Crossing the Blood-Brain Barrier:

Developing Alector's Next Generation of Investigational Therapies for Neurodegeneration

Disclaimer and Forward-Looking Statements

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, including our blood-brain barrier technology platform, Alector Brain Carrier (“ABC”); our plans, timelines and expectations related to our product candidates, including our ABC technology platform, and our other clinical and pre-clinical programs, including with respect to the availability of data, the initiation of future clinical trials and plans and expectations regarding planned regulatory filings with respect to such programs; 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 pandemics or other public health outbreaks 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	**Alector's Leadership in Neurodegeneration** *Arnon Rosenthal, Ph.D., Chief Executive Officer, and Peter Heutink, Ph.D., Chief Scientific Officer, Alector*	**12:00-12:15 pm**
02	**The State of Drug Delivery Across the BBB** *Zhiqiang An, Ph.D., Professor & Robert A. Welch Distinguished University Chair in Chemistry and Director of the Texas Therapeutics Institute at UTHealth Houston*	**12:15-12:35 pm**
03	**Alector Brain Carrier: Our Proprietary BBB Approach** *Eric Brown, Ph.D., Lead Scientist, ABC Platform, Alector*	**12:35-12:55 pm**
04	**Alector Brain Carrier: Potential Applications** *Maxime Ah Young-Chapon, Ph.D., Lead Scientist, GCase Program, Alector*	**12:55-1:15 pm**
05	**Closing Remarks and Q&A** *Peter Heutink, Ph.D., Chief Scientific Officer, Alector*	**1:15-1:30 pm**

Alector's Leadership in Neurodegeneration

Arnon Rosenthal, Ph.D.
Chief Executive Officer
Alector

Peter Heutink, Ph.D.
Chief Scientific Officer
Alector

Enhanced Long-Term Future with Alector Brain Carrier (ABC) Platform

	2024				2025				2026				2027			
Anticipated	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Clinical Readouts				▲ AL002 AD Phase 2					Latozinemab FTD-*GRN* Phase 3				AL101 AD Phase 2			

Expanding our ability to deliver first and best-in-class therapies for degenerative brain disorders

ABC: An Integral Part of Alector Drug Discovery Platform

- **Novel Targets**
  Brain Penetrant Proteins, Enzymes & Antibodies
- **Validated targets**
  Best-in -Class Brain-Penetrant Proteins, Enzymes & Antibodies
- **2nd Gen Targets**
  Brain-Penetrant Proteins, Enzymes & Antibodies
- **Non-Protein drugs**
  Best-in-Class Brain Penetrant

→

- Years in the making
- Enables targeting diseases that require protein replacement
- Enables lower dosing, better brain distribution & subQ delivery
- Enables development of 2nd gen. drugs for clinical programs
- Enables development of best-in-class drugs for validated targets
- Enables brain delivery of non-protein drug modalities

Expanded Partnering Opportunities

Partnerships →
- Proteins
- Enzymes
- Antibodies
- Nucleic Acids

Partnering Opportunities with Drug Modalities Experts

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

- Pioneering science grounded in human genetics, immunology and neurobiology
- Ongoing Phase 2 studies in AD (TREM2 & PGRN) and pivotal Phase 3 study in FTD (PGRN)
- Diverse and differentiated research portfolio integrating the company's proprietary Alector Brain Carrier (ABC) technology platform

alector™ Image Credit: decade3d - anatomy /Shutterstock.com

Alector Brain Carrier (ABC): Enhanced Delivery of Biologics Across the BBB

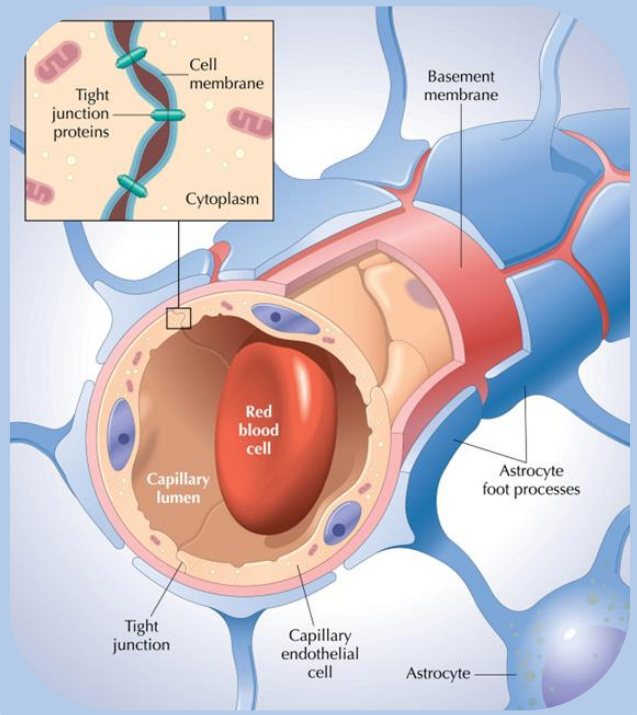
Another tool that supports next-generation and novel immuno-neurology programs

Challenge

- BBB poses a challenge for how much drug gets into the brain

BBB

Maintains homeostasis and protects by restricting access

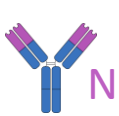
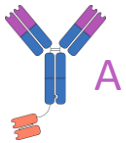
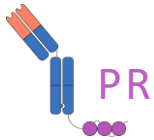
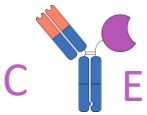


Potential Solution

- ABC is our proprietary technology designed to enhance brain penetration of therapeutic molecules

https://www.netterimages.com/the-blood-brain-barrier-labeled-hansen-physiology-1e-physiology-james-a-perkins-4921.html

Alector Brain Carrier (ABC) Technology Platform Complements Late-Stage Portfolio

PROGRAMS	Exploring the potential to develop next-generation, brain-penetrant product candidates PGRN: FTD-*GRN* TREM2: AD PGRN: AD CLINICAL GCase + ABC: PD GCase + ABC: LBD GPNMB + ABC: PD UD TARGETS + ABC: AD, PD, ALS PRECLINICAL
MODALITIES	 NAKED ANTIBODIES  ANTIBODIES+ABC  PROTEINS+ABC  ENZYMES+ABC
THERAPEUTIC AREA	NEURODEGENERATION
STRATEGY	IMMUNO-NEUROLOGY: HUMAN GENETICS + IMMUNOLOGY + NEUROSCIENCE

alector™ UD = undisclosed

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

TARGET	CANDIDATE	RESEARCH	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	ALECTOR'S COMMERCIAL OWNERSHIP	RIGHTS
PGRN	Latozinemab	FTD-*GRN*					U.S. 50-50 profit share with co-promote and tiered double-digit royalties ex-U.S.	GSK
	AL101	AD						GSK
TREM2	AL002	AD					Global 50-50 profit share with opt-in	abbvie
GPNMB	ADP027-ABC	PD					100%	alector
GCase	ADP050-ABC	PD, LBD					100%	alector
UD	ADP052-ABC	AD, PD					100%	alector
UD	ADP054-ABC	ALS, AD, PD					100%	alector
UD	ADP056-ABC	AD					100%	alector

IP portfolio across all programs contains 60+ patent families, which include 100 issued patents and >500 pending patent applications directed to more than 20 targets and/or technologies

ABC = Alector Brain Carrier
UD = undisclosed

The State of Drug Delivery Across the BBB

Zhiqiang An, Ph.D.

Professor & Robert A. Welch Distinguished University Chair in Chemistry and Director of the Texas Therapeutics Institute at UTHealth Houston

Disclosure Statement

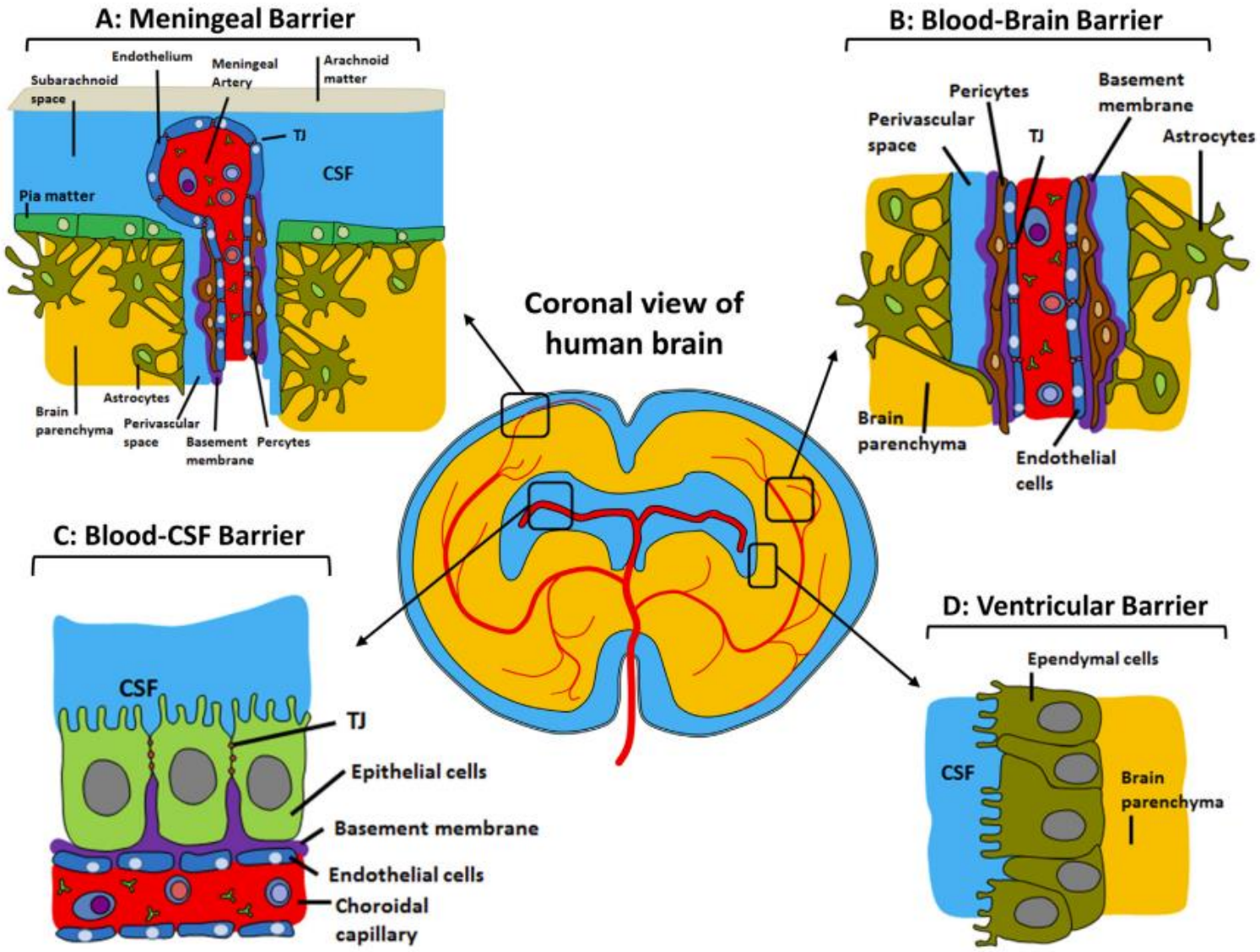
Scientific Advisory Board and/or Equity

- Immune-Onc Therapeutics, Inc.
- Incendia Therapeutics
- CrossBridge Bio

Sponsored Research

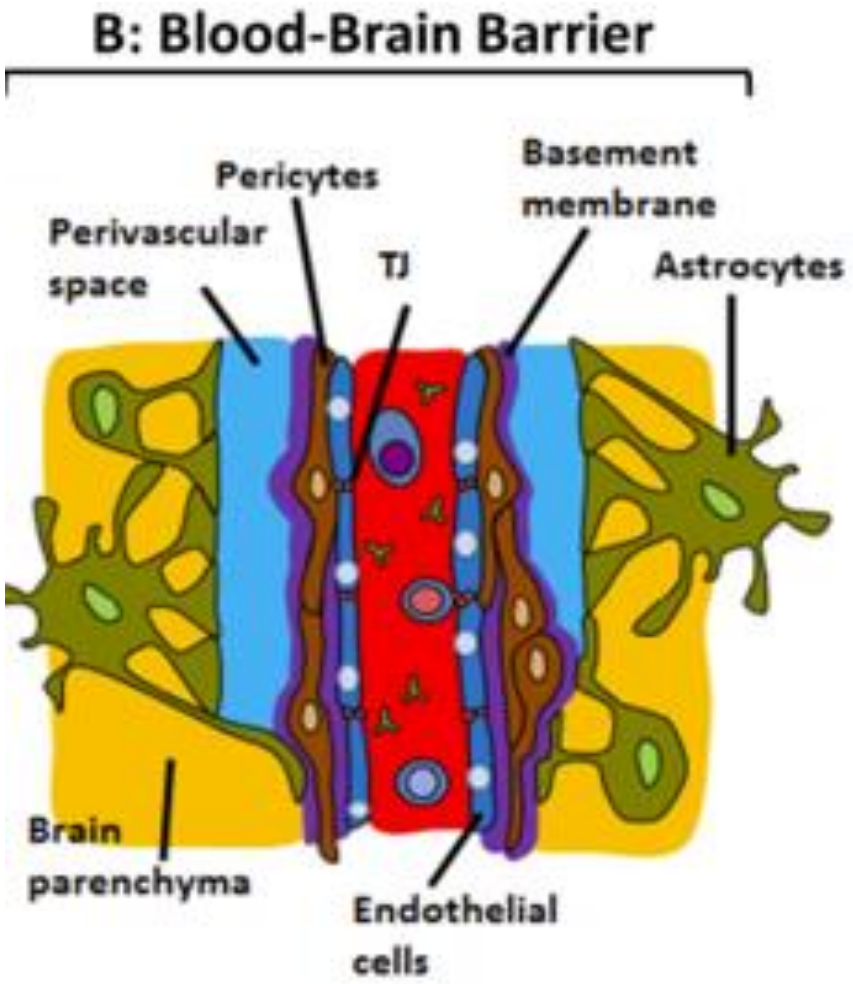
- Merck Research Labs

The Brain is a Privileged Site with Highly-Regulated Interfaces that Control the Movement of Substances and Cells in and out of the Brain



Neuropharmacology 120 (2017) 38e55

The Blood-Brain Barrier (BBB)



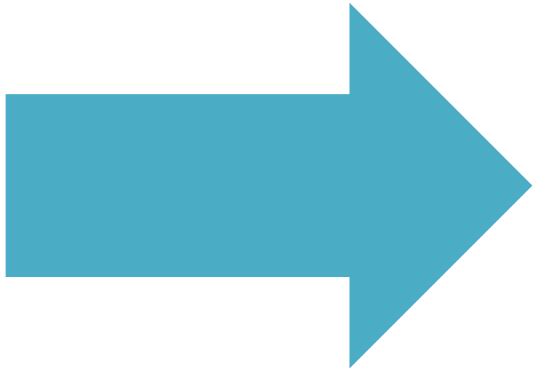
- The BBB consists of the tight brain endothelium, (BECs), pericytes, and astrocytes.
- Drug trafficking across the BBB is exceptionally challenging and tightly regulated.
- Despite these challenges the highly vascularized nature of the brain presents a potential avenue for drug delivery.

Neuropharmacology 120 (2017) 38e55

Leveraging BBB Delivery to Address Low Uptake Challenges

Limitations

Therapeutics have a low, yet significant, rate of penetration through the BBB of about 0.1 to 0.2% of the plasma level



Opportunities

To enhance brain penetration, researchers design therapeutics targeting BBB receptors to facilitate their passage to the brain

BBB Therapeutic Applications

Multiple Routes of Administration and Delivery Vehicles Through the BBB

Routes of Administration

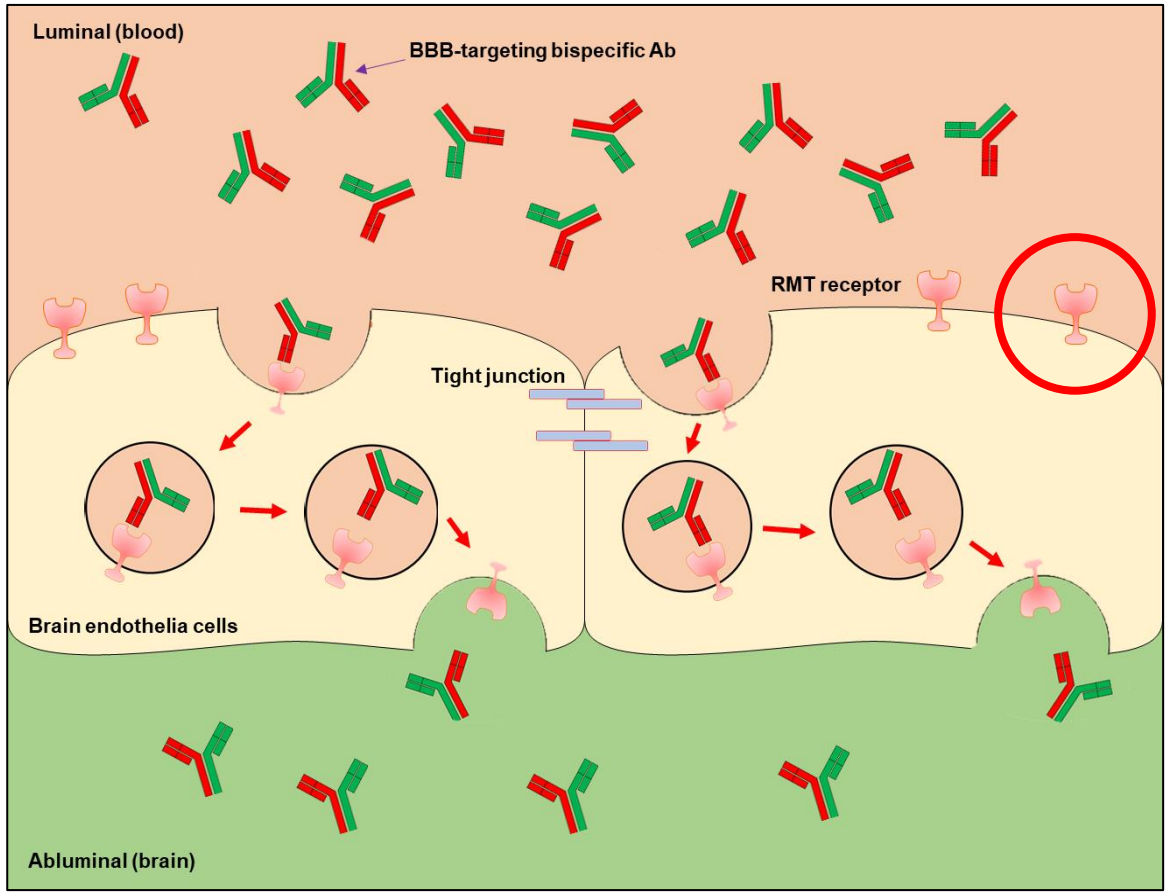
- Direct brain injection
- Intrathecal and intraventricular delivery into the CSF
- Intranasal brain delivery bypassing the BBB
- Diffusion
- Physical: Transcranial electric and magmatic stimulations (Ultrasound)
- Chemical: Mannitol (Intra-arterial injection) to enhance BBB permeability

Delivery Vehicles

- Utilizing viral vectors (AAV9 and AAVrh10) for gene therapy delivery
- Clathrin transporter: ExQor clathrin nanoparticles
- Gectosomes for CNS gene delivery (100-120 nm)
- Nanoparticles decorated with Tf peptide to deliver cargo
- Extracellular vesicles (EV)
- Receptor-mediated transcytosis
  - TfR and CD98hc

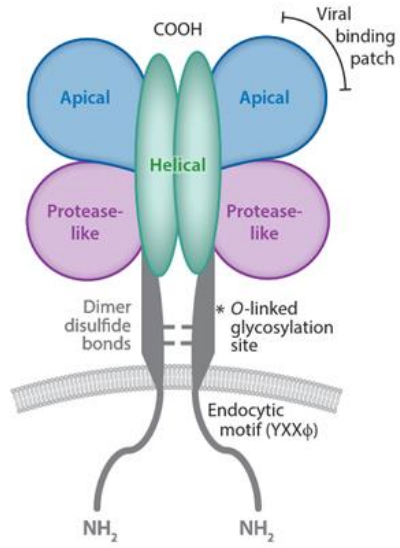
Crossing the BBB

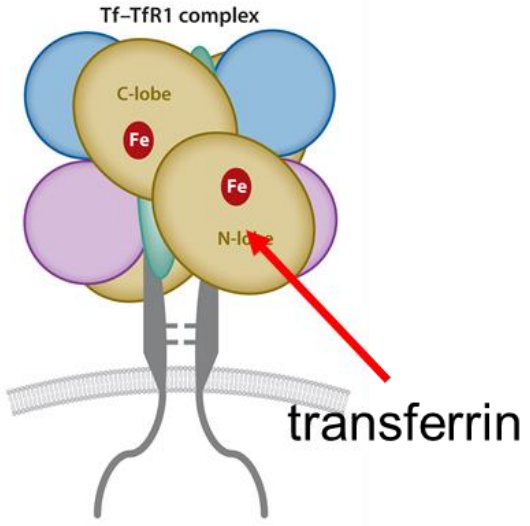
Receptor-Mediated Transcytosis



Transferrin Receptor (TfR)

One of the most studied Receptor-Mediated Transcytosis receptors for delivery of large-molecule drugs crossing the BBB

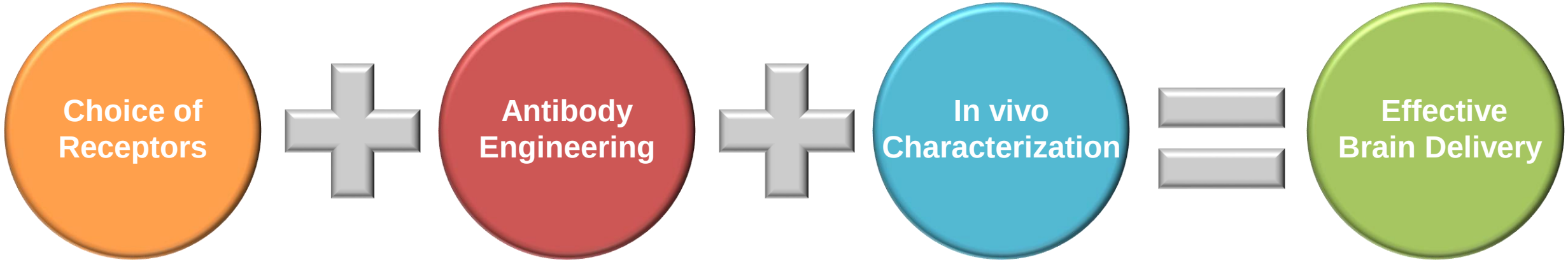




- Binds Transferrin
- Type 2 transmembrane receptor
- Highly expressed on BBB

DOI: 10.1016/j.drudis.2006.10.013
Neuropharmacology 120 (2017) 38e55

Considerations for Obtaining Effective Brain Antibody and Protein Delivery



- RMT receptor is highly expressed in BECs
- Species-of-interest validation
- Requirement for non-human primate cross-reactivity

- Effects of valency
- Antibody fusion format engineering
- Brain carrier affinity modulates uptake and safety
- Antibody effector function
- Avoid competition with natural ligands
- Structural stability
- Retention of optimal cargo activity

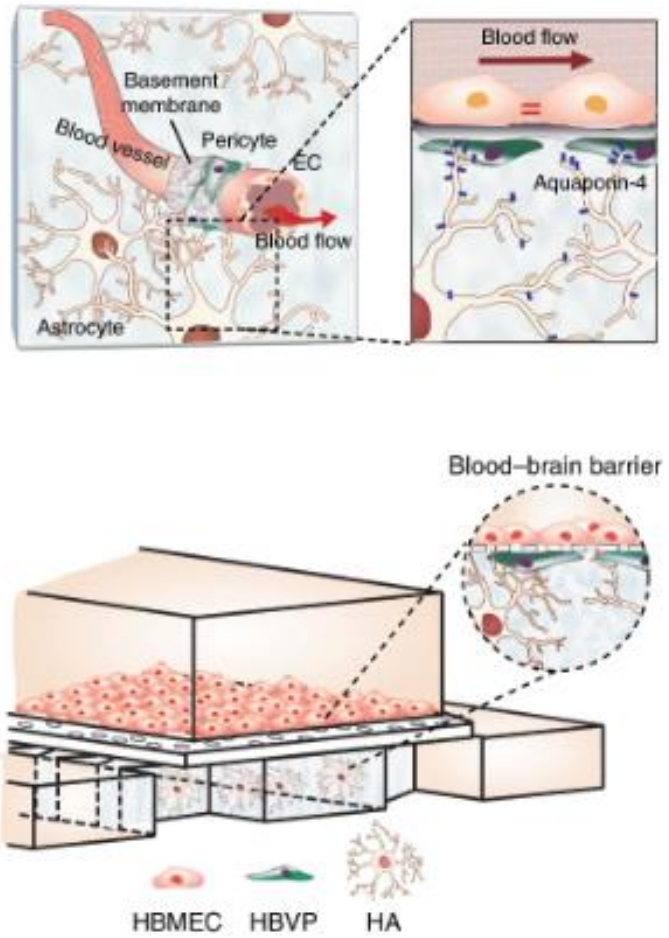
- Blood circulation time
- Brain distribution verified by imaging
- Brain uptake quantification in perfused, vessel depleted brain
- In vivo efficacy improvement required as final verification

Zhao et al., Antib Ther, 2022

BBB Drug Delivery: Future Directions

- *In vitro* BBB models – such as tissues from hiPSCs (human induced pluripotent stem cells)
- Development of mathematical models of brain uptake through the BBB
- Where in the brain we want to deliver drugs
- *In vitro* vs *in vivo* models
- Mouse vs human translatability
- Novel RMT targets with CNS-restricted expression to avoid systemic toxicities

In vitro model: BBB on a chip[1]



1) Ahn et al, Nature Comms 2020

Alector Brain Carrier: Our Proprietary BBB Approach

Eric Brown, Ph.D.

Lead Scientist, ABC Platform

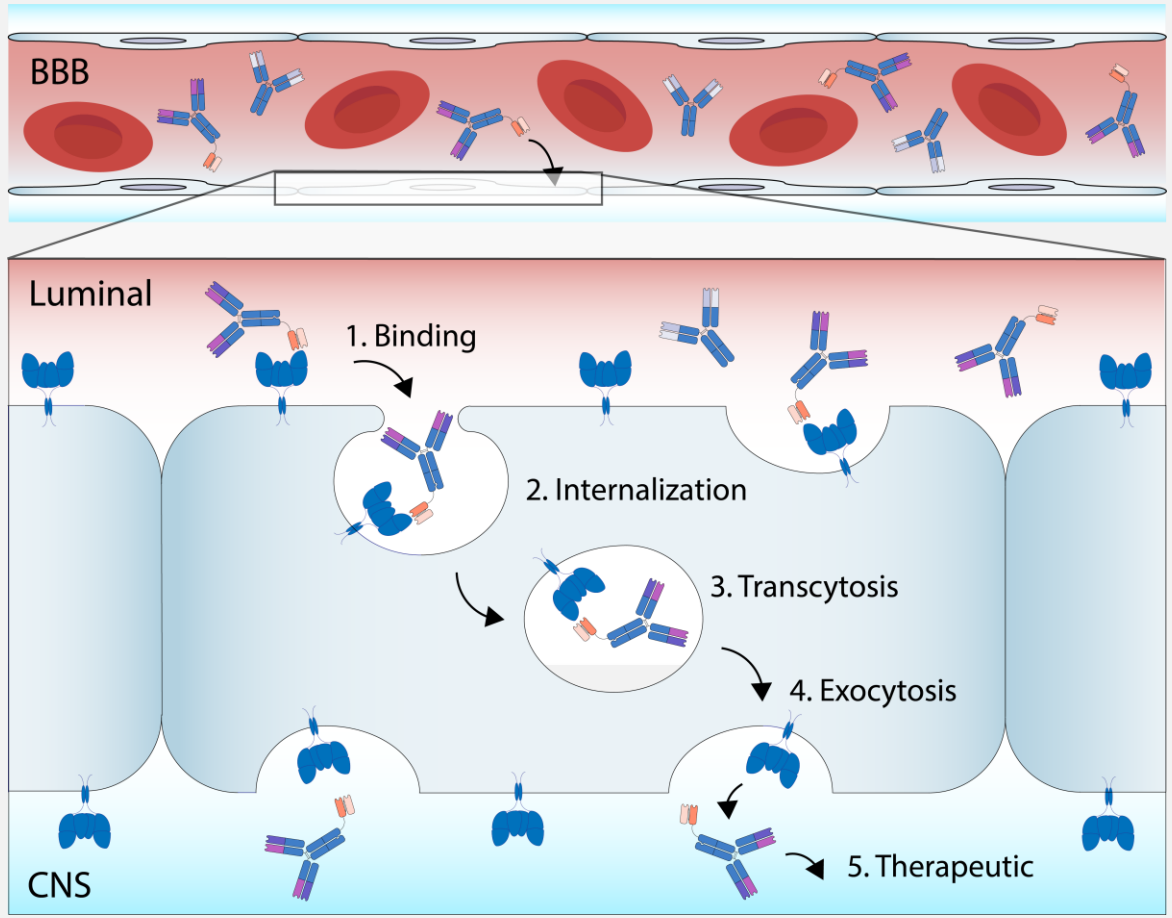
Alector

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

Alector Brain Carrier (ABC)

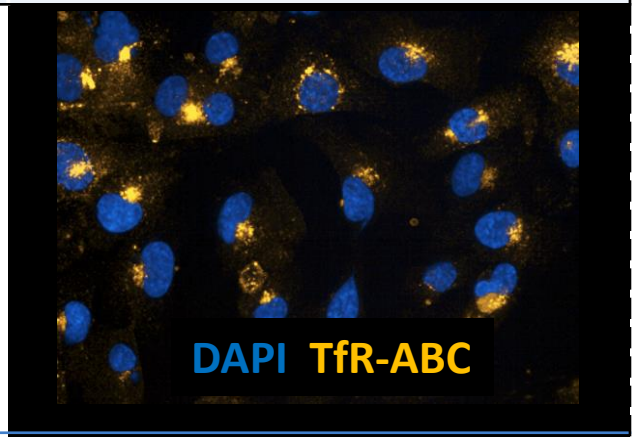
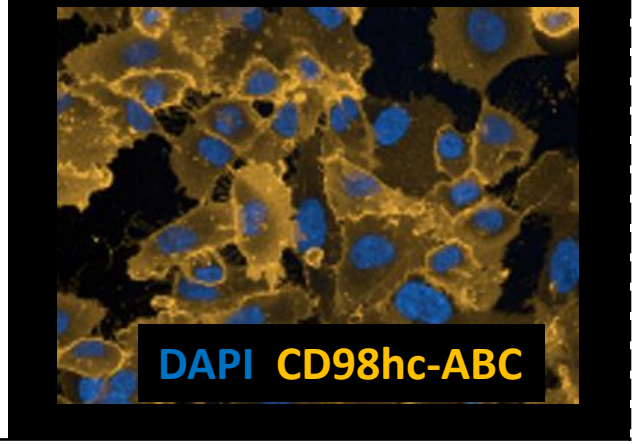
- BBB technology that enables **precise** and **non-invasive peripheral delivery** of therapeutics to the brain
- **Versatile** and **tunable** design seeks to optimize **efficacy** and **safety**
- Validated for brain uptake with **multiple therapeutic cargos**
- Enables the potential to **widen the 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

TfR and CD98hc Offer Distinct Advantages for Cargo Selection

Target	Receptor Function	CNS Cell Expression	BBB Expression Level	Localization	Trafficking of ABC in Brain Endothelial Cell Line
Transferrin Receptor (TfR)	Iron transport receptor	Neuronal, microglia	High	Punctate, endolysosomal	
CD98hc/ Slc3a2	Amino acid transport complex	Broad	High	Broad, cell surface	

Therapeutic cargo will also impact target cell localization and trafficking

hCMEC/D3 cells; 2h incubation, huIgG detection; 40x

Alector data on file

Exploring Our Distinctive ABC Strategies for Brain Drug Delivery

01

VERSATILITY

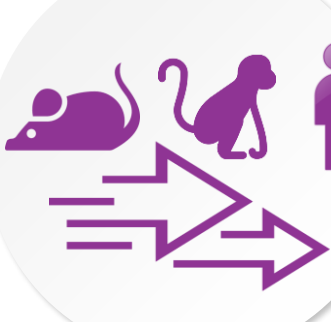
Adaptable for antibodies, proteins, enzymes and other cargos

02

TUNABILITY

Optimized affinity panels for diverse cargo to fit MOA, elevate efficacy and safety

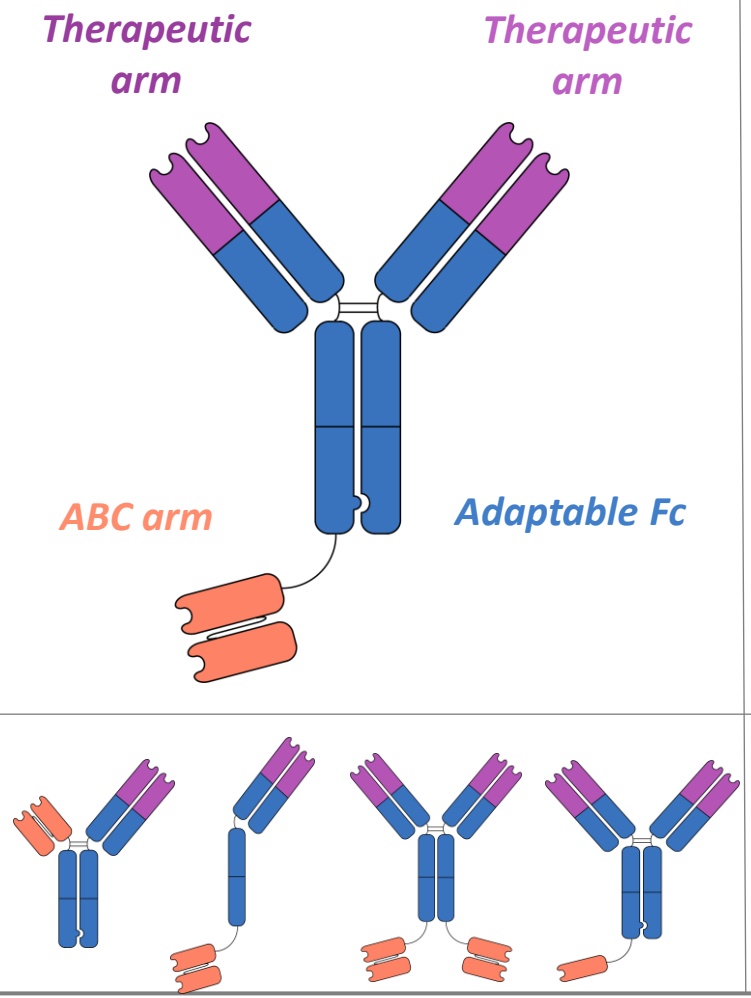
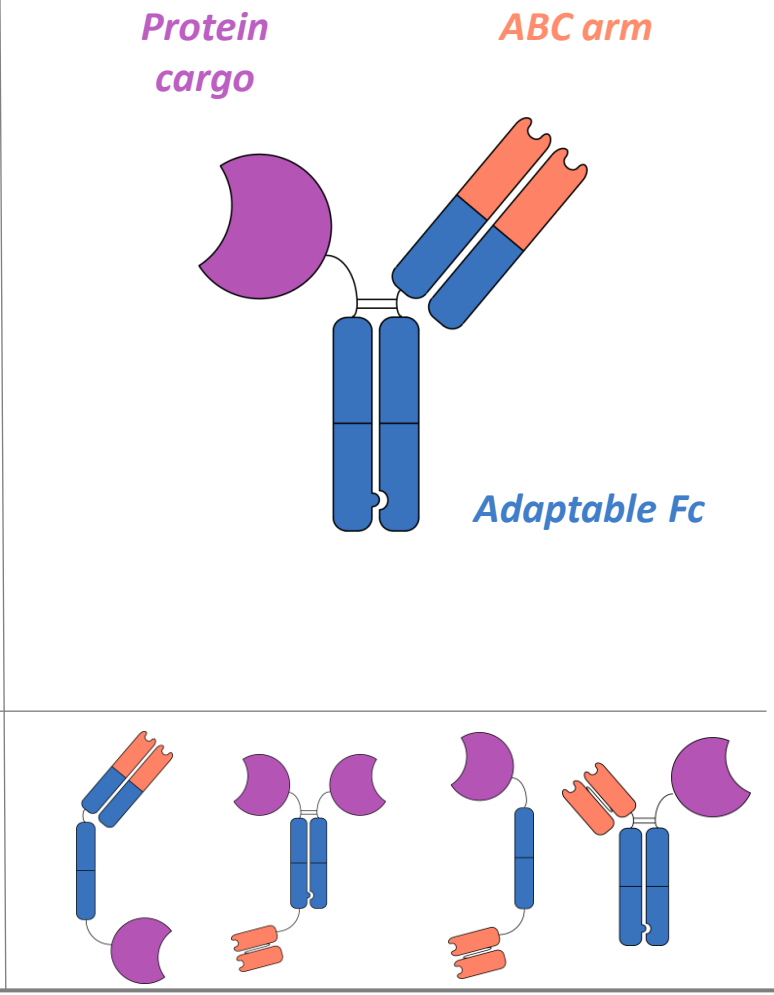
03



TRANSLATABILITY

Enables rapid translation of molecules to clinical candidates

Versatility: ABC Formats Tailored to Deliver Biotherapeutic Cargos

Versatile Features	Example #1: Antibody Cargo	Example #2: Protein/Enzyme Cargo
• ABCs as Fab, scFv and VHh for multi-specific formats • Adaptable Fc optimizing effector function and half life • Tailored for antibodies, proteins, enzymes, and nucleic acid • CD98hc enables use of bivalent formats and active Fc		

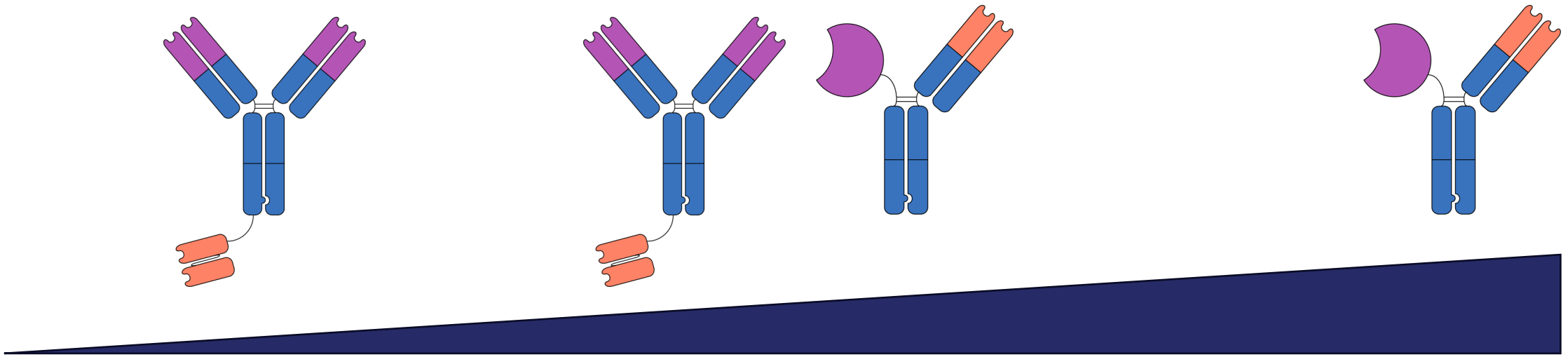
Tunability: Broad Affinity Toolbox for Optimal Cargo-ABC Pairing

Low to moderate affinity ABCs

- Improve efficacy and safety window
- Suitable for antibody cargos

Moderate to high affinity ABCs

- Rapid brain uptake and clearance
- Suitable for enzyme/protein cargos

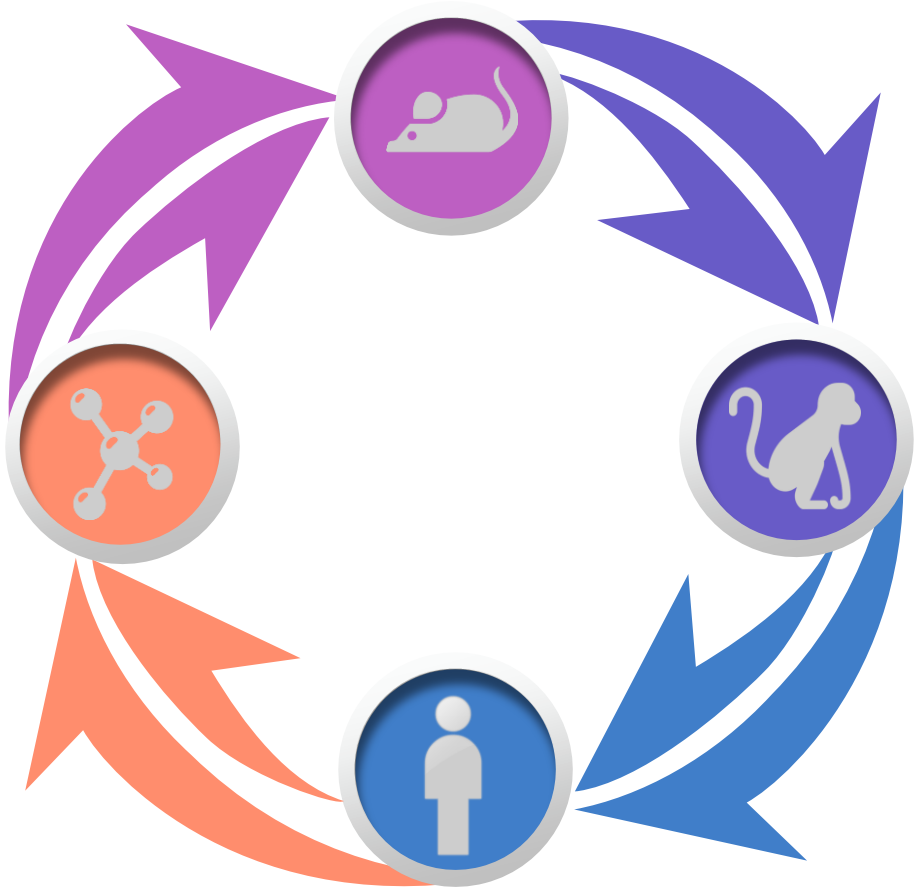


Affinity to BBB receptor ---->

ABC platform has validated brain uptake across a wide range of affinities to TfR and CD98hc

Translatability: Ensuring Rapid Progression to the Clinic

Rapid *In vivo* Screening
HTP screening format used in hTfR and hCD98hc expressing mice



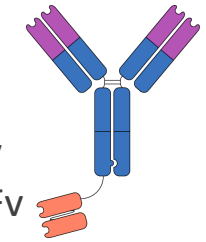
Translatable Biology
Affinity matched mTfR-ABC and mCD98hc-ABC surrogates for rapid testing in disease models

Developability Assessment
Early screening to ensure cargo-ABC combinations are suitable therapeutics

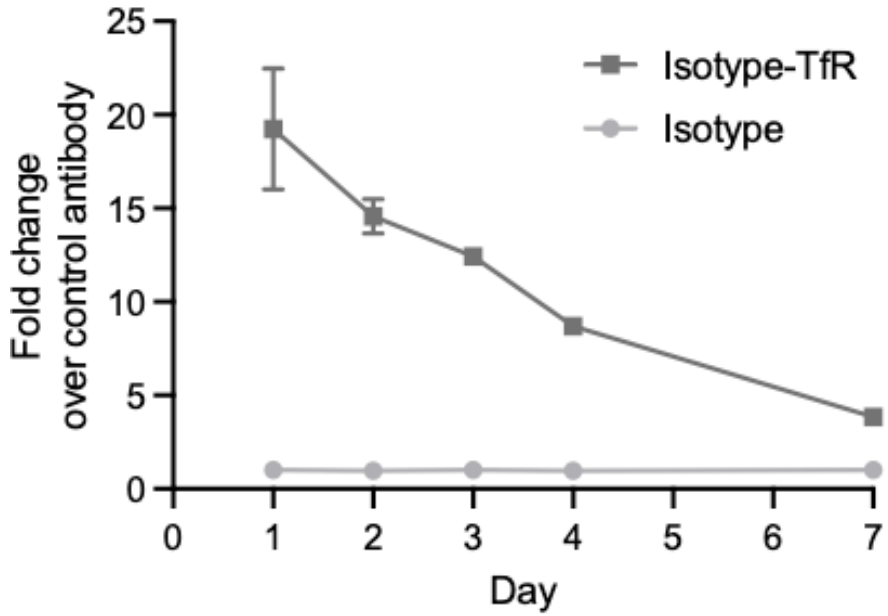
Translatable Safety
Equivalent affinities to human and cyno-BBB receptors

TfR-ABC Platform

TfR-ABC Dramatically Enhances Brain Uptake in hTfR KI Mice



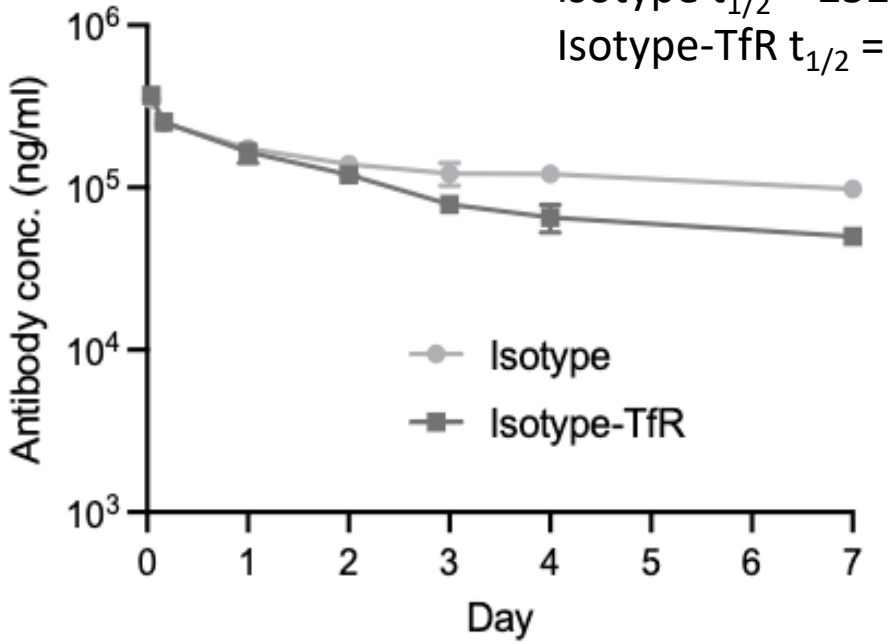
TfR-ABC Enhanced Brain Uptake (Isotype Fab cargo)



Antibody level in vessel-depleted brain fraction post 20mg/kg iv dose, n=3/group

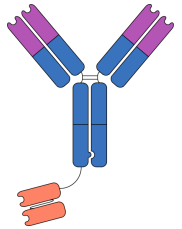
TfR-ABC Minimally Impacted Serum Clearance

Isotype $t_{1/2}$ = 252hr
Isotype-TfR $t_{1/2}$ = 154hr

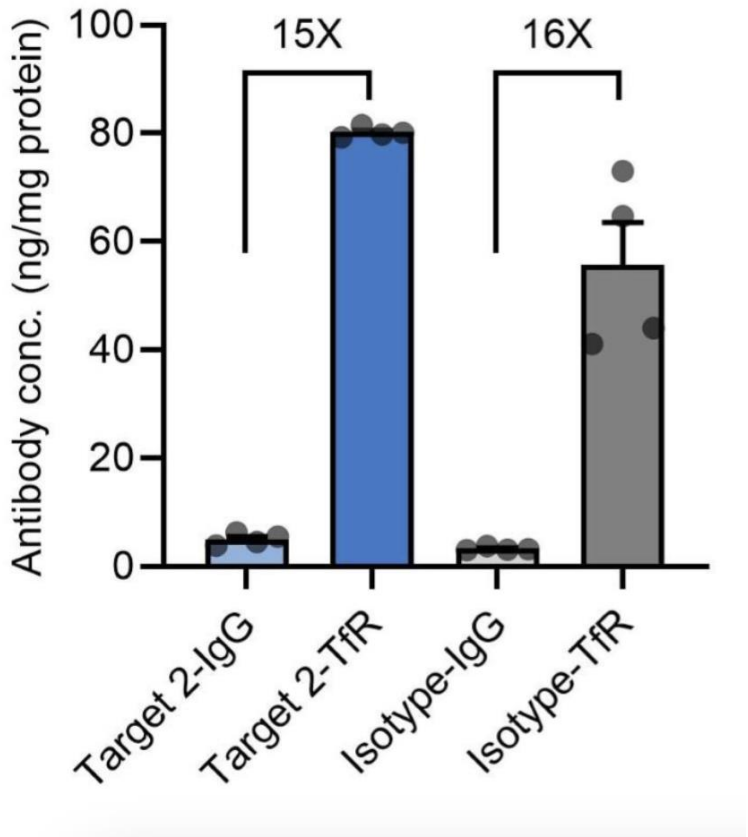


Antibody level in serum post 20mg/kg iv dose, n=3/group

TfR-ABC Facilitates Efficient Brain Uptake of Multiple Cargos in Mice

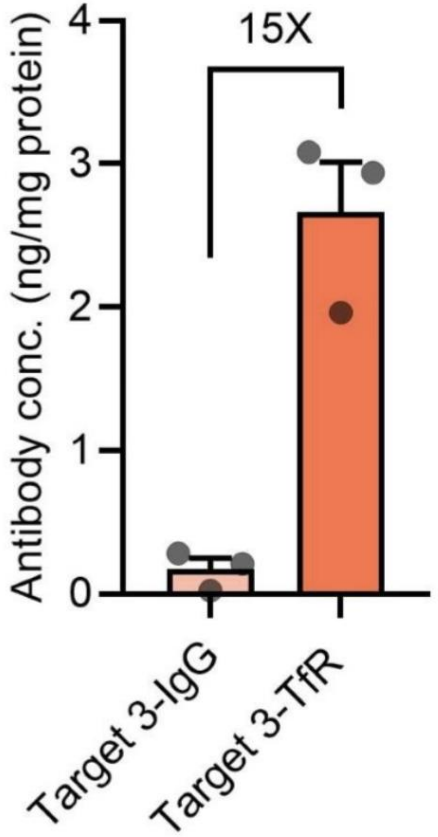


Target 2 - 20mg/kg



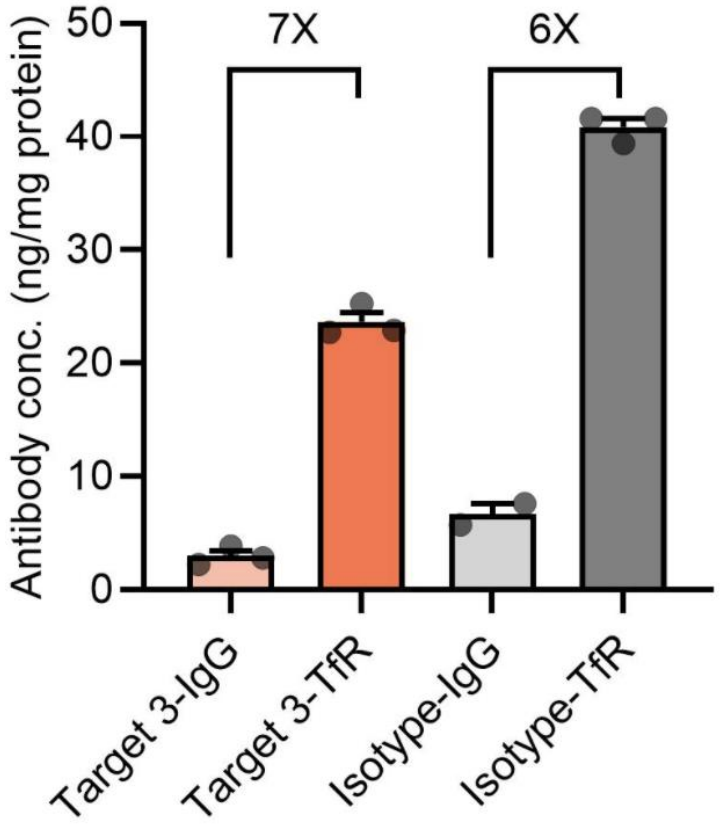
24hr post 20mg/kg iv dose, n=3/group

Target 3 - 5mg/kg



24hr post 5 mg/kg iv dose, n=3/group

Target 3 - 50mg/kg

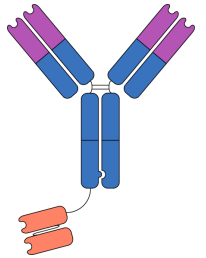


24hr post 50 mg/kg iv dose, n=3/group

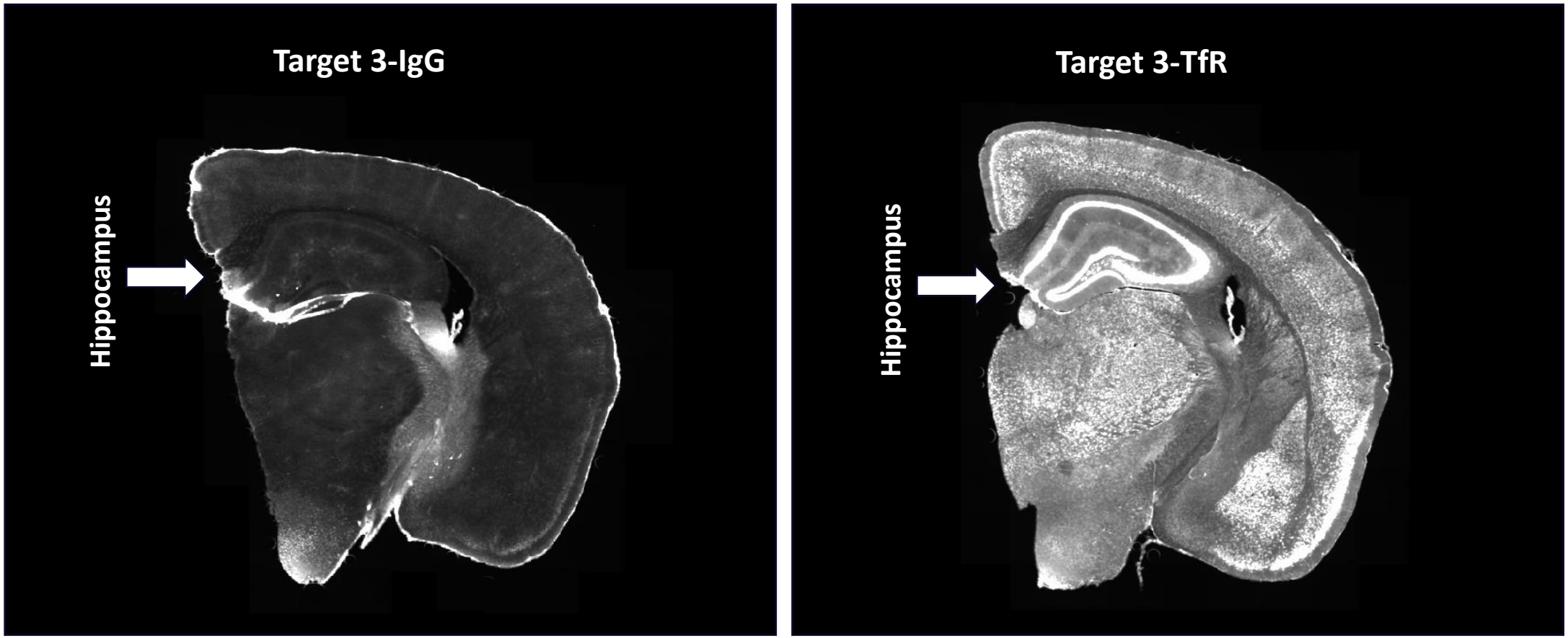
Antibody level in vessel-depleted brain fraction

TfR-ABC Drives Widespread Biodistribution in Mouse Brain

- Strong staining of neurons across brain regions due to combination of TfR and Target 3 binding
- Biodistribution of TfR-ABC molecule is highly cargo-dependent



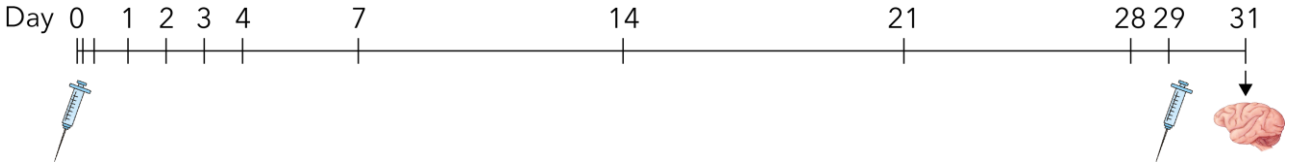
	Treated without ABC	Treated with TfR-ABC
Deep Brain Penetration with TfR-ABC	Target 3-IgG	Target 3-TfR

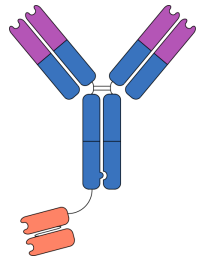


Anti-human antibody visualized post 50mg/kg iv dosing

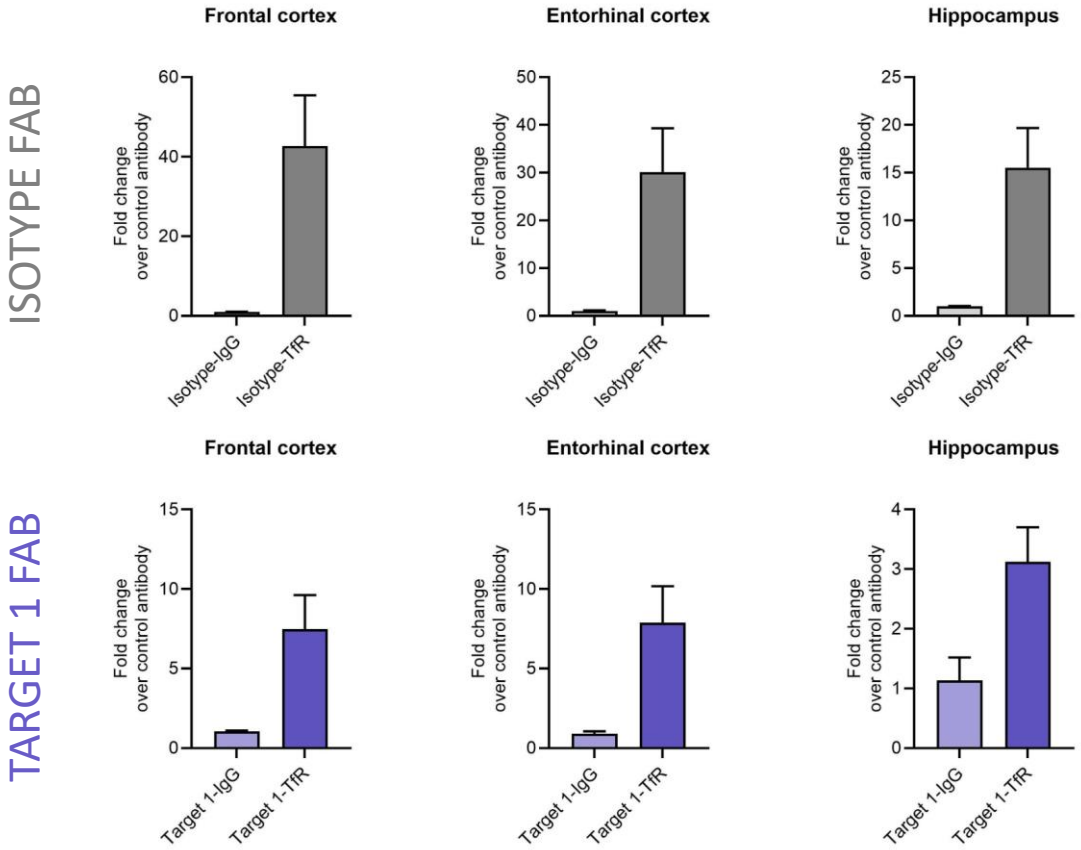
Alector data on file

TfR-ABC Shows Translatable Brain Uptake in NHPs



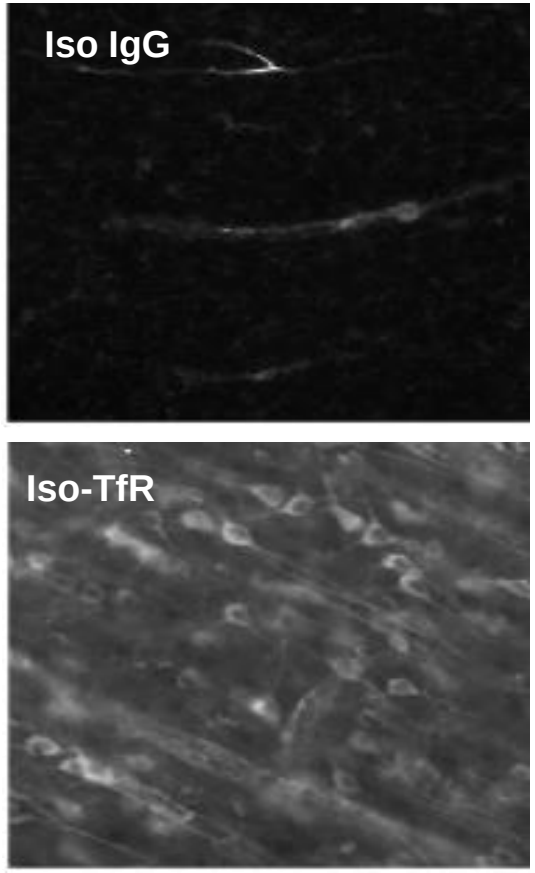


Antibody Levels in Vessel-depleted Brain Fraction Show Enhanced Brain Uptake



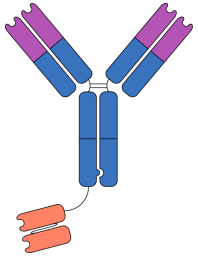
(n=3, 20mg/kg dose, +/-SEM), 48hrs post 2 monthly doses

Widespread Uptake in NHP Brain

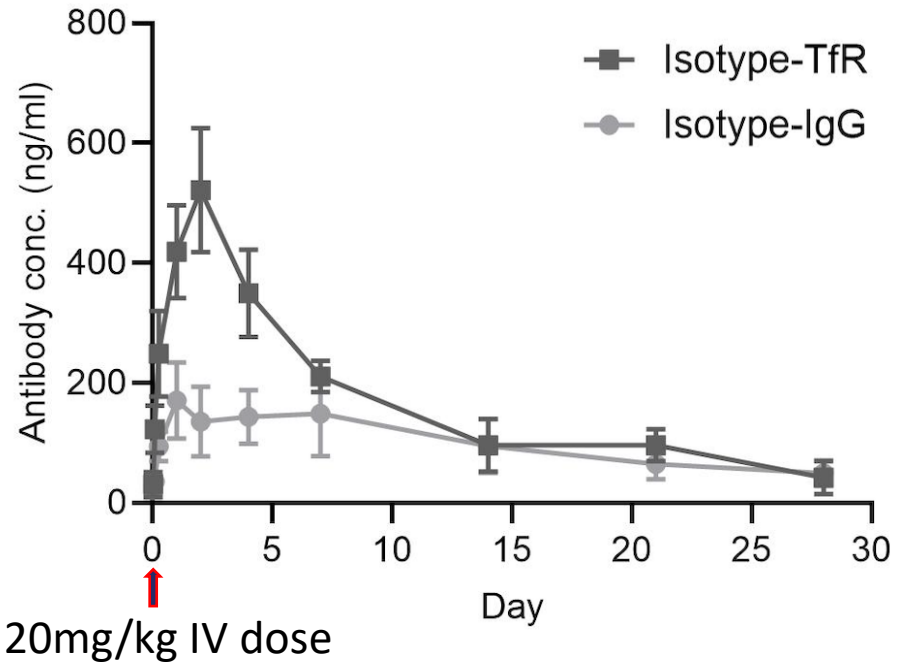


20x; frontal cortex; 48h post 2nd dose on d29

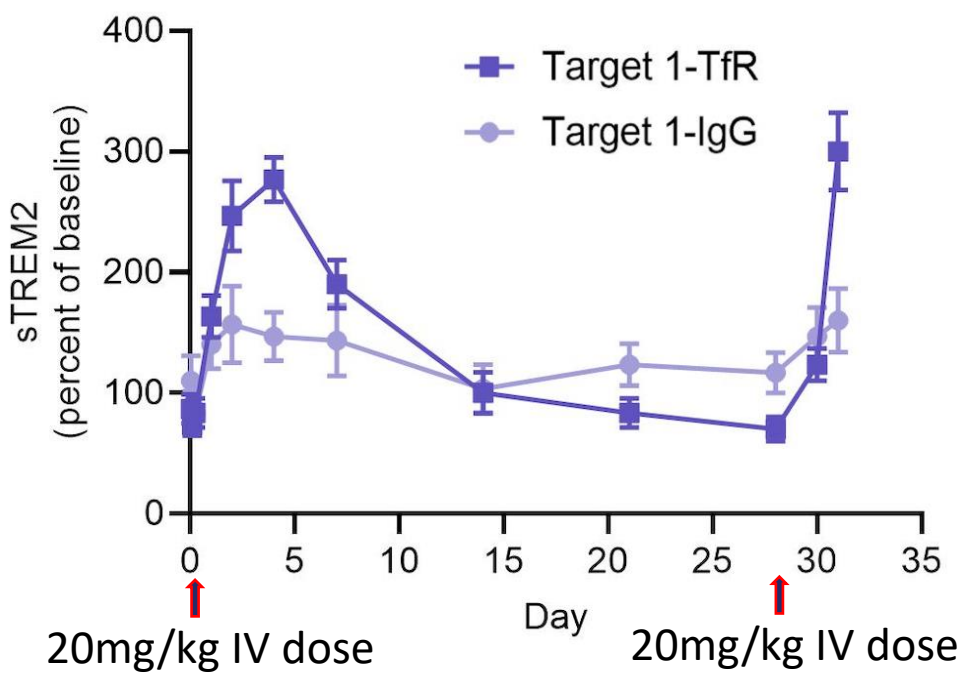
TfR-ABC Sustains Strong PK/PD Effects Up to 2 Weeks in NHP



CSF PK in IV Dosed NHP

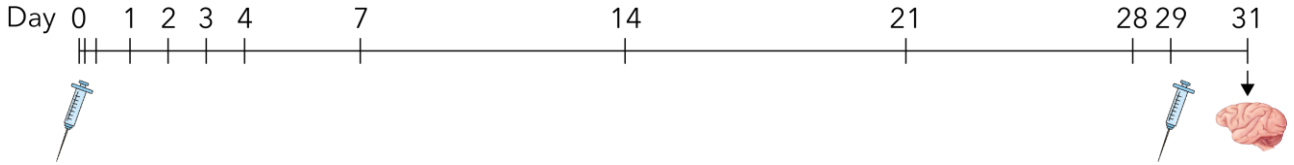


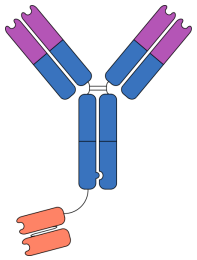
Elevation of CSF biomarker in IV Dosed NHP



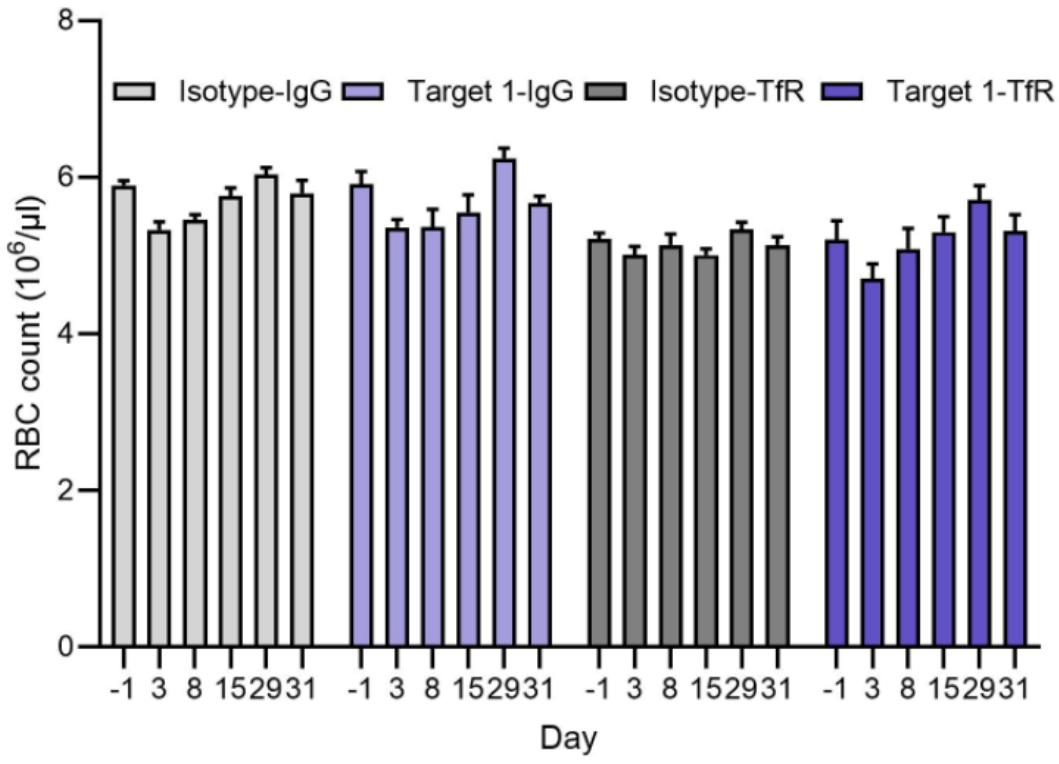
- Increased CSF antibody level seen for 2 weeks post IV dose
- 20mg/kg TfR targeting reaches equivalent CSF PD biomarker C_{max} as Target1-IgG dosed at 80 and 250mg/kg

No Clinical Findings or Anemia in NHPs Dosed with TfR-ABC

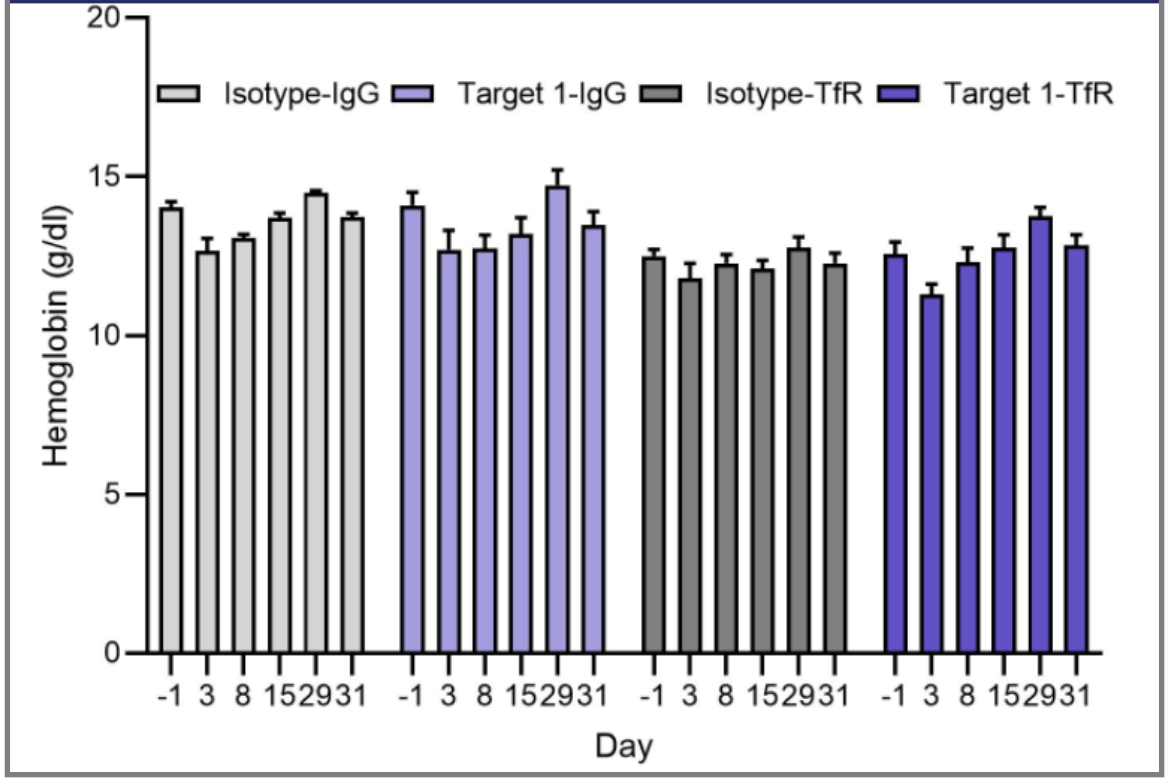




Red Blood Cell (RBC) Counts



Hemoglobin Levels



20mg/kg IV dosing on Day 1 and Day 29, n=3, +/- SEM

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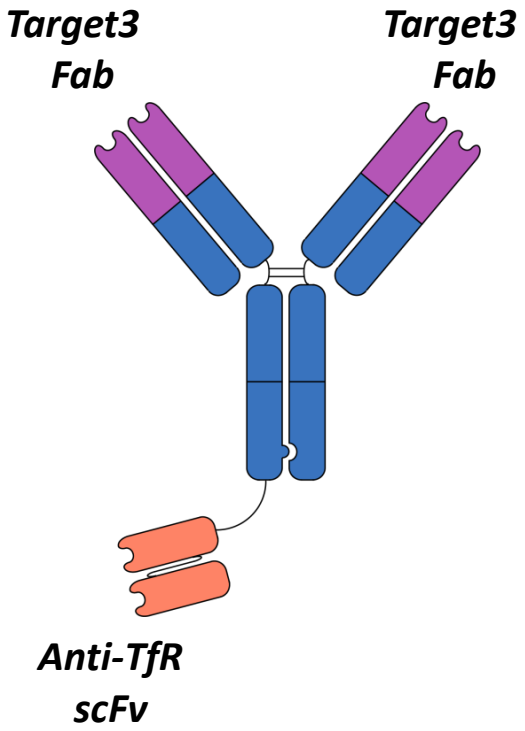
TfR-ABC Has Favorable Manufacturability and Potential for Subcutaneous Administration

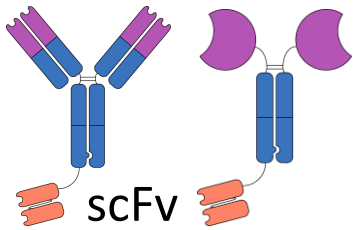
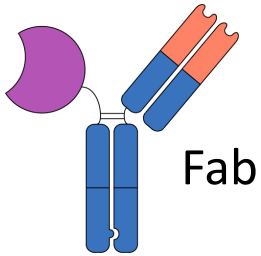


Assays	Assessment rationale	Results
Concentratability	High concentration stability	✓
Heat Stress	Accelerated stability	✓
Freeze/Thaw	Storage stability	✓
Low pH Stress	Viral inactivation	✓
Thermostability	Melting temperature	✓
Hydrophobic interaction	Non-specific interactions	✓

Increasing concentration

	% Monomer (SEC-HPLC)				
	25mg/ml	50mg/ml	75mg/ml	100mg/ml	150mg/ml
Formulation buffer	96.6	96.5	96.3	96.2	96.1
PBS buffer	96.8	96.4	96.4	96.3	96.4

Broad TfR-ABC Toolbox Available in scFv and Fab Formats to Pair with Cargo

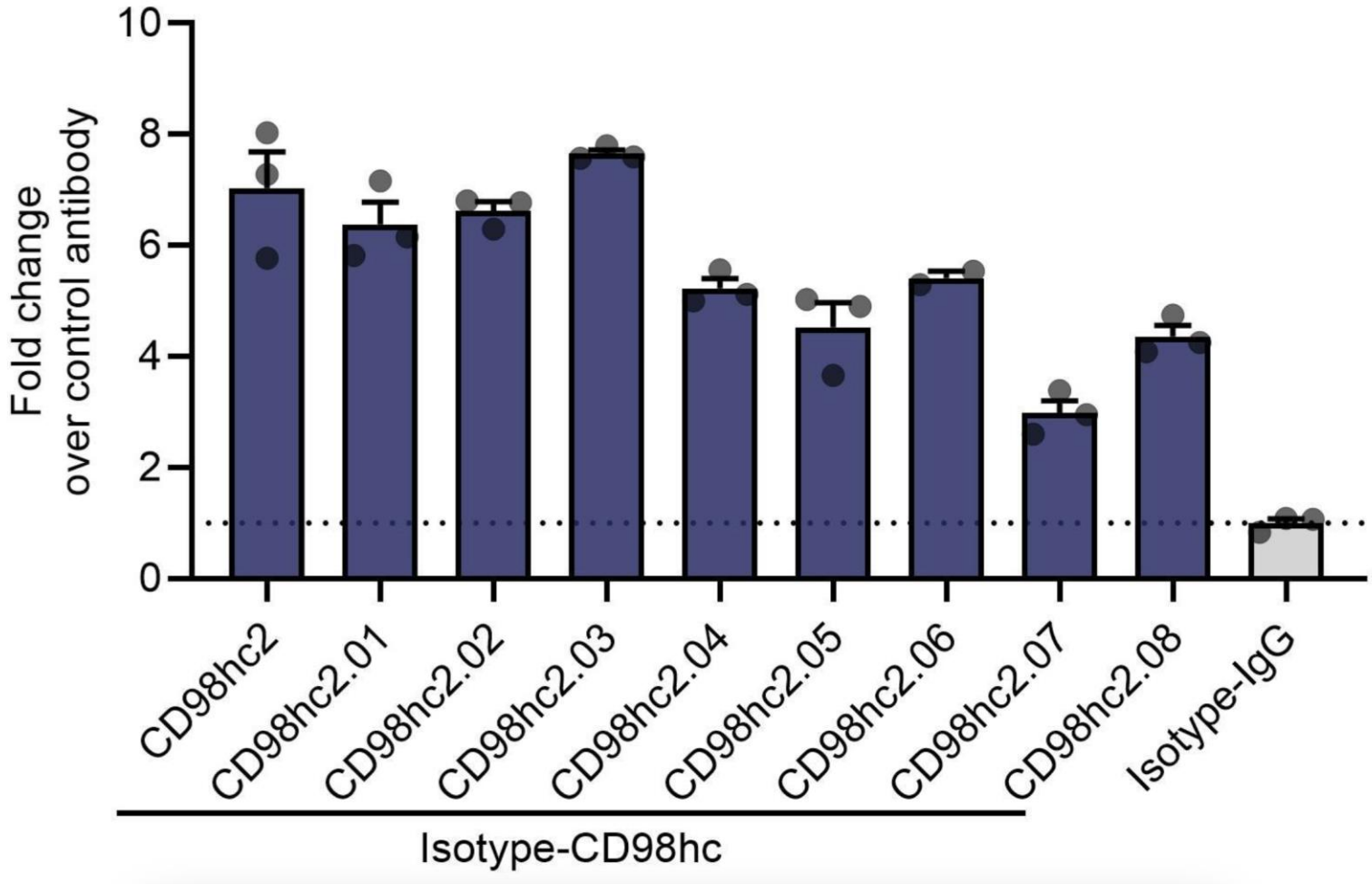
Format/ Use case	Affinity range	Human leads			Mouse surrogates	
		Variant	Human K_D (nM)	Cyno K_D (nM)	Variant	Mouse K_D (nM)
	High	hTfR.1	28	17	mTfR.1	77
	Moderate	hTfR.2 hTfR.3	193 513	60 691	mTfR.2 mTfR.3	170 680
	Low	hTfR.4 hTfR.5	2300 3810	1560 3335	mTfR.4	5000
	High	hTfR.1	19	9	mTfR.1	38
	Moderate	hTfR.2 hTfR.3	127 639	158 435	mTfR.2 mTfR.3	124 539
	Low	hTfR.4 hTfR.5	1210 4720	1320 2810	mTfR.4	2955

Affinity to hu/cyno/mu TfR apical domain

CD98hc-ABC Platform

CD98hc-ABC Hit Panels Significantly Enhance Brain Uptake in hCD98hc KI Mice

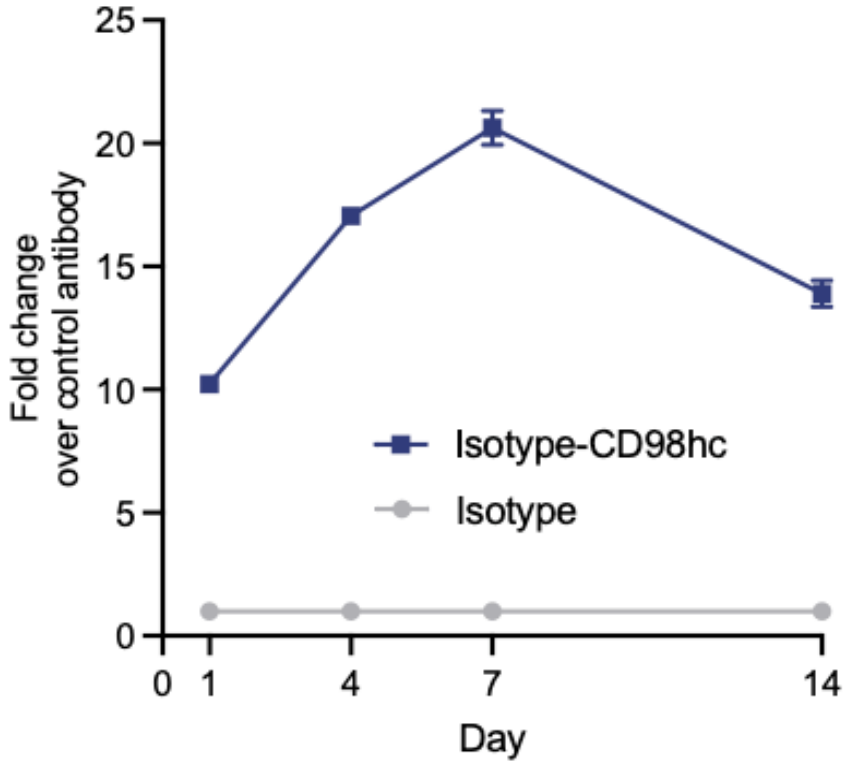
High throughput in vivo screening format identified hits with up to 8-fold increase in brain uptake



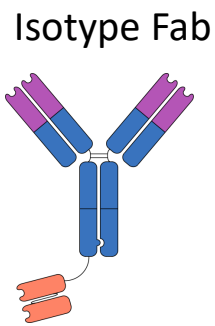
48hr post 20mg/kg iv dose, Vessel-depleted brain fraction , n=3/group

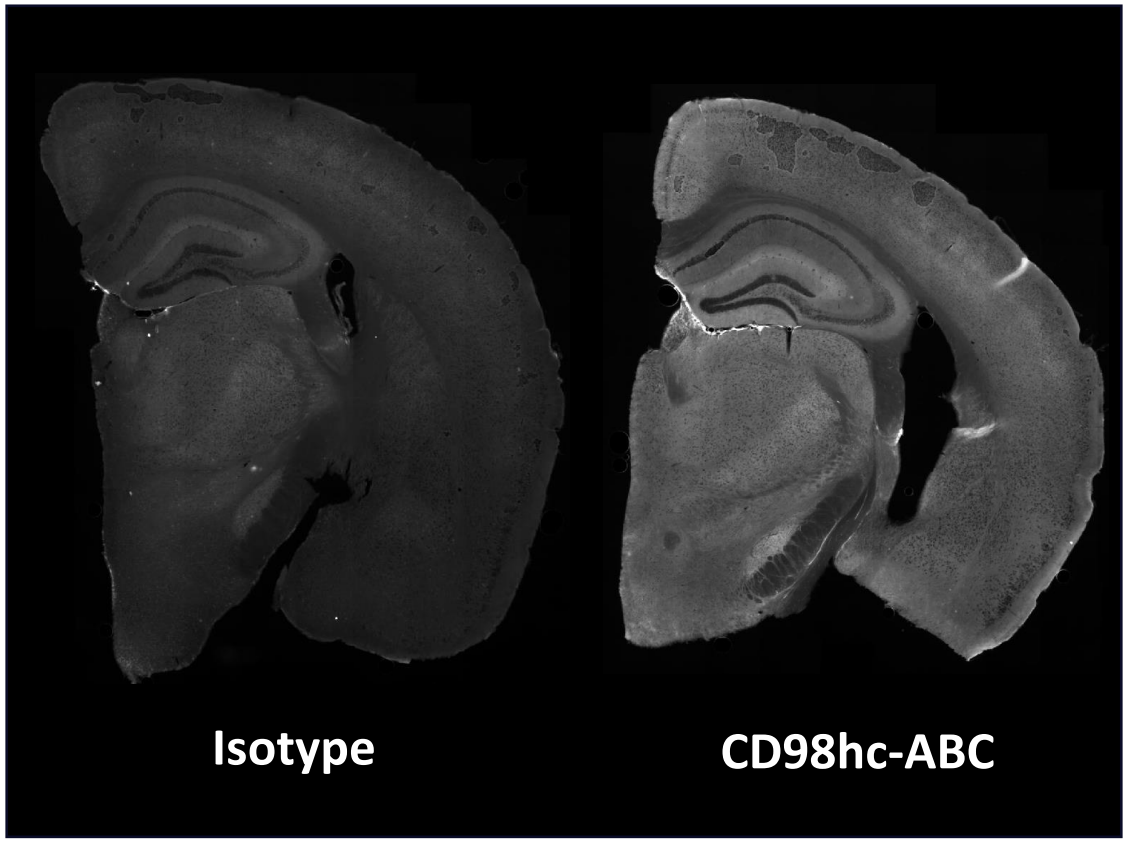
CD98hc-ABCs: Enhanced Brain Delivery with Sustained Pharmacokinetics

Prolonged Brain Uptake to Parenchymal Fraction in hCD98hc ECD KI$^{+/+}$ Mice



Antibody level in vessel-depleted brain fraction post 20mg/kg iv dose, n=3/group

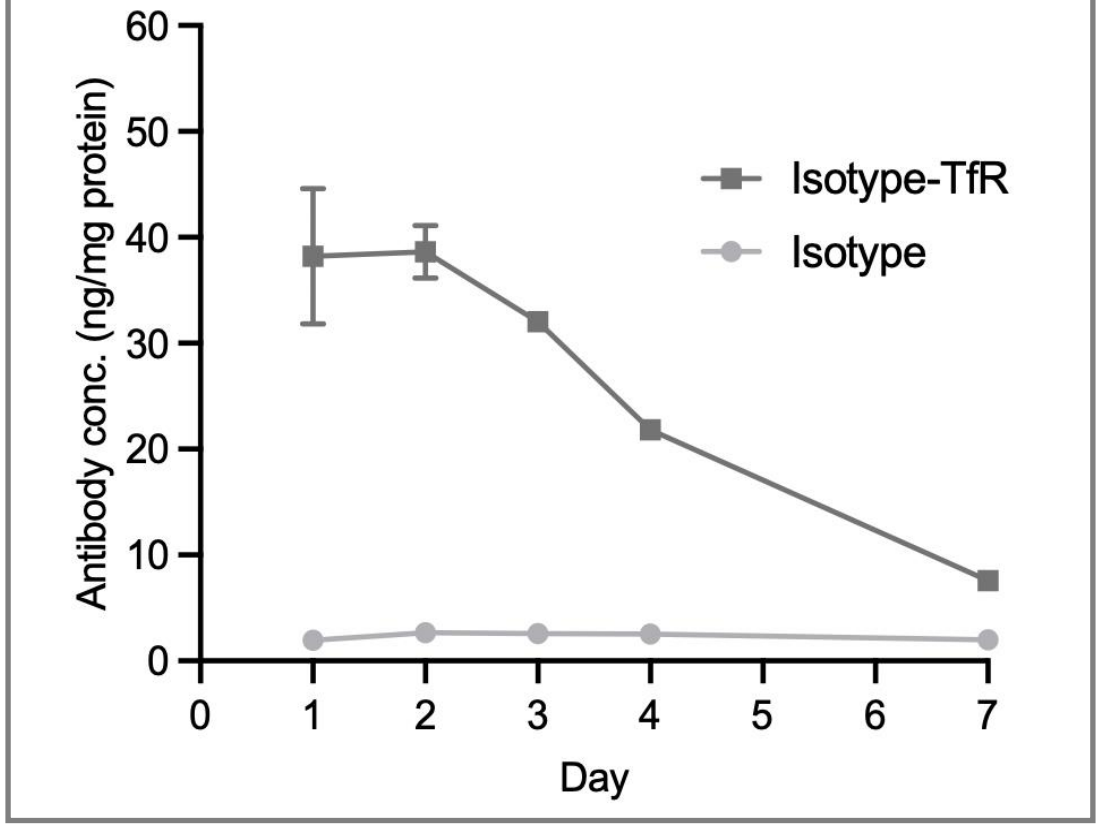




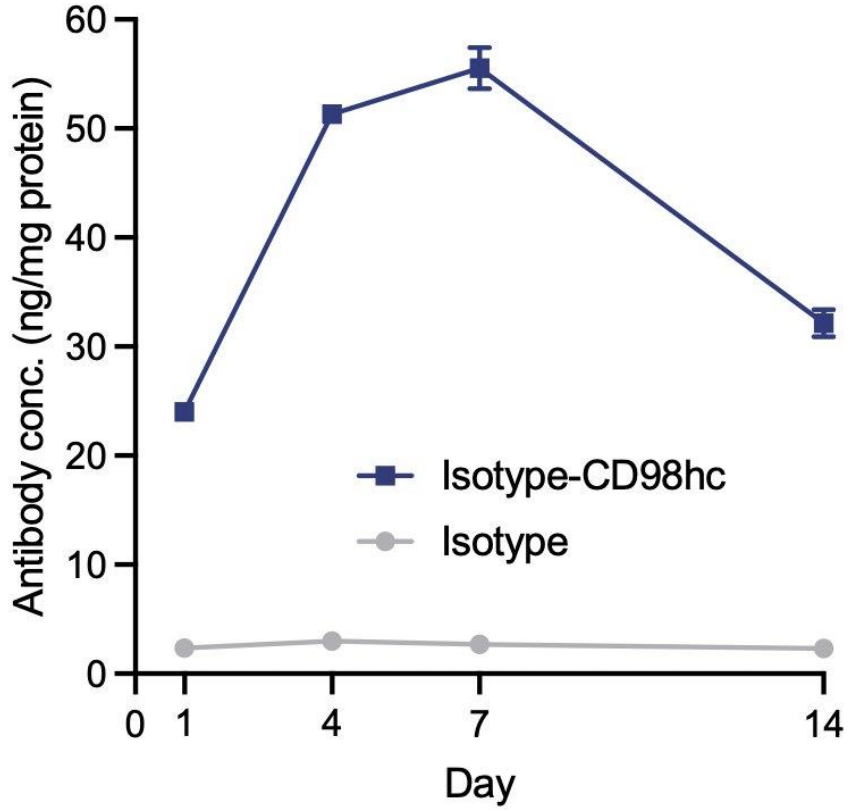
Anti-human antibody visualized 7d post-iv dosing (20 mg/kg)

Brain Uptake Differences Between CD98hc-ABC and TfR-ABC to Pair with Diverse Cargos

Rapid Brain Uptake with TfR-ABC



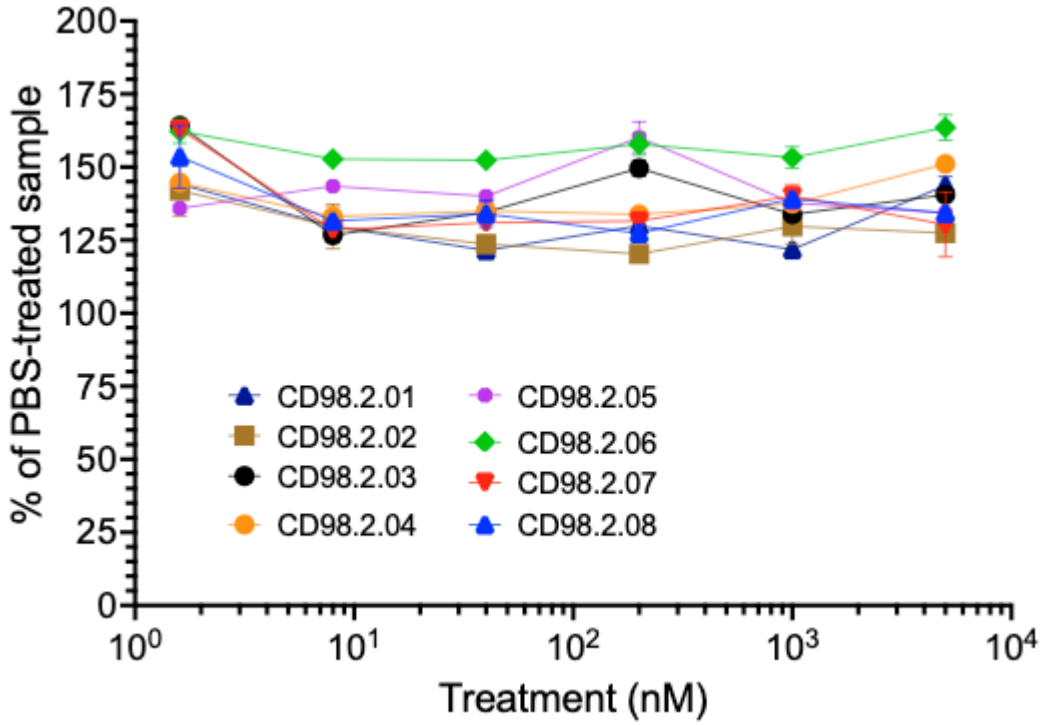
Potential for Sustained Brain Uptake with CD98hc-ABC



Antibody level in vessel depleted mouse brain post iv dose (n=3/group, 20mg/kg dose, +/-SEM)

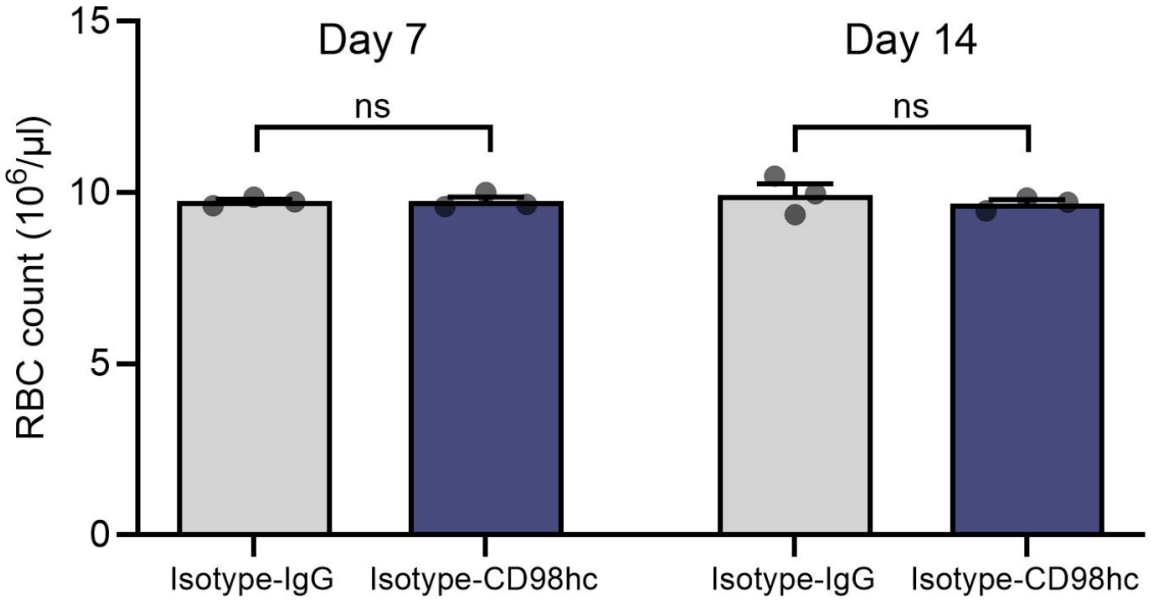
CD98hc-ABC Show Favorable Initial In Vitro and In Vivo Murine Safety Profiles

In vitro: No decrease in Amino Acid Uptake



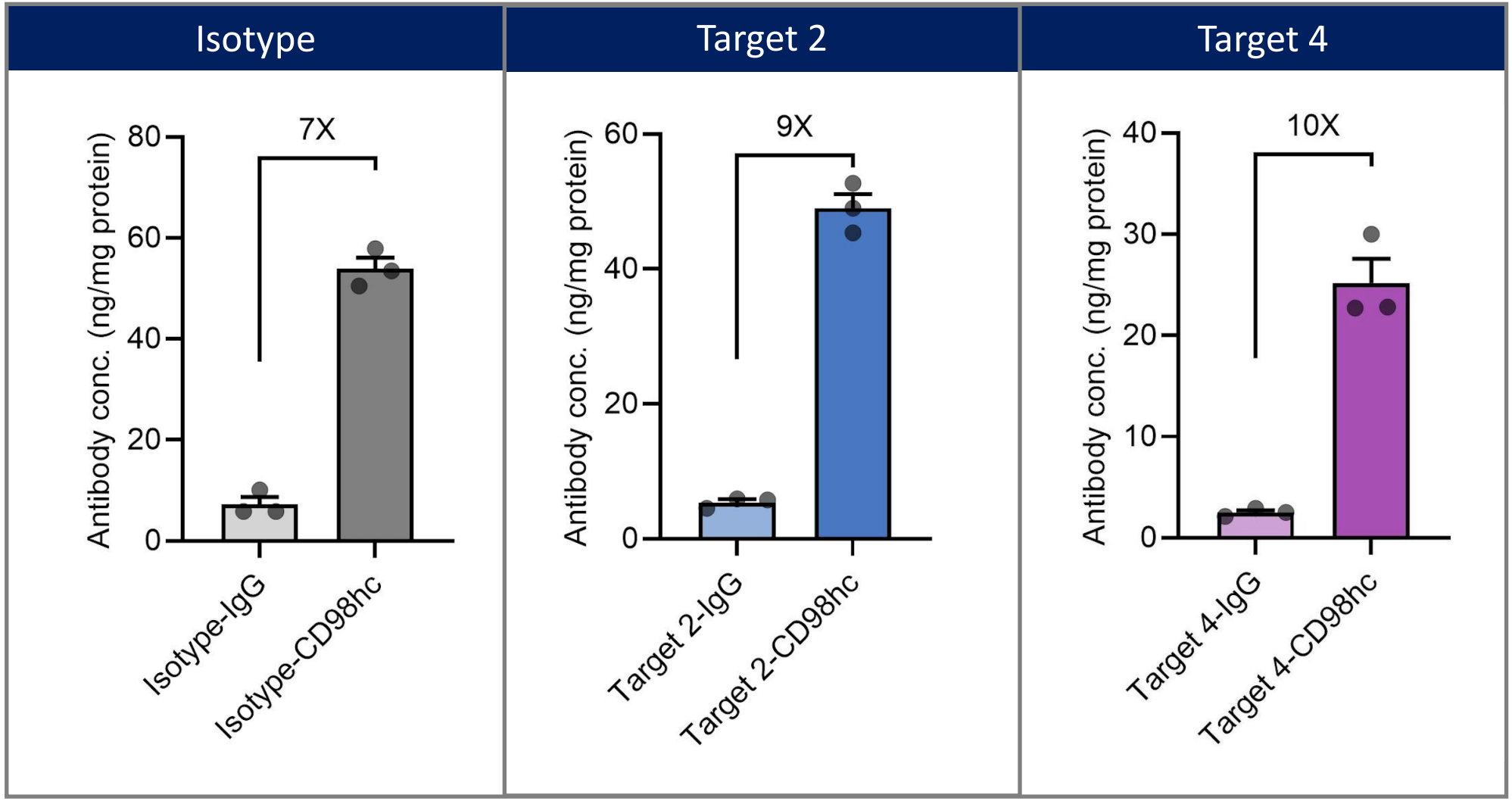
Amino acid levels 16hr post antibody treatment in hCMEC/D3 cells

In vivo: No notable changes in hematological parameters



Hematology post iv dose (n=3/group, 20mg/kg dose, +/-SEM)

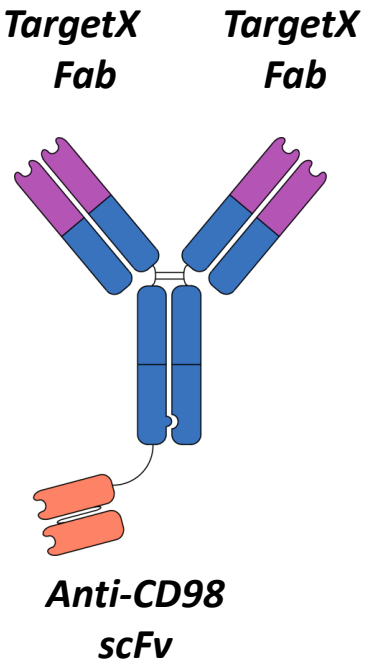
CD98hc-ABC Facilitates Efficient Brain Uptake of Multiple Cargos in Mice



Antibody level in vessel-depleted brain fraction 72hrs post 20mg/kg iv dose, n=3/group

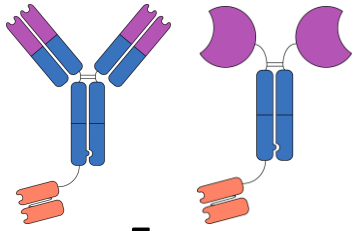
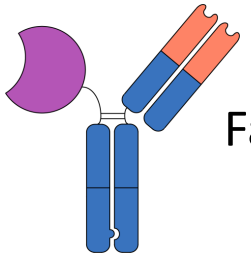
CD98hc-ABC Shows Favorable Manufacturability with Multiple Therapeutic Payloads

Assays	Assessment rationale	Target2-CD98	Target3-CD98	Target4-CD98
2-week Heat Stress	Accelerated stability	✓	✓	✓
Freeze/Thaw	Storage stability	✓	✓	✓
Low pH Stress	Viral inactivation	✓	✓	✓
Hydrophobic interaction	Non-specific interactions	✓	✓	✓



✓ Exceeds cut-off ✓ Acceptable

CD98hc-ABC Toolbox Available in scFv and Fab Formats to Pair with Cargo

Format/Use Case	Affinity Range	Variant	Hu CD98hc ECD Binding K_D (nM)	Cyno CD98hc ECD Binding K_D (nM)
 scFv	High	CD98.2 CD98.2.03	60 93	51 73
	Moderate	CD98.2.09 CD98.2.08	268 378	259 534
 Fab	High	CD98.2 CD98.2.03	58 99	51 73
	Moderate	CD98.2.09 CD98.2.08	128 447	176 709

ABC Key Strengths and Current Status

		TfR-ABC	CD98hc-ABC
Platform Advantages	Binding moiety and formats	Fab, scFv, VHH Flexible formats	Fab, scFv, VHH Flexible formats
	Affinity range	10-5000nM	1-500nM
	Fc compatibility	Compatible with Fc engineering	Compatible with Fc engineering
	Matched hu/cyno affinities	Yes	Yes
	Matched mouse surrogates	Yes	In progress
Brain Uptake	Absolute level	18nM in NHP frontal cortex[1]	19nM in murine brain[2]
	Fold increase	15-40x in NHP brain regions[1]	>20x in murine brain[2]
Program Application	Antibody cargos	5	3
	Protein cargos	confirmed	confirmed

alector™ Alector data on file

1) 48hrs post 20mg/kg iv dose
2) 1wk post 20mg/kg iv dose

Alector Brain Carrier: Potential Applications

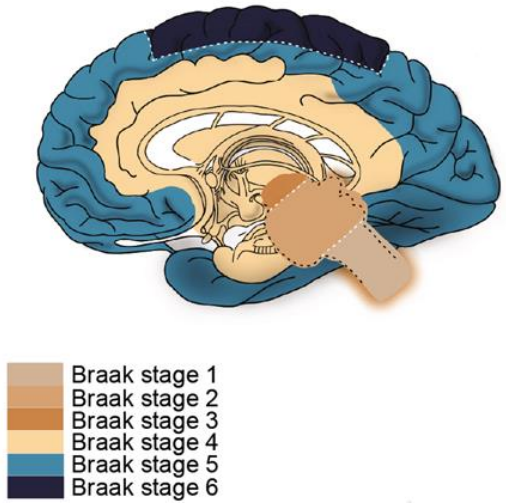
Maxime Ah Young-Chapon, Ph.D.

Lead Scientist, GCase Program

Alector

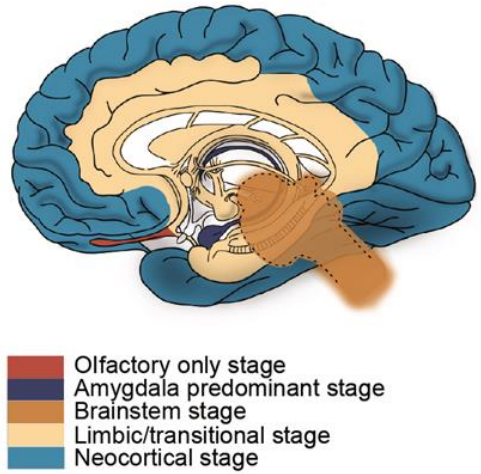
GBA1 Gene Mutations Are a Major Risk Factor for Several Neurodegenerative Diseases

Parkinson's Disease (PD)[8]



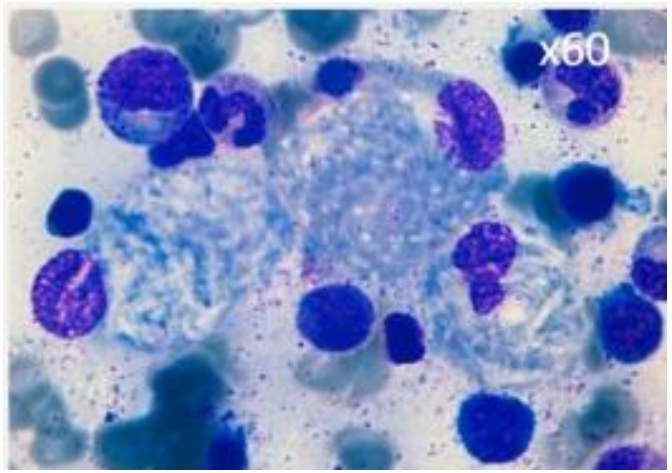
- ~10 million patients worldwide[1]
- 5-15% are *GBA1* mutation carriers[2]
- Activity is reduced in non-carriers[2]
- Increase risk and earlier age of onset[2]

Lewy Body Dementia (LBD)[8]



- ~5-8 million patients worldwide[3]
- 3-30% are *GBA1* mutation carriers[4]
- Activity is reduced in non-carriers[4]

Gaucher Disease (GD)[9]



- ~125,000 patients worldwide[5]
- *GBA1* mutations are causal
- GD type 1 have increased risk of PD[6]
- GD type 2 and 3 are neuronopathic[7]

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
8. Used with permission of Springer Nature BV, from Brain regions susceptible to alpha-synuclein spreading, Guo, YJ et al, 27, 1997; permission conveyed through Copyright Clearance Center, Inc.
9. Stirnemann J et al. Int J Mol Sci. 2017 Feb 17;18(2):441.

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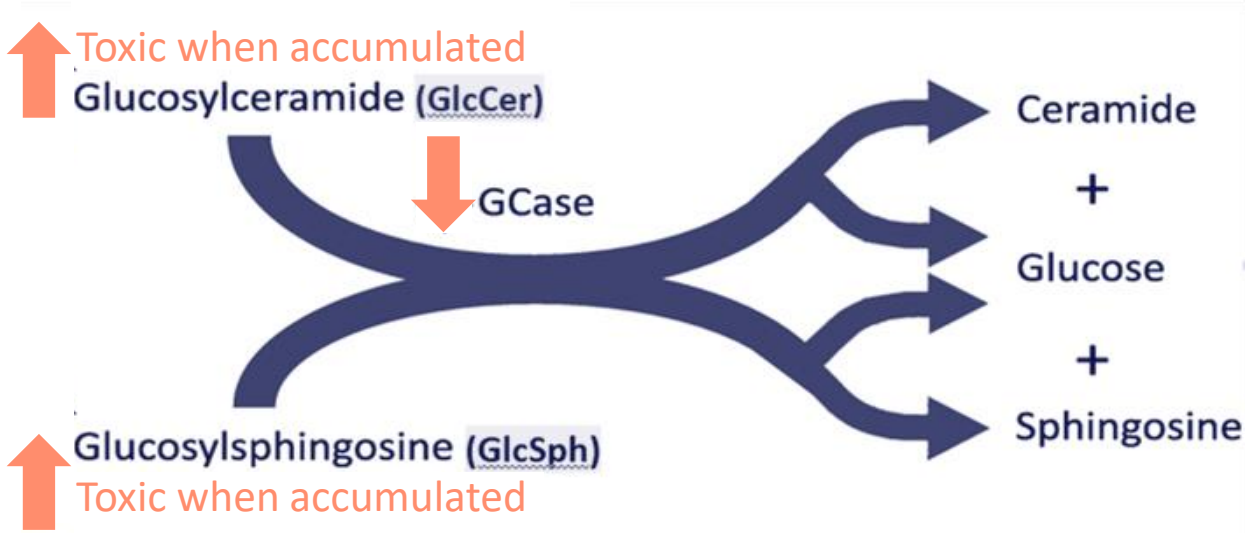
GCase-ABC ERT as a Potential Investigational Therapy in Gaucher Disease, PD, and LBD

GCase is a Lysosomal Enzyme That Breaks Down Glycolipids[1]

- GCase, or glucocerebrosidase, is an enzyme encoded by the *GBA1* gene.
- Pivotal role in the degradation of glycosphingolipids (GlcCer and GlcSph) within lysosomes.
- Mutations in the *GBA1* gene lead to accumulation of its substrates Glucosylceramide and Glucosylsphingosine.
- Lipid substrates accumulation is the underlying cause of GD and an increased risk of PD and LBD.

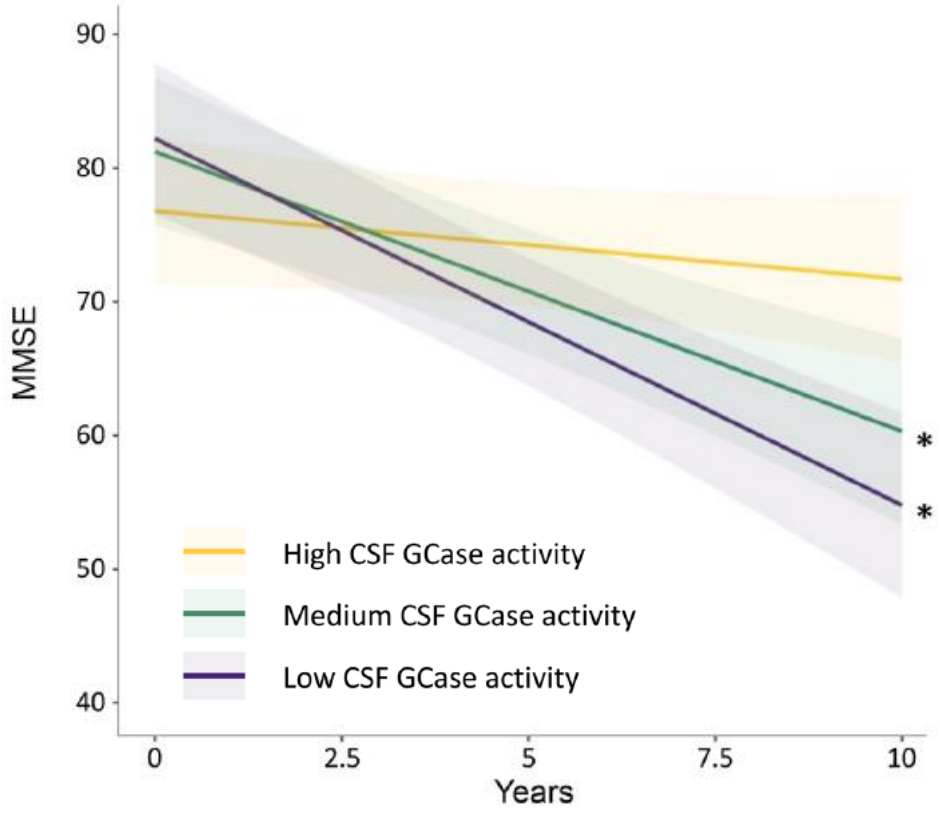
GCase Hydrolyzes GlcCer and GlcSph[2]



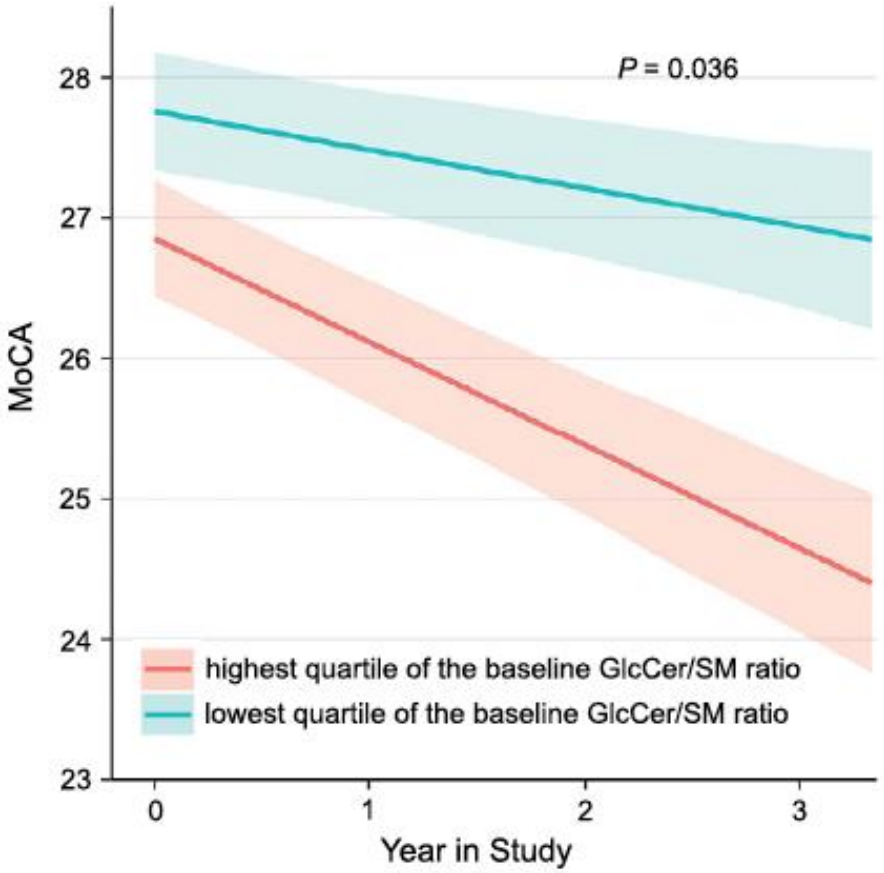
1. Boer DEC, et al. Glucocerebrosidase: Functions in and Beyond the Lysosome. *J Clin Med*. 2020 Mar 9;9(3):736.
2. Do, J. et al. Mol Neurodegeneration 14, 36 (2019). (http://creativecommons.org/licenses/by/4.0/).

Observational Studies Provide Rationale for GCase Enzyme Replacement Therapy (ERT)

Patients with lower CSF GCase activity at diagnosis progress faster



Parkinson's Disease patients with higher CSF substrate levels progress faster



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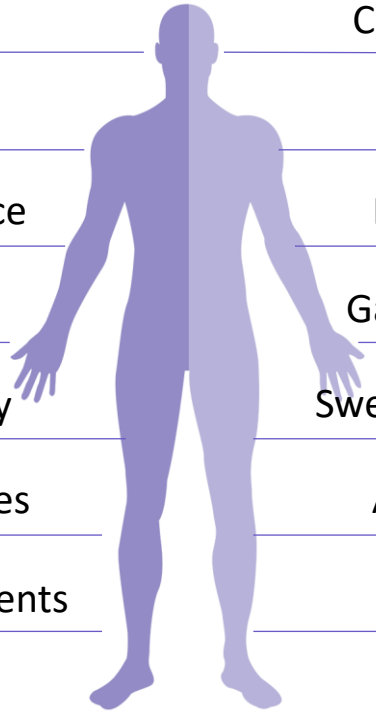
2021 Huh et al. *NPJPD* Glucosylceramide in cerebrospinal fluid of patients with GBA-associated and idiopathic Parkinson's disease enrolled in PPMI
2023 Oftedal et al. *Translational Neurodegeneration* Early GCase activity is a predictor of long-term cognitive decline in Parkinson's disease

Parkinson’s Disease (PD)

A chronic, progressive neurodegenerative disease affecting movement and cognition

Motor Impairments	Non-motor Impairments
Bradykinesia	Cognitive impairment
Hypersalivation	Sleeping disorders
Posture imbalance	Mood disturbances
Trembor	Gastrointestinal issues
Muscular rigidity	Sweat, olfactory disorders
Walking difficulties	Anxiety, depression
Freezing of movements	Pain



Prevalence: ~10 million people WW with PD. ~ 90,000 Americans are diagnosed with PD each year.[1]

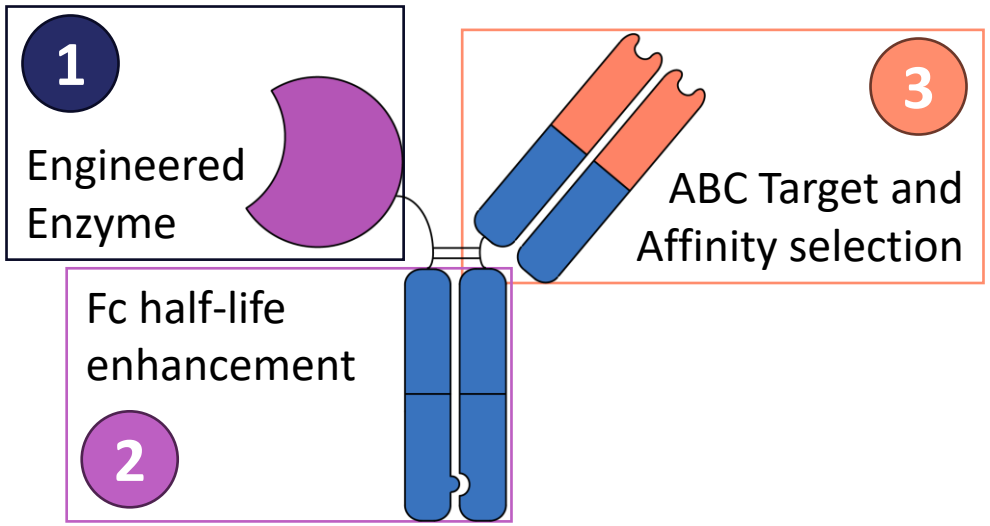
Demographics: Typically diagnosed > 60, but approximately 4% of patients develop symptoms before the age of 50.[1]

Unmet Need: No disease-modifying treatments approved to halt or slow progression of PD.[2]

Genetics: Approximately 10% of PD is familial and caused by single gene mutations.[3]

1. Parkinson’s Foundation Statistics
2. Kieburtz K, et al. A New Approach to the Development of Disease-Modifying Therapies for PD; Fighting Another Pandemic. *Mov Disord*. 2021 Jan;36(1):59-63.
3. Klein C, et al. Genetics of Parkinson's disease. *Cold Spring Harb Perspect Med.* 2012 Jan;2(1):a008888.

ABC Platform to Enable Brain-Penetrant GCase ERT



Versatility

- Optimal ABC format for GCase fusion

Tunability

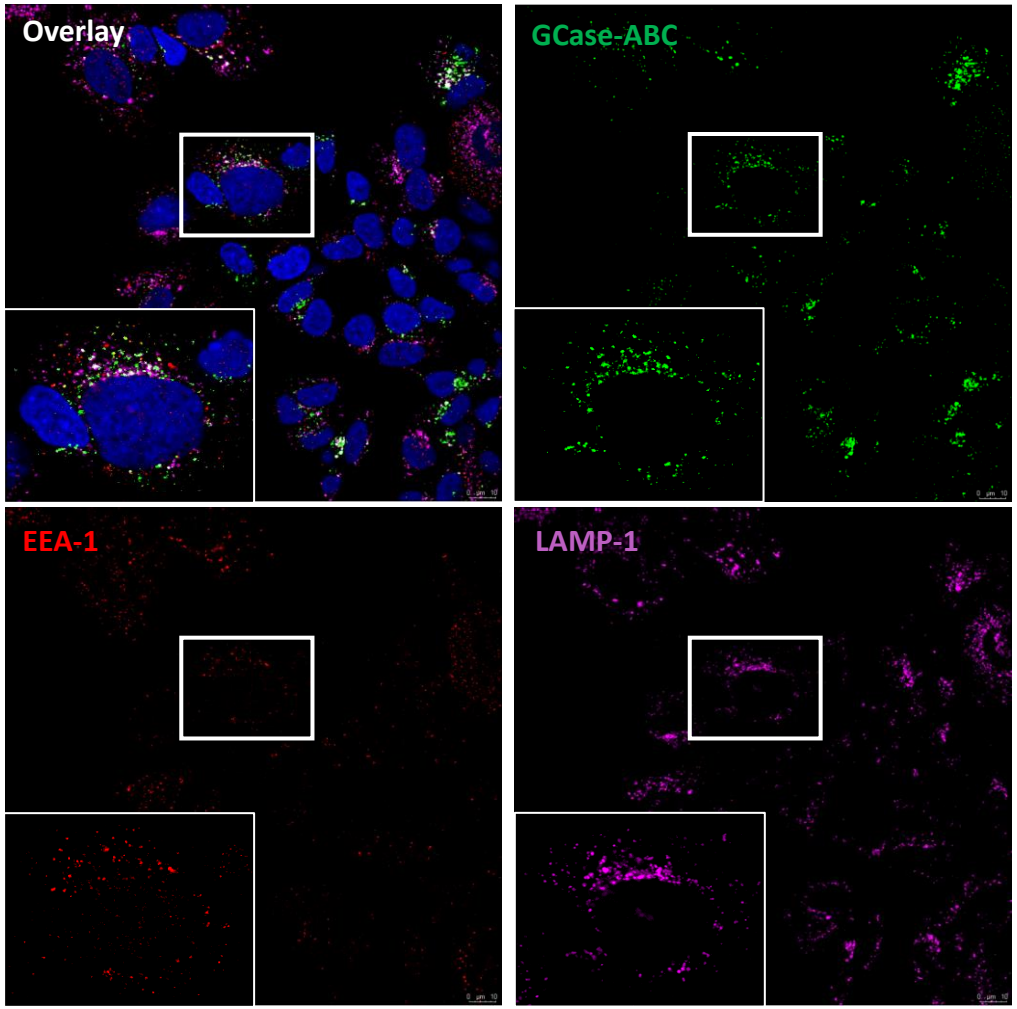
- ABC target and affinity optimized for maximum delivery and safety

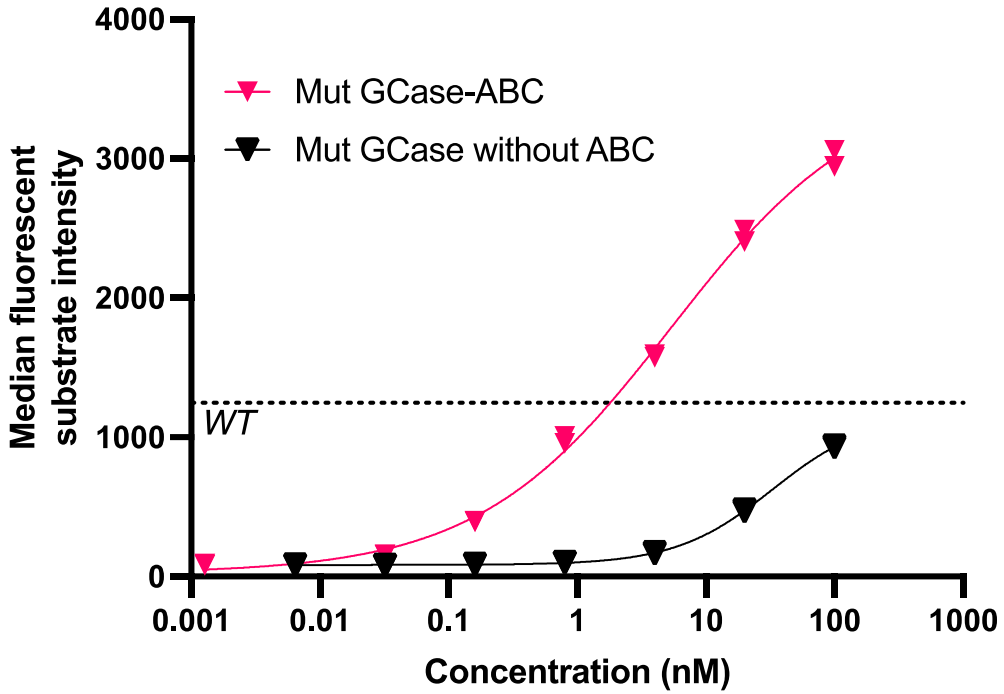
Translatability

- Affinity-matched anti-mouse and anti-human moieties allows validation in genetic mouse models

ABC Allows Delivery of Protein Cargo to Lysosomes and Rescue of GCase Activity

SH-SY5Y GBA1 KO

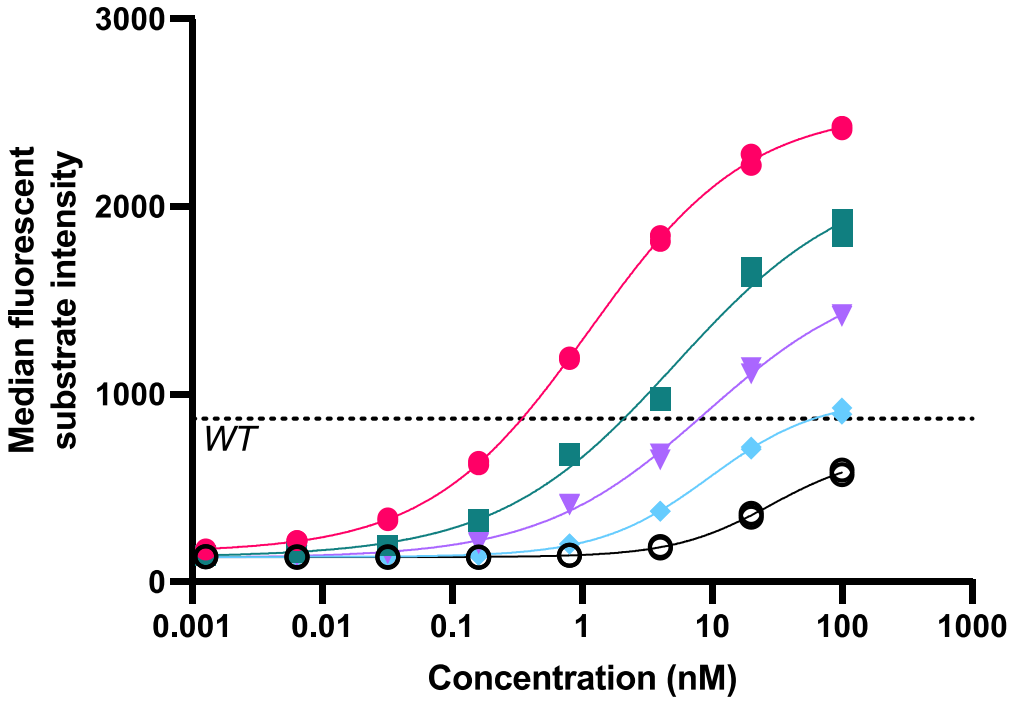




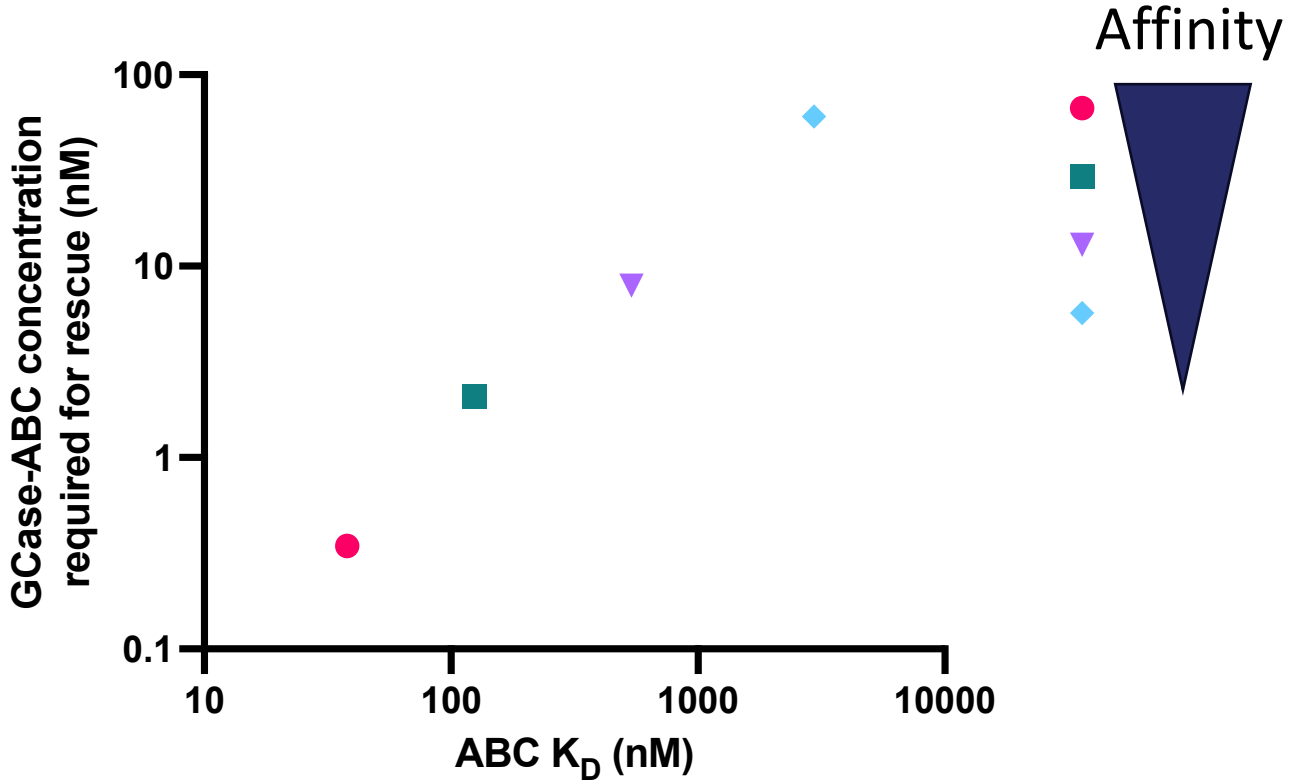
Alector data on file

ABC Affinity Was Tuned to Optimize Uptake in Vitro

GCase-ABC can rescue GCase activity in Gba1$^{-/-}$ neuroblastoma cells

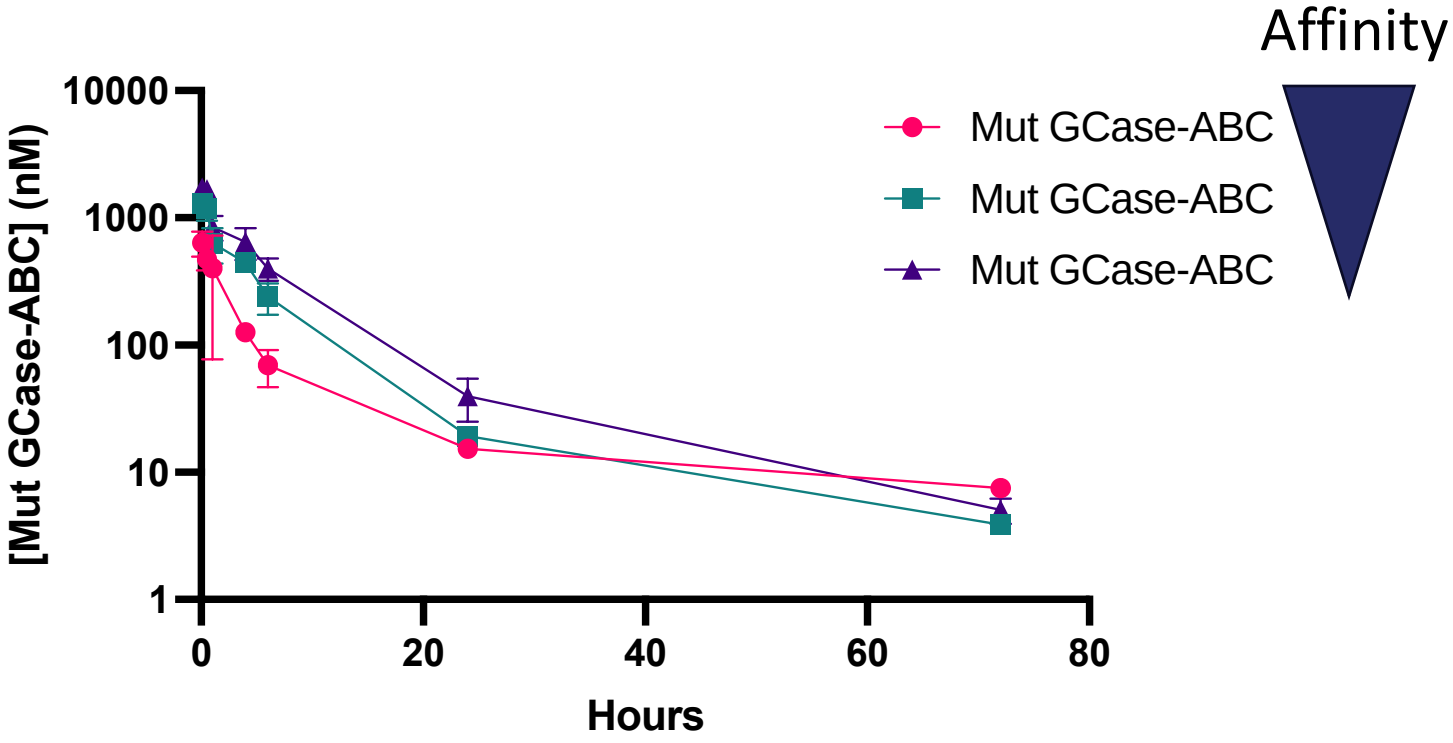


Higher ABC affinity reduces concentration required for rescue

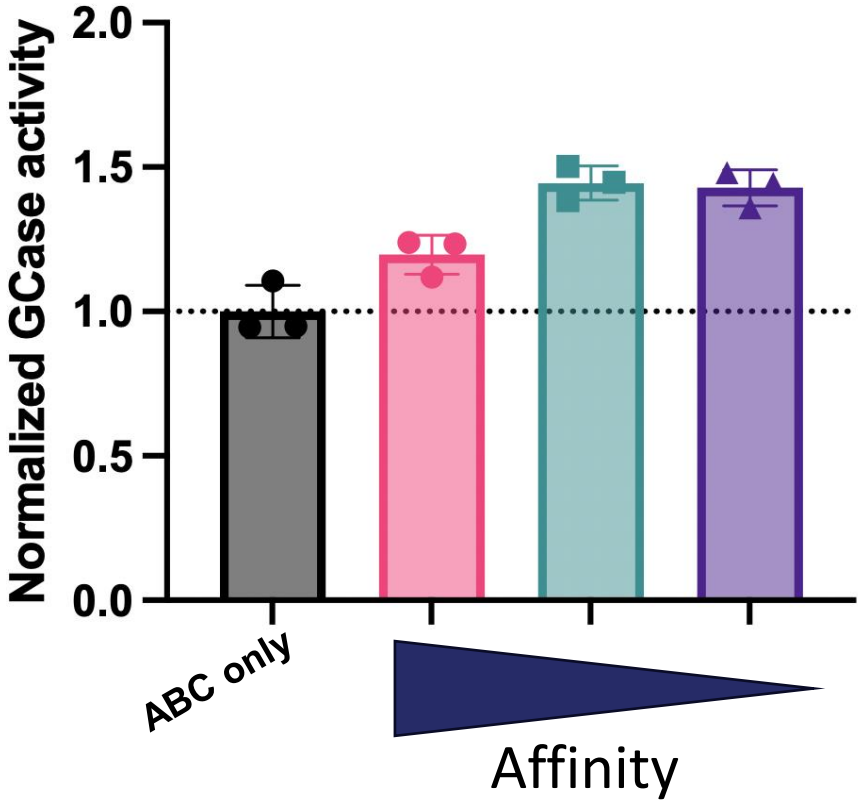


ABC Affinity Was Tuned to Optimize Uptake in Vivo

Decreasing ABC affinity enhances blood exposure



Lower ABC affinity enhance GCase delivery to brain parenchyma



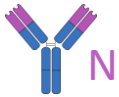
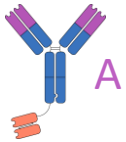
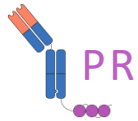
Alector data on file

ABC Platform to Enable Brain-Penetrant GCase ERT

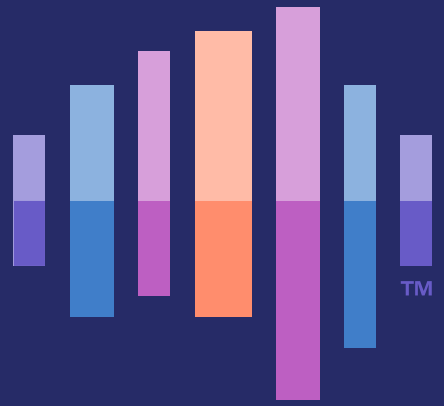
- Mutations in GBA1 increase the risk of Parkinson's Disease
- Brain-penetrant enzyme replacement therapy may rescue GCase deficiency in GBA1 mutation carriers
- ABC moiety greatly enhances ability of recombinant GCase to rescue glucocerebrosidase activity in GBA1 knockout neuroblastoma cell lines
- Versatility of our ABC platform allows us to experimentally determine affinity range for optimum cell uptake and parenchymal delivery
- GCase-ABC can increase glucocerebrosidase activity by over 40% in the brain of wild-type mice

Closing Remarks and Q&A

ABC Fuels Long-Term Value Creation

PROGRAMS	Exploring the potential to develop next-generation, brain-penetrant product candidates PGRN: FTD-*GRN* TREM2: AD PGRN: AD CLINICAL GCase + ABC: PD GCase + ABC: LBD GPNMB + ABC: PD UD TARGETS + ABC: AD, PD, ALS PRECLINICAL
MODALITIES	 NAKED ANTIBODIES  ANTIBODIES+ABC  PROTEINS+ABC  ENZYMES+ABC
THERAPEUTIC AREA	NEURODEGENERATION
STRATEGY	IMMUNO-NEUROLOGY: HUMAN GENETICS + IMMUNOLOGY + NEUROSCIENCE

alector™ UD = undisclosed



Thank you