

Crossing the Blood-Brain Barrier: Developing Alector’s Next Generation of Investigational Therapies for Neurodegeneration



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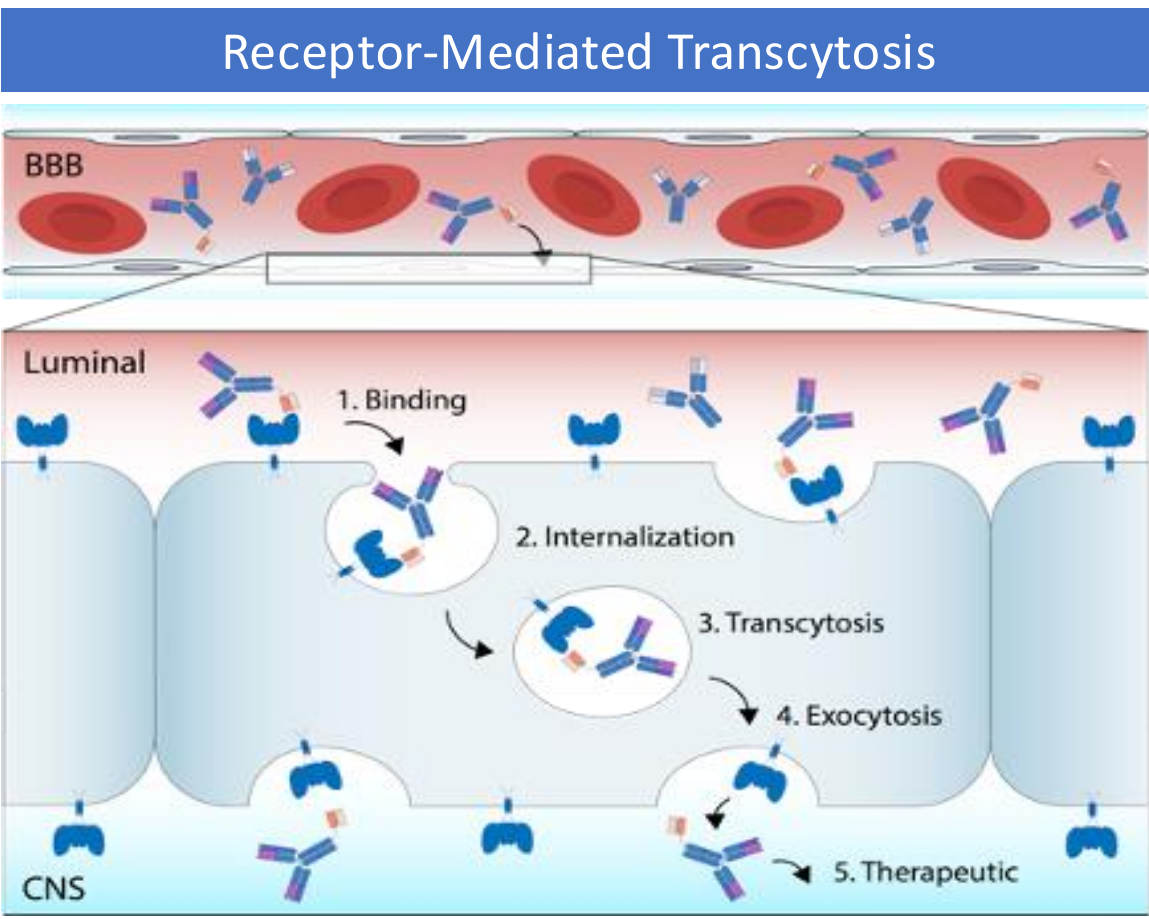
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Introduction to Alector Brain Carrier (ABC) Platform

Alector Brain Carrier (ABC) platform is Alector’s Blood-Brain Barrier (BBB) technology platform, designed to enable precise targeting and non-invasive peripheral delivery of therapeutics to the brain. ABC technology utilizes receptor-mediated transport through receptors such as transferrin receptor (TfR) or CD98hc.

Our core design features for the ABC Platform are:

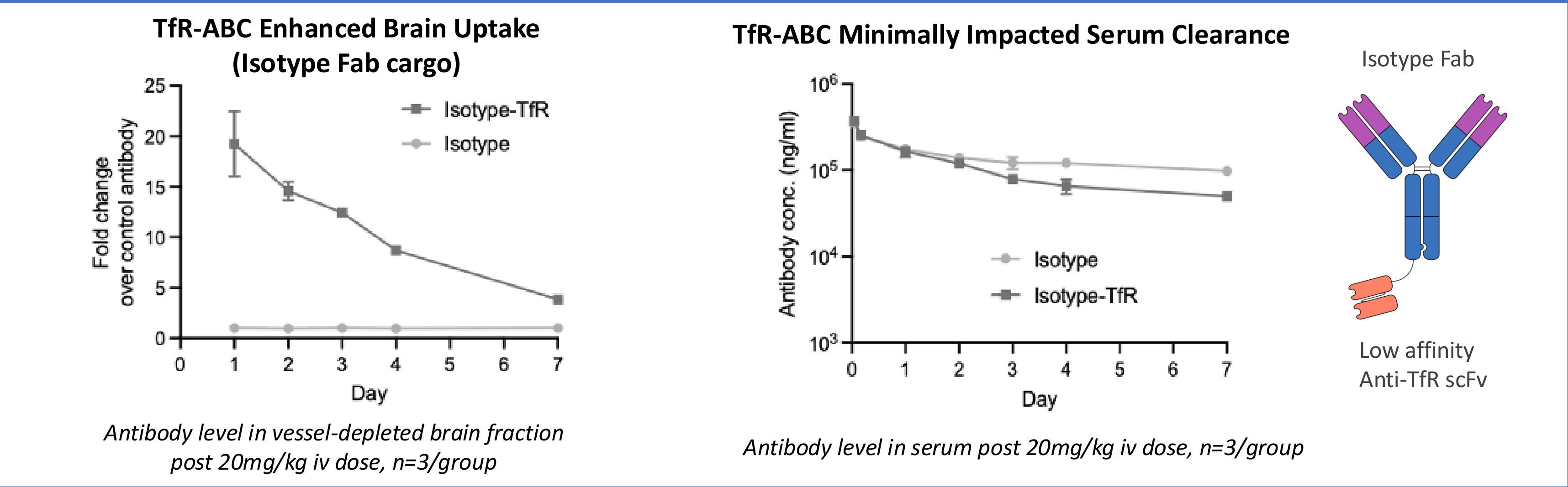
- Versatility:** Adaptable for antibodies, proteins, enzymes and other cargos
- Tunability:** Optimized affinity panels for diverse cargo to fit MOA, elevate efficacy and safety
- Translatability:** Enable rapid translation of molecules to clinical candidates though matched hu/cyno binding and affinity-matched murine surrogates for use in disease models



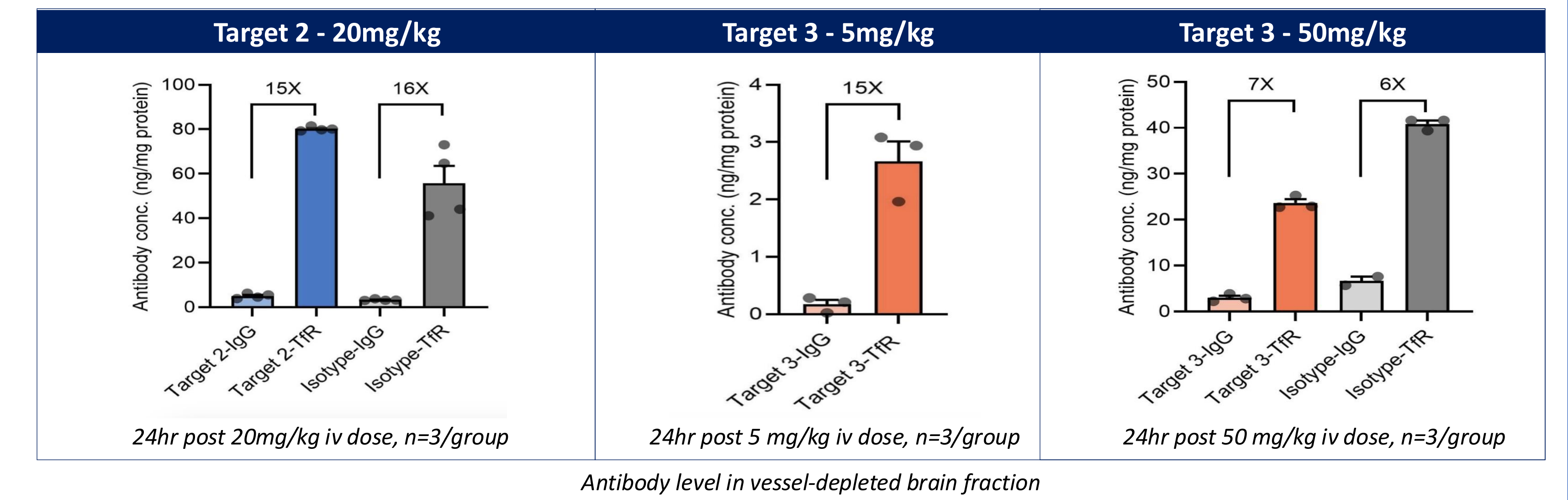
ABC Formats Tailored to Deliver Biotherapeutic Cargos

Features of ABCs	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 - Validated brain uptake across a wide range of affinities to TfR and CD98hc		

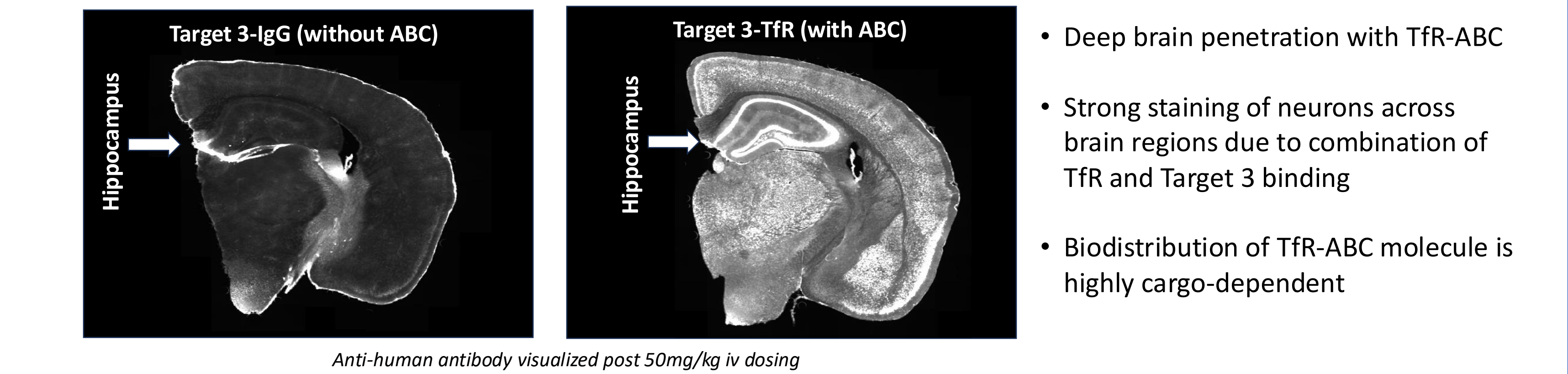
TfR-ABC Dramatically Enhances Brain Uptake in hTfR KI mice



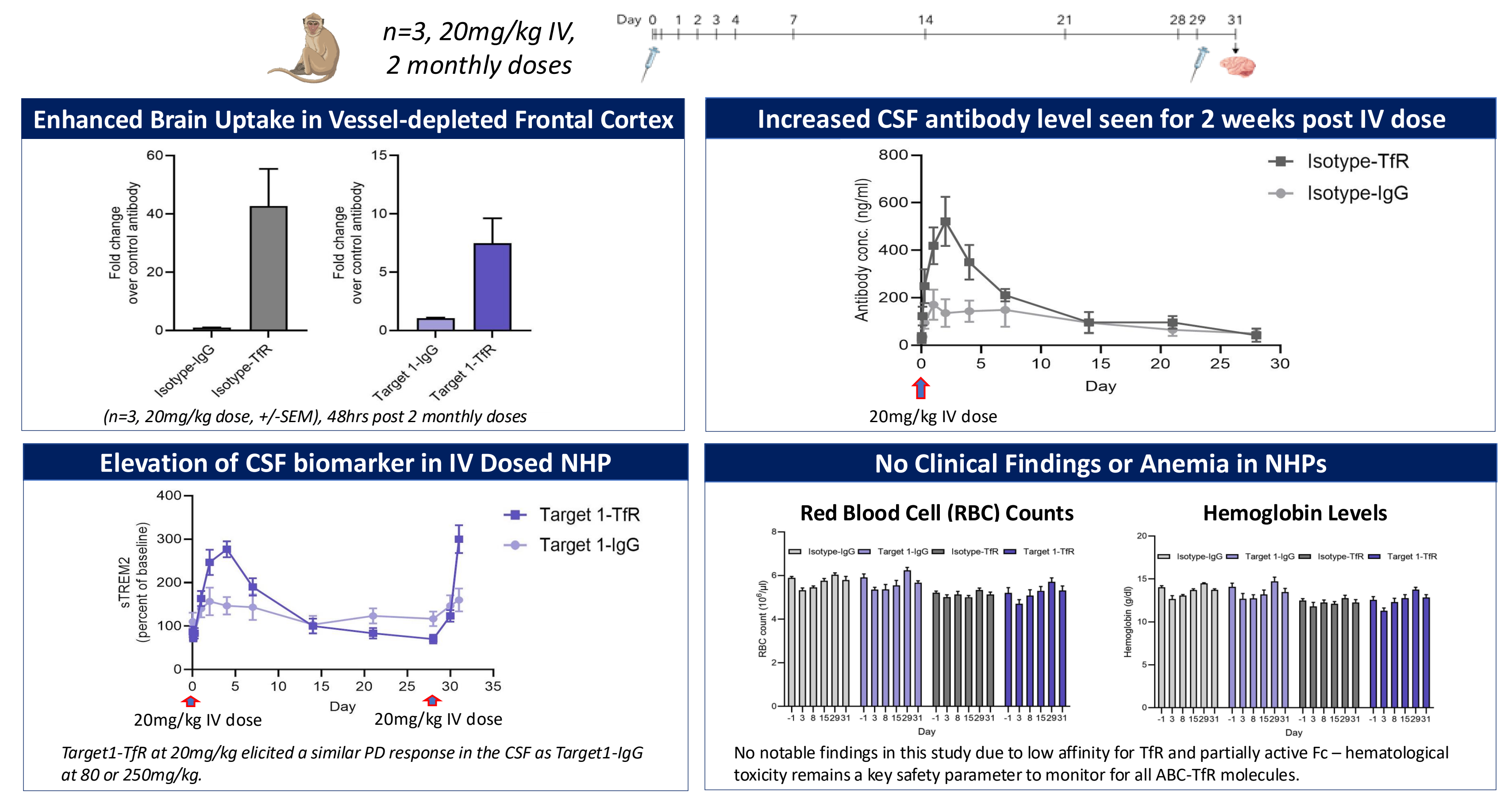
TfR-ABC Facilitates Efficient Brain Uptake of Multiple Cargos in Mice



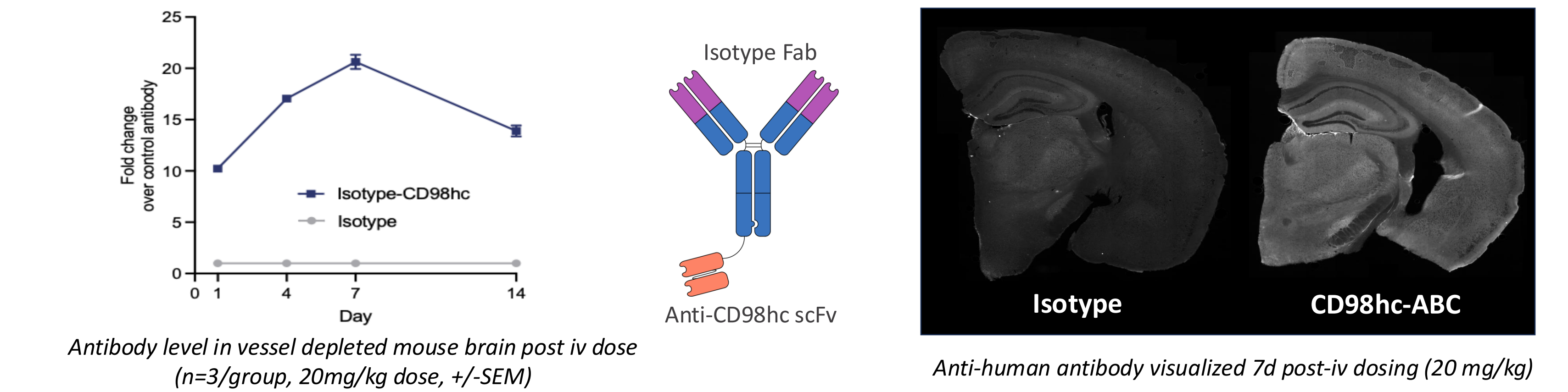
TfR-ABC Drives Widespread Biodistribution in Mouse Brain



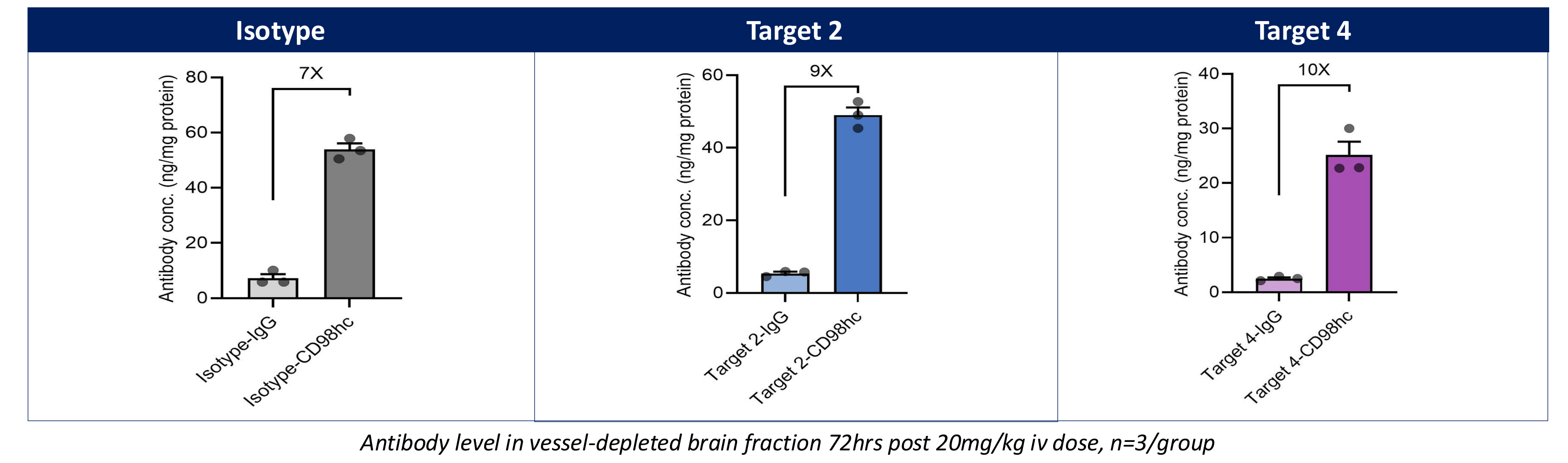
TfR-ABC Shows Enhanced Brain Uptake and Sustained Strong PK/PD Effects in NHPs



CD98hc-ABC Enhances Brain Delivery with Sustained PK in hCD98 KI mice



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



ABC Key Strengths and Current Status

	TfR-ABC	CD98hc-ABC
Platform Advantages	Binding moiety and formats	Fab, scFv, VHH Flexible formats
	Affinity range	10-5000nM 1-500nM
	Fc compatibility	Compatible with Fc engineering
	Matched hu/cyno affinities	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
	Protein cargos	confirmed

1) 48hrs post 20mg/kg iv dose

2) 1wk post 20mg/kg iv dose

Conclusion

Alector’s ABC platform utilizes receptor-mediated transport receptors, such as TfR and CD98hc, to deliver biotherapeutic cargos across the BBB with enhanced brain uptake, widespread biodistribution, and sustained strong PK/PD in mice and NHPs. The platform’s versatility, tunability and translatability allows for broad applicability across multiple programs to allow rapid translation of molecules to clinical candidates.