

TfR1-binding peptides to transport antibodies across blood-brain-barrier in cynomolgus monkeys

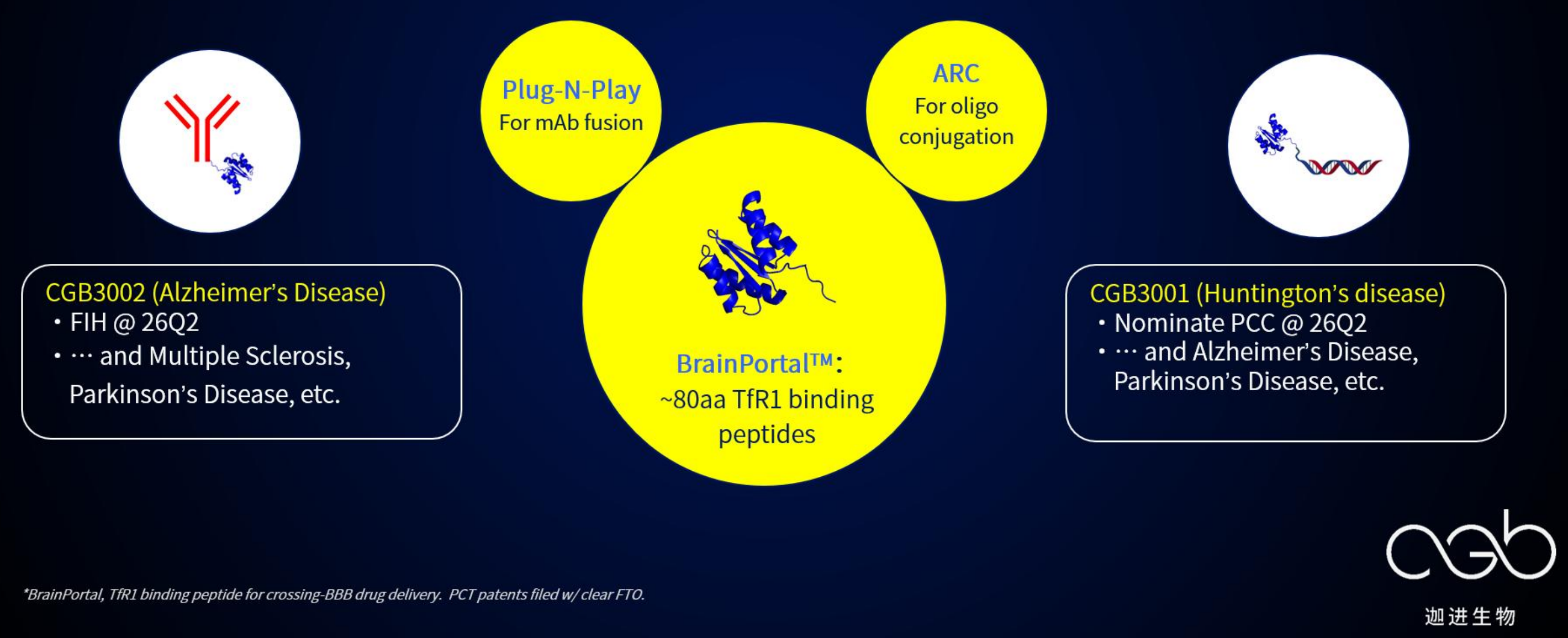
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Introduce BrainPortal Platform

- BrainPortal is a product of AI empowered peptide discovery engine, designed to bind hTfR1 and transport therapeutic antibodies and oligos across blood-brain-barrier

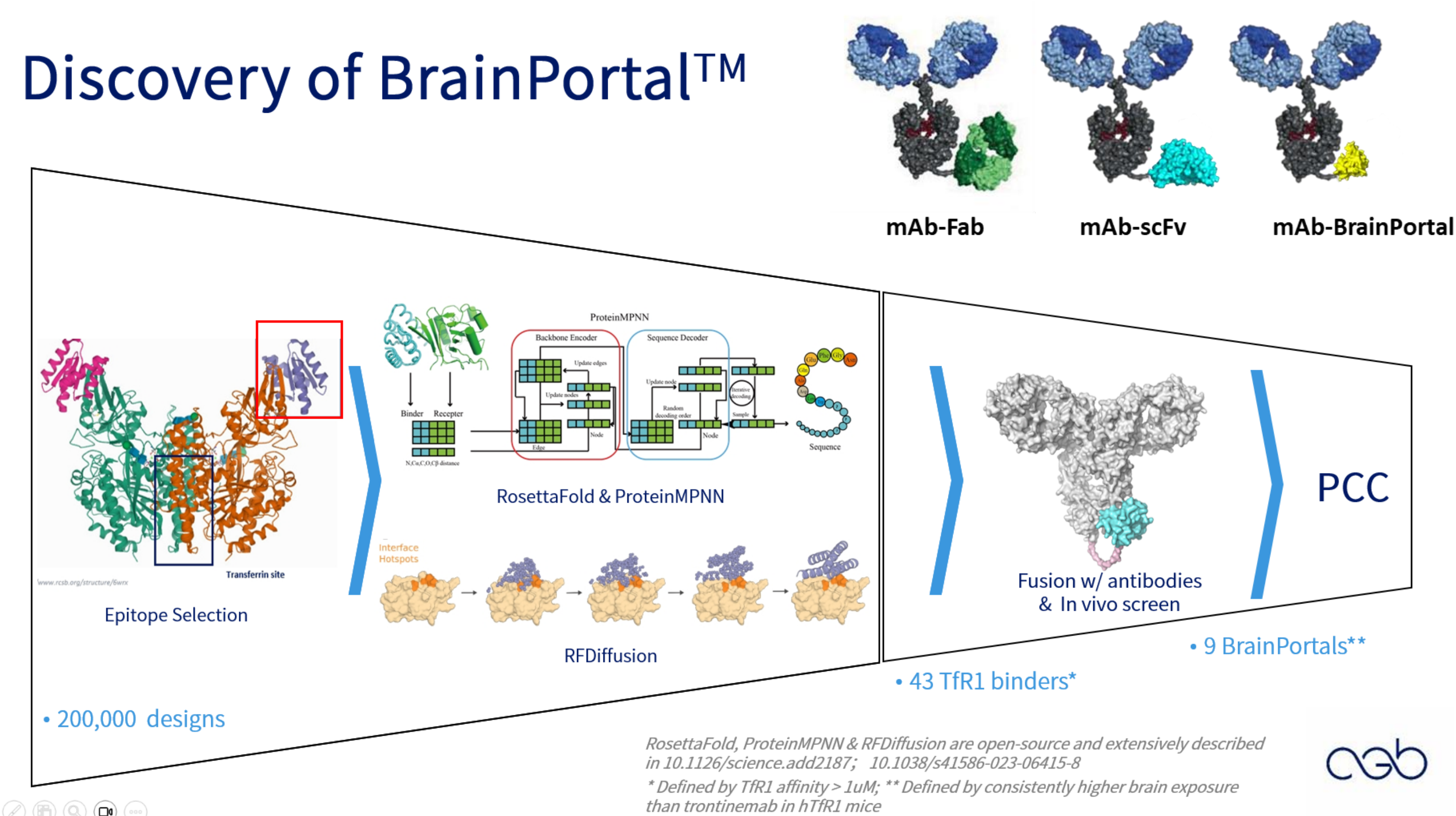
BrainPortal™, AI empowered peptide transporters for cross-BBB drug delivery



BrainPortal Identification

- A library of TfR1 binding peptides is *de novo* designed and identified by *in vitro* panning and *in vivo* screening
- During *in vivo* screening using 5 different antibodies as cargo, a total of 9 peptides demonstrated superior brain delivery efficiency over published Fab/scFv
- Other features of BrainPortal included
 - Smaller size and “Plug-N-Play”
 - Fully natural amino acids and self-folded in CHO-K1
 - Optimized TfR1 affinity with fast on-and-off kinetics
 - Target apical domain & limited competition to transferrin
 - No binding to TfR2

Discovery of BrainPortal™



BrainPortal Boosts Whole Brain Exposure of Antibodies by 11-26x @ hTfR1 Mouse

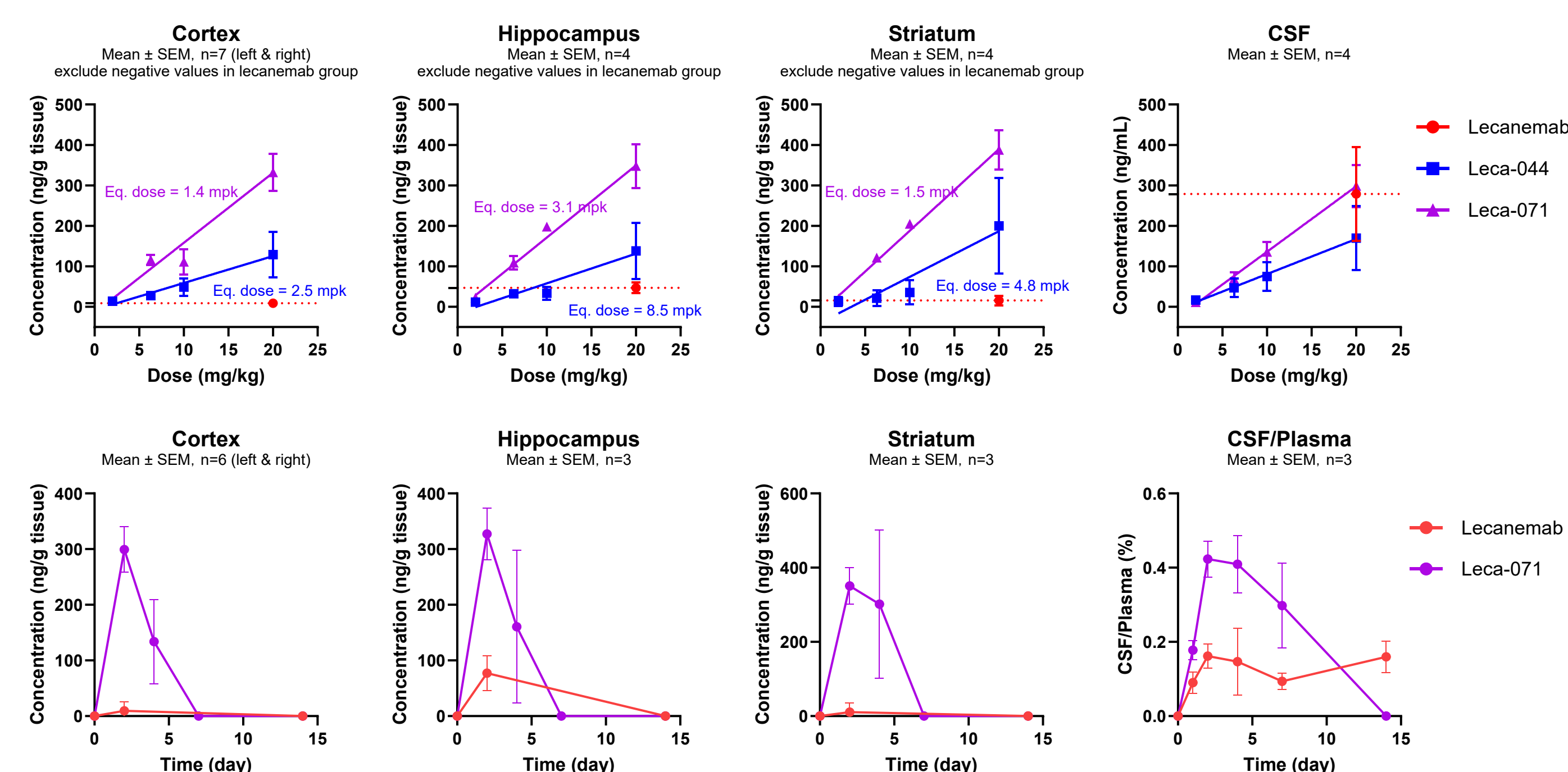
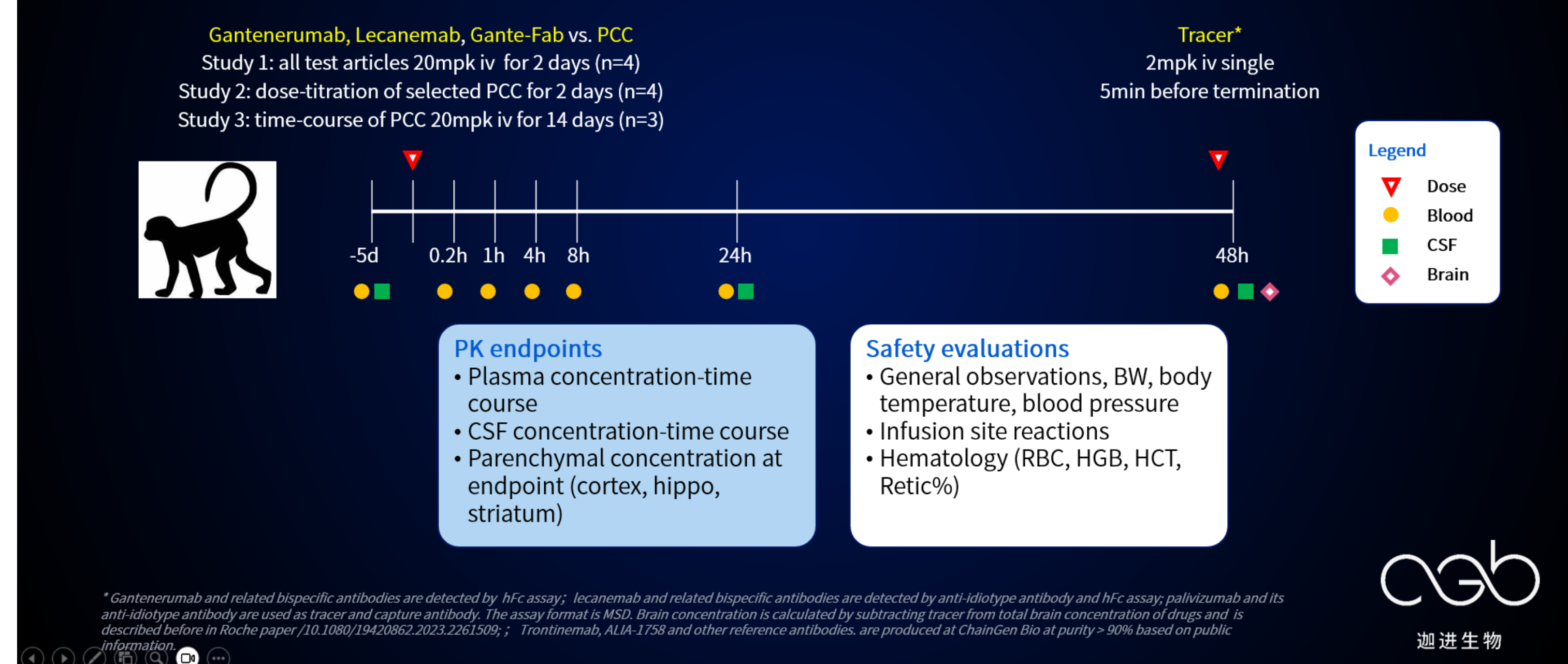
	Gantenerumab	Lecanemab	Donanemab	Prasinezumab	Ocrelizumab	Other cargos
Nake mAb (ng/g tissue)	57	38	132	192	150	
Positive control	220 (4x)		1,027 (8x)			
+44	173 (3x)	975 (25x)	2740 (21x)	1,864 (10x)	3,626 (24x)	
+71	425 (7x)	764 (20x)	Poor expression	1,598 (8x)	3,230 (22x)	
+98	421 (7x)	764 (20x)	2,333 (18x)	1,641 (9x)	3,919 (26x)	
+99	319 (6x)	642 (17x)	884 (7x)	2,127 (11x)	3,525 (24x)	
+103	717 (13x)	399 (10x)	1,911 (14x)	1,302 (7x)	1,925 (13x)	
+ 4 others					2560- 4227 (12-19x)	

Ongoing discovery

Delivery of Antibody in NHP

- A total of three PK studies were designed in NHP, Lecanemab-071 was selected as the best candidate for lecanemab brain delivery
- Repeated dose tox in NHP up to 100mpk pointed mostly to anemia risk

NHP Study Design



Delivery of siRNA in hTfR1 Transgenic Mice

- Brain delivery of siRNA was enabled by ARC, a proprietary conjugation platform
- First validation using siRNA targeting a house-keeping gene demonstrated 3-22x boost in brain exposure and ~50% of knockdown in transgenic mice

BrainPortal Boosts Brain Exposure of siRNA by 3-22x & Silences Target Gene by up to 63%

Brain Exposure	Cortex	Hippo	Striatum	Cereb.	Spinal cord	%HPRT mRNA	Cortex	Hippo	Striatum	Cereb.	Spinal cord
Naked siRNA	1x	1x	1x	1x	1x	Naked siRNA	92.1	93.1	87.3	90.2	103.4
+ design 1	18x	22x	5x	15x	3x*	+ design 1	45.3	76.5	72.4	70.9	36.8
+ design 2	8x	9x	3x	6x	1.4x*	+ design 2	60.7	51.6	64.8	61.8	64.8
C57 + design 2	Minimal	Minimal	Minimal	Minimal	Minimal	C57 + design 2	102.4	100.2	100.1	100.2	105.2

* 3mpk iv qw x3. Sample is collected at 14 days after last dose, n=5. Thoracic is not reachable for brain perfusion. Meanwhile, thoracic collection could not be free of blood and muscles. PK data could be misleading. Protocol optimization is needed.

Summary

- BrainPortal is a brain-delivery platform featured
 - Small size, diversified sequences, and unique conformations vs. Fab etc.
 - Fully natural amino acids, self-folded and fermentable vs. other peptide platforms
 - Self-evolving and universally applicable on antibodies, siRNAs and peptide and enzymes
- FIH is planned 2026. Stay tuned for more.