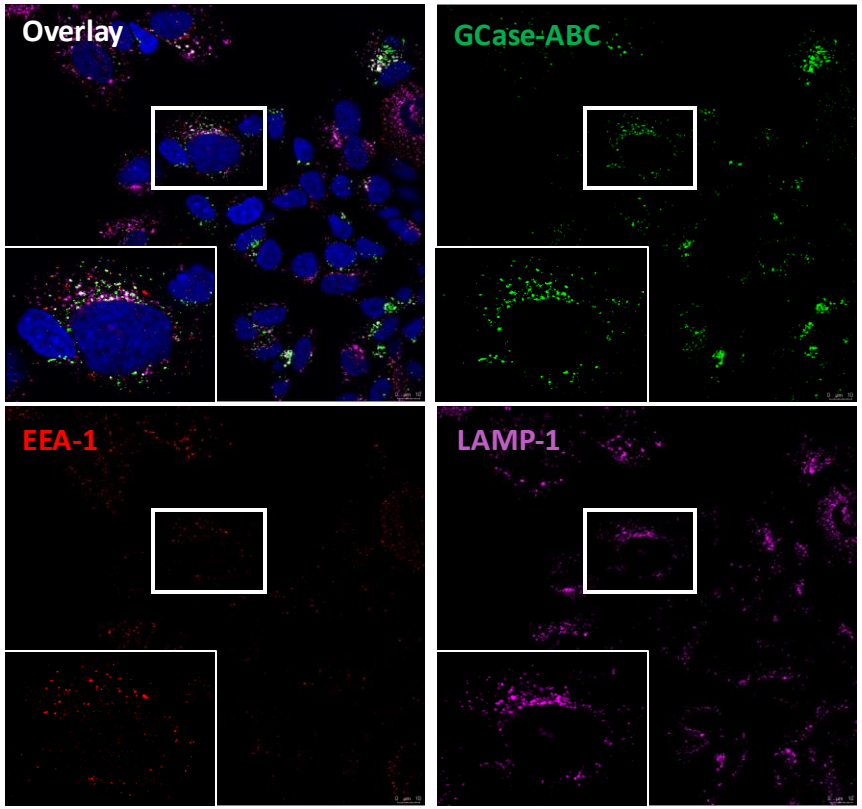


Optimal Drug Format

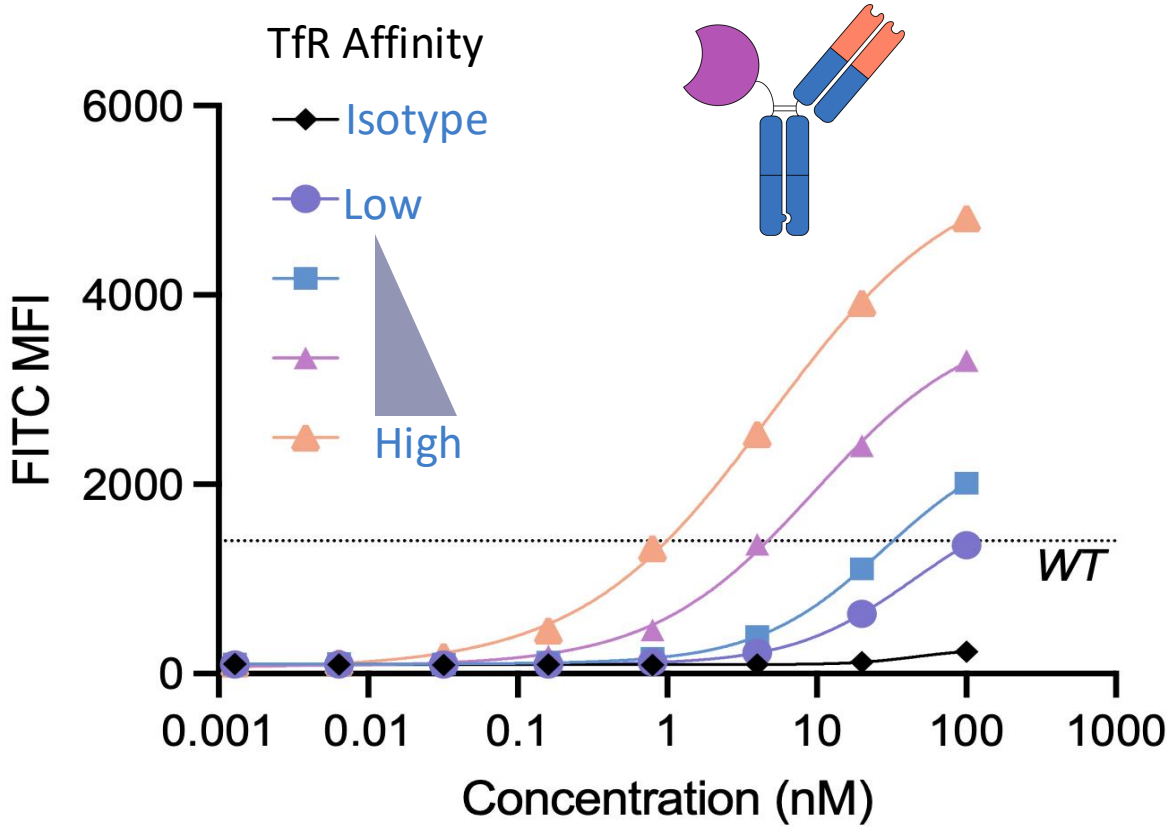
Silenced Constant Region

AL050 Affinity Was Optimized for Cell Rescue and Lysosomal Uptake

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



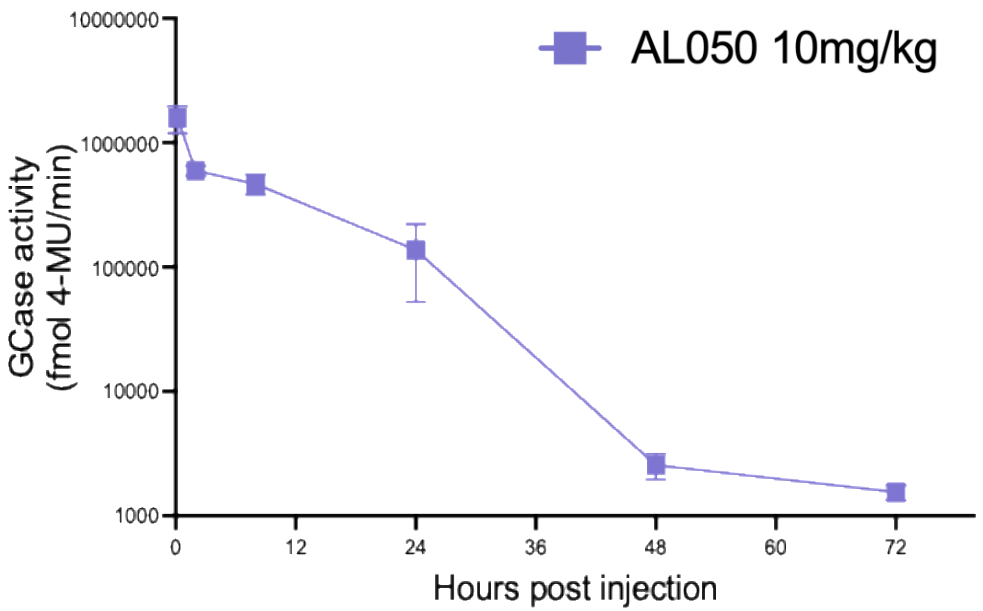
Ability of AL050 to Rescue GCase Activity in GBA1$^{-/-}$ Neuroblastoma Cells Is TfR-Affinity-Dependent



EEA-1 = Early endosome antigen 1
LAMP-1 = Lysosomal associated protein 1

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

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**

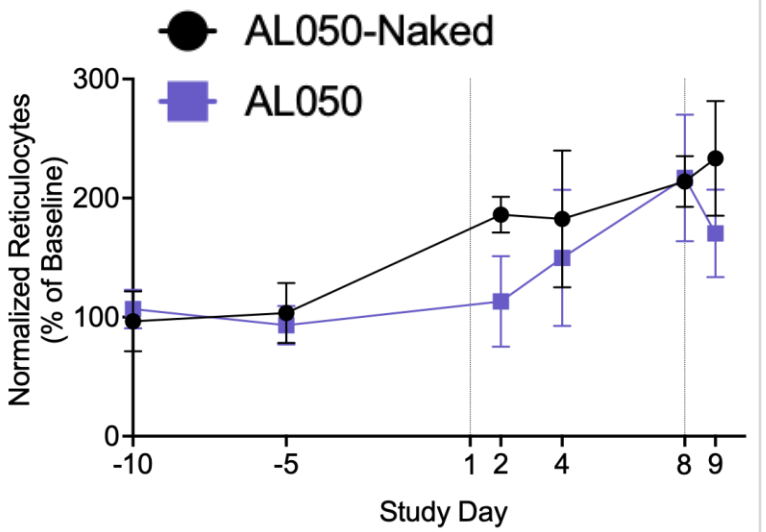
Velaglucerase alfa:

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

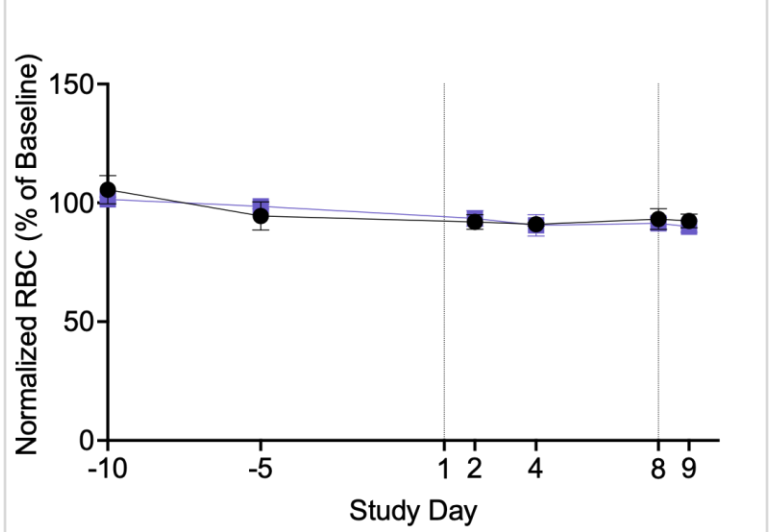
- European Medicines Agency (EMA), **Cerezyme EPAR – Scientific discussion**. European Medicines Agency (EMA)
- Therapeutic Goods Administration (TGA, Australia), **AusPAR: Velaglucerase alfa (VPRIV)**. Therapeutic Goods Administration (TGA)
- EMA, **VPRIV EPAR – Public assessment report** European Medicines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

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

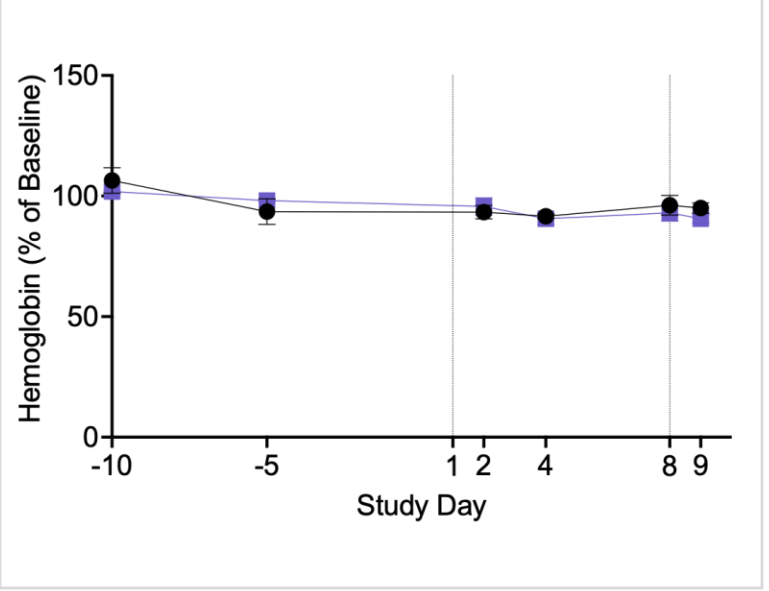
Reticulocyte Counts in Normal Range



Red Blood Cell Counts Were Not Affected



Hemoglobin Levels Were Not Affected

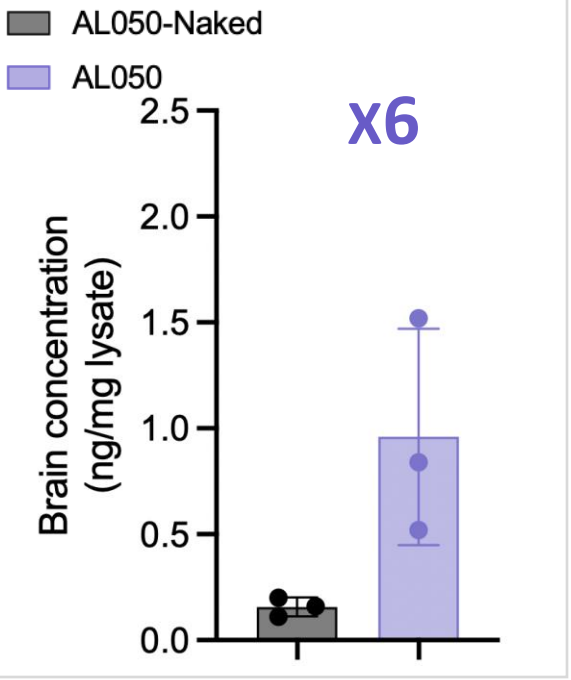


Three NHP per group were injected on days 1 and 8 (vertical lines).

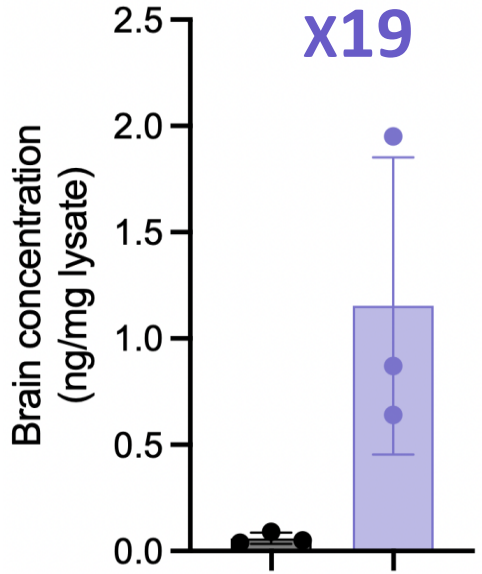
ABC Enhances Brain Delivery and Activity of Engineered GCase

Brain Delivery

Substantia Nigra

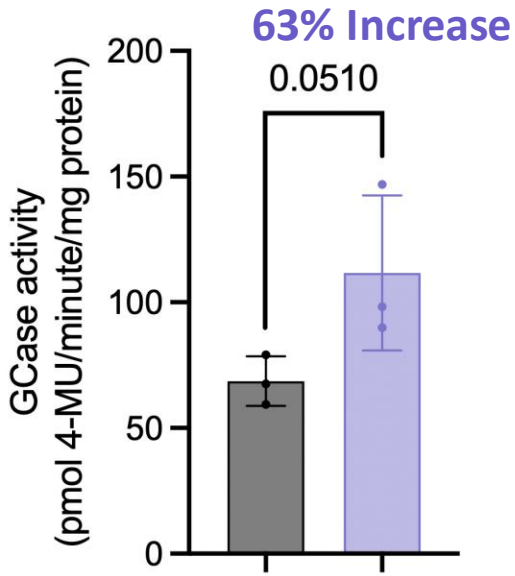


Putamen

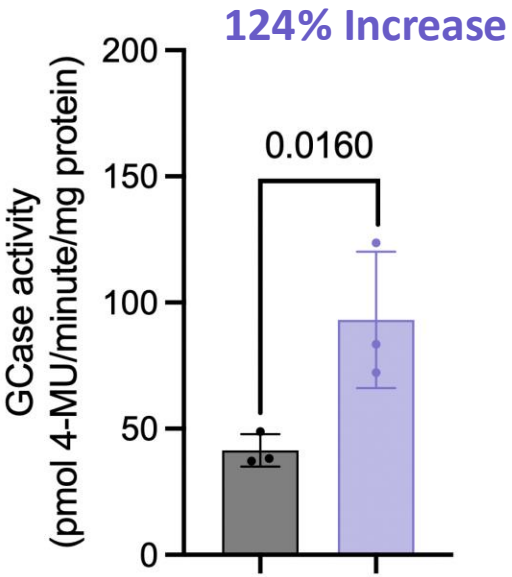


Brain Activity

Substantia Nigra



Putamen



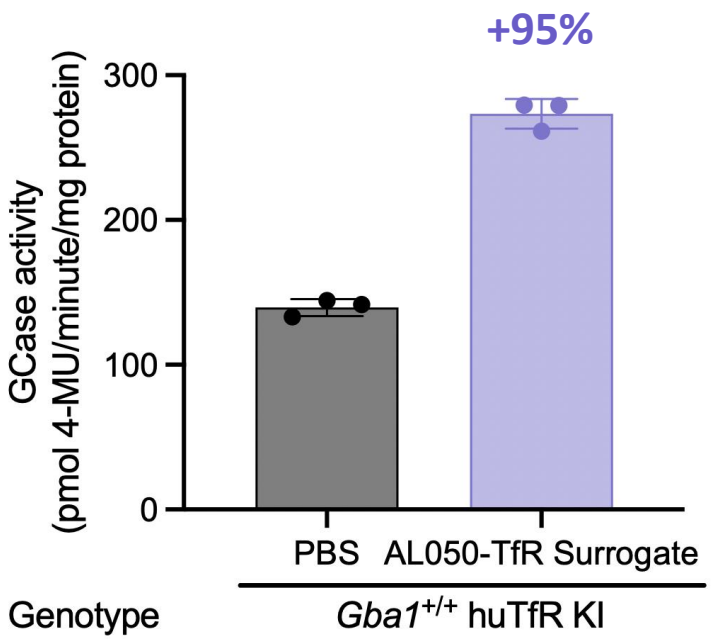
Three NHP per group were injected on days 1 and 8.
Brain tissues were collected 24 hours after the second injection and drug levels were measured in the vessel-depleted fraction.

alector

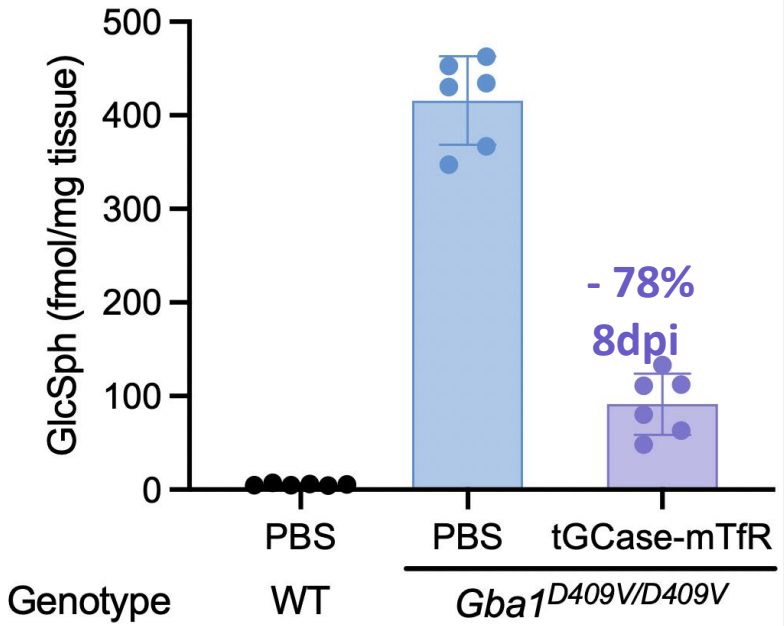
*Samples below lower limit of detection graphed at LLOD.

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

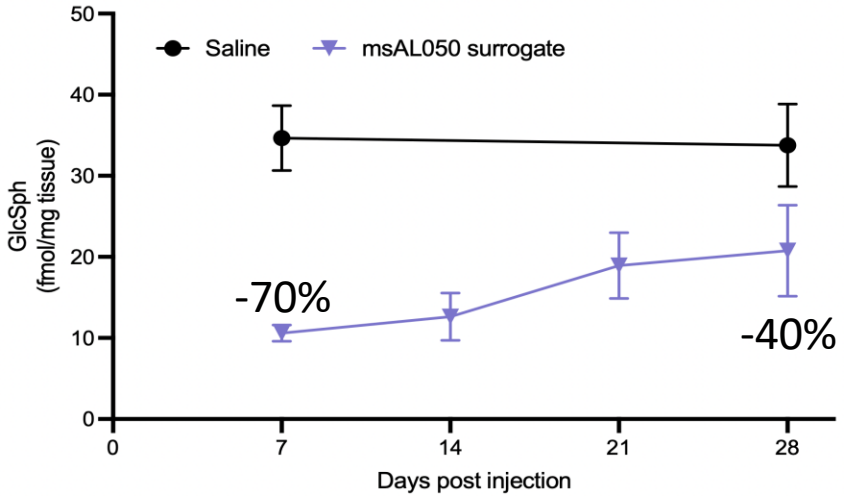
GCase-ABC Increases Brain GCase



GCase-ABC Reduces GlcSph



Durable (28d) Reduction in Brain GlcSph



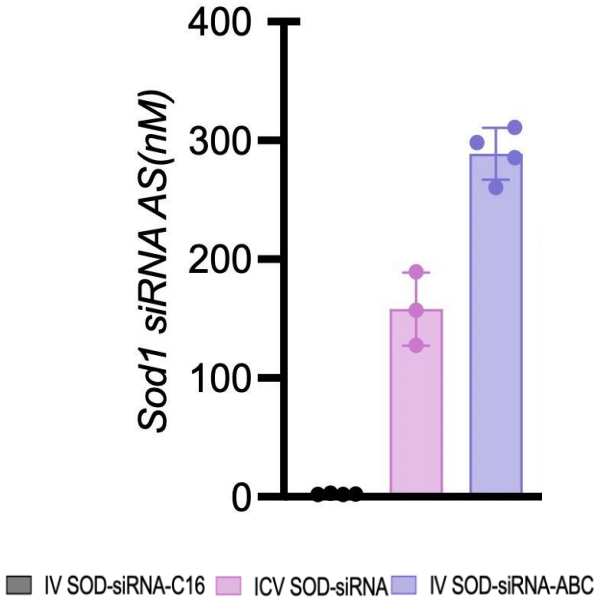
Wild-type or Gba1-mutant mice were injected once (left, right) or twice (middle) with PBS, or 10mg/kg AL050-huTfR Surrogate(left), tool GCase-msTfR (middle), or AL050-msTfR Surrogate (right).

Alector Brain Carrier (ABC)—Enabled siRNA Programs

siRNA-ABC: Support Effective Brain Distribution with Peripheral Delivery

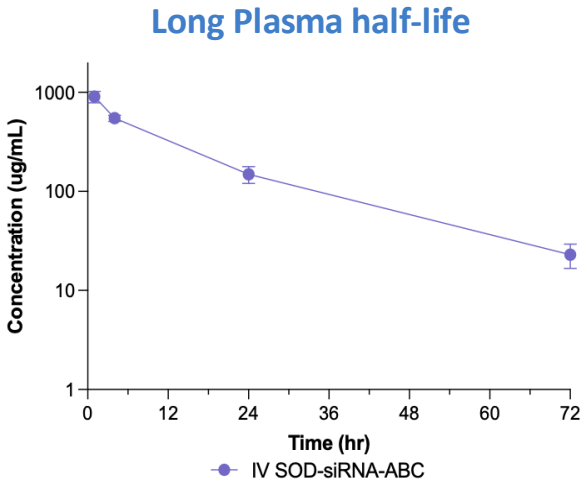
HIGH BRAIN PENETRATION

- ABC enables high brain penetration with peripheral delivery



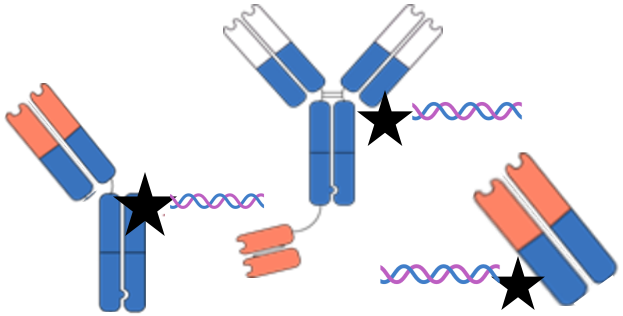
PHARMACOKINETICS

- Long plasma half-life compared to chemically stabilized siRNA without ABC[1], enabling durable transport from the serum to the brain



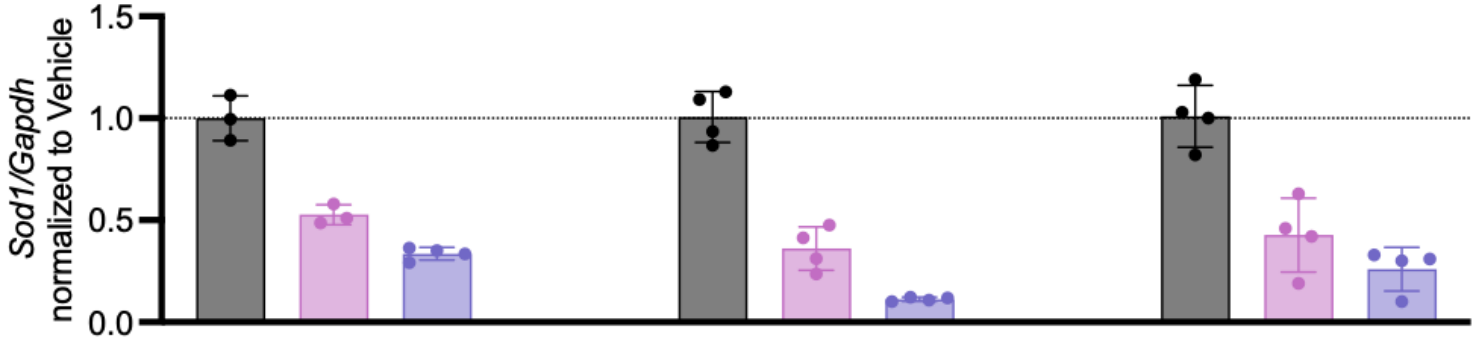
PARAMETERS TESTED

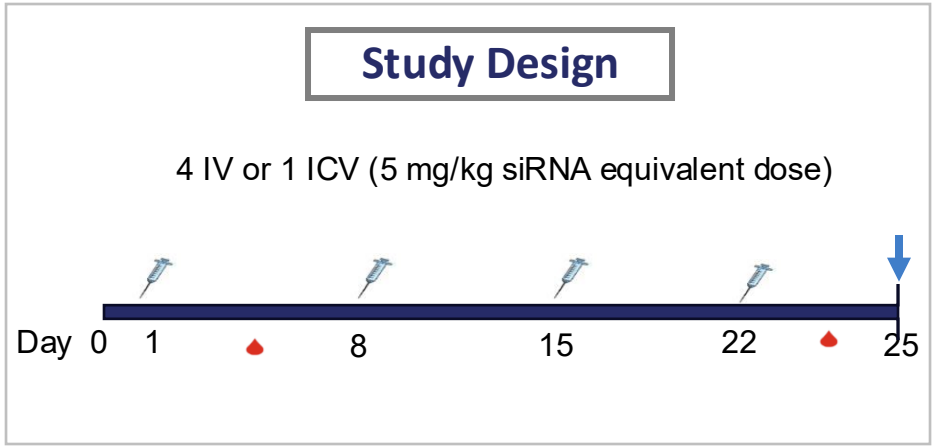
- ~1,000-fold range of TfR affinities
- Multiple drug configurations
- Multiple siRNA linkers *(cleavable, e.g., Val-Cit and non-cleavable, e.g., SMCC)*
- Multiple siRNA modifications (*e.g., 2'-OMe, PS, etc)*

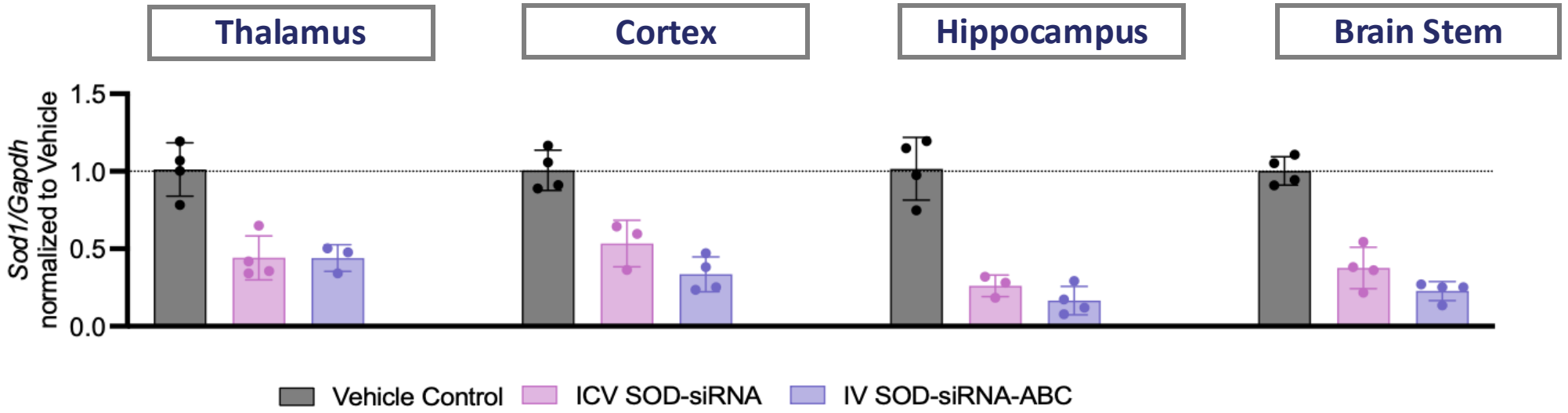


SOD1- Superoxide dismutase; 1. Jeon, J.Y., Ayyar, V.S. & Mitra, A. Pharmacokinetic and Pharmacodynamic Modeling of siRNA Therapeutics – a Minireview. *Pharm Res* **39**, 1749–1759 (2022); *Journal of Nanobiotechnology* **volume 21**, Article number: 381 (2023)

Peripheral Delivery of Sod1 siRNA-ABC matches or is Better Than ICV Delivery:
50-89% Knockdown Across Multiple Rodent Brain Structures







Thank You