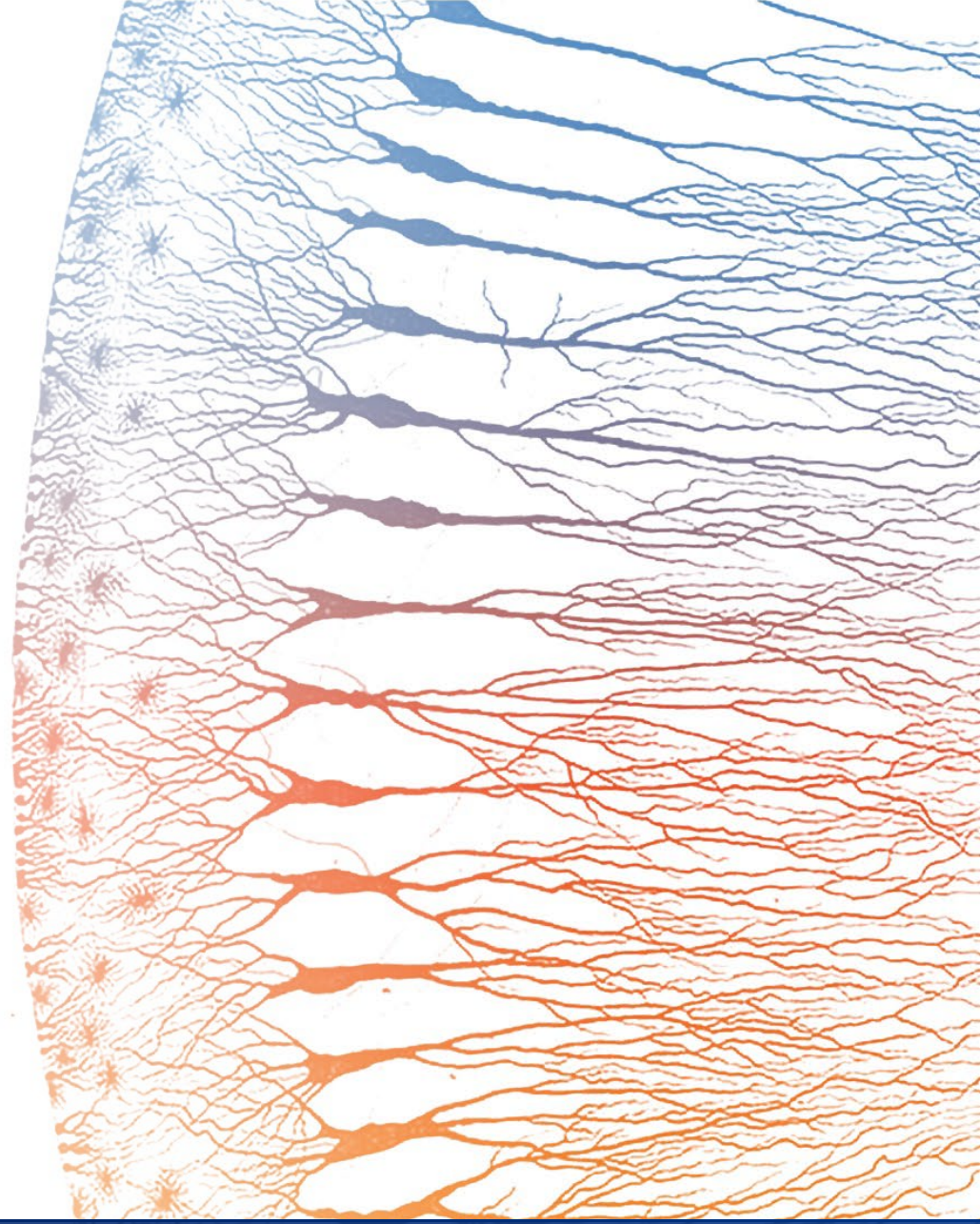
Discovery of AAV9-derived CNS capsids evading pre-existing neutralizing antibodies

Damien Maura, Ph.D
Senior Scientist II, Novel Capsid Discovery

ASGCT 28th Annual meeting
AAV Gene Transfer (A): Crossing the Blood-Brain Barrier
Wednesday May 14th, 2025



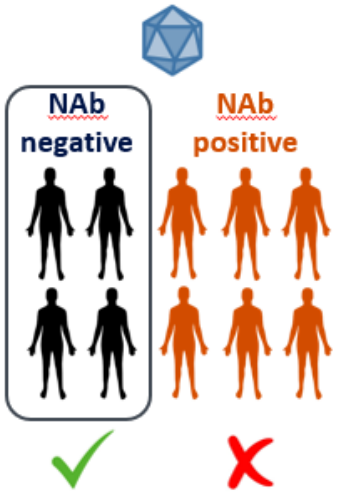
Disclosures

- Damien Maura is a full-time employee of Voyager Therapeutics

Leveraging TRACER platform to de-immunize Voyager's CNS capsids and increase patient eligibility for AAV gene therapy

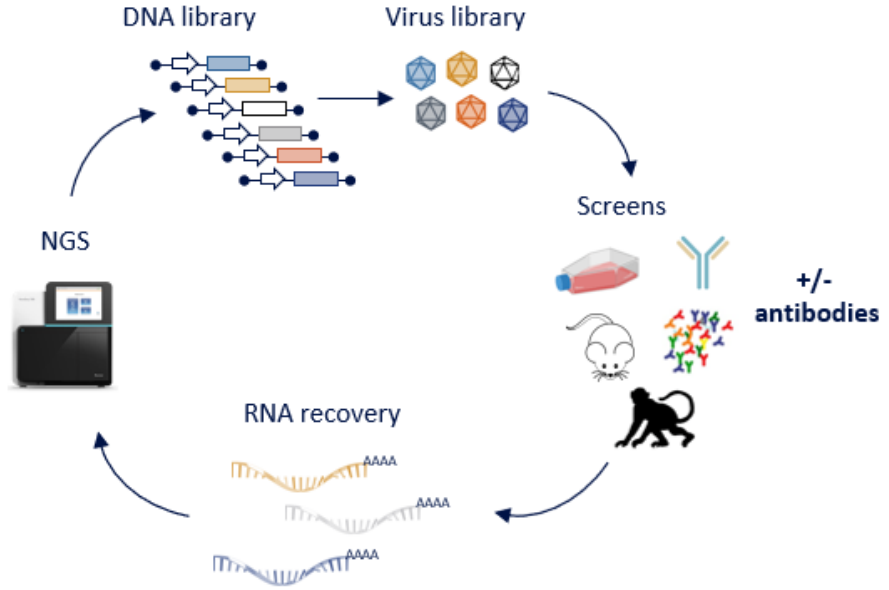
voyager therapeutics

CNS capsid



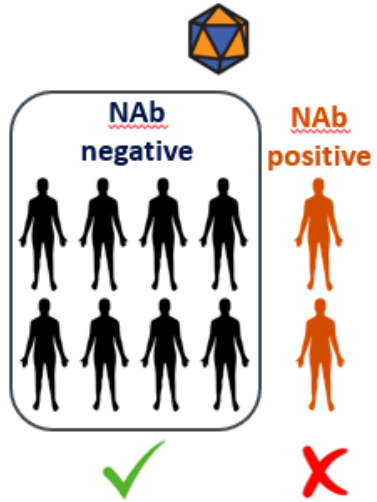
30 - 65% AAV9 NAbs seroprevalence depending on the studies

TRACER capsid engineering to remove antibody epitopes



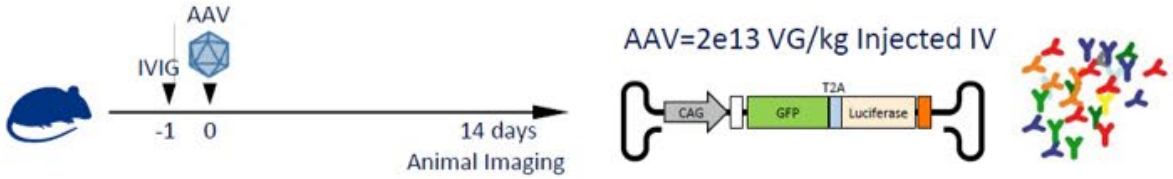
Capsid structure & literature used to prioritize capsid regions to randomize

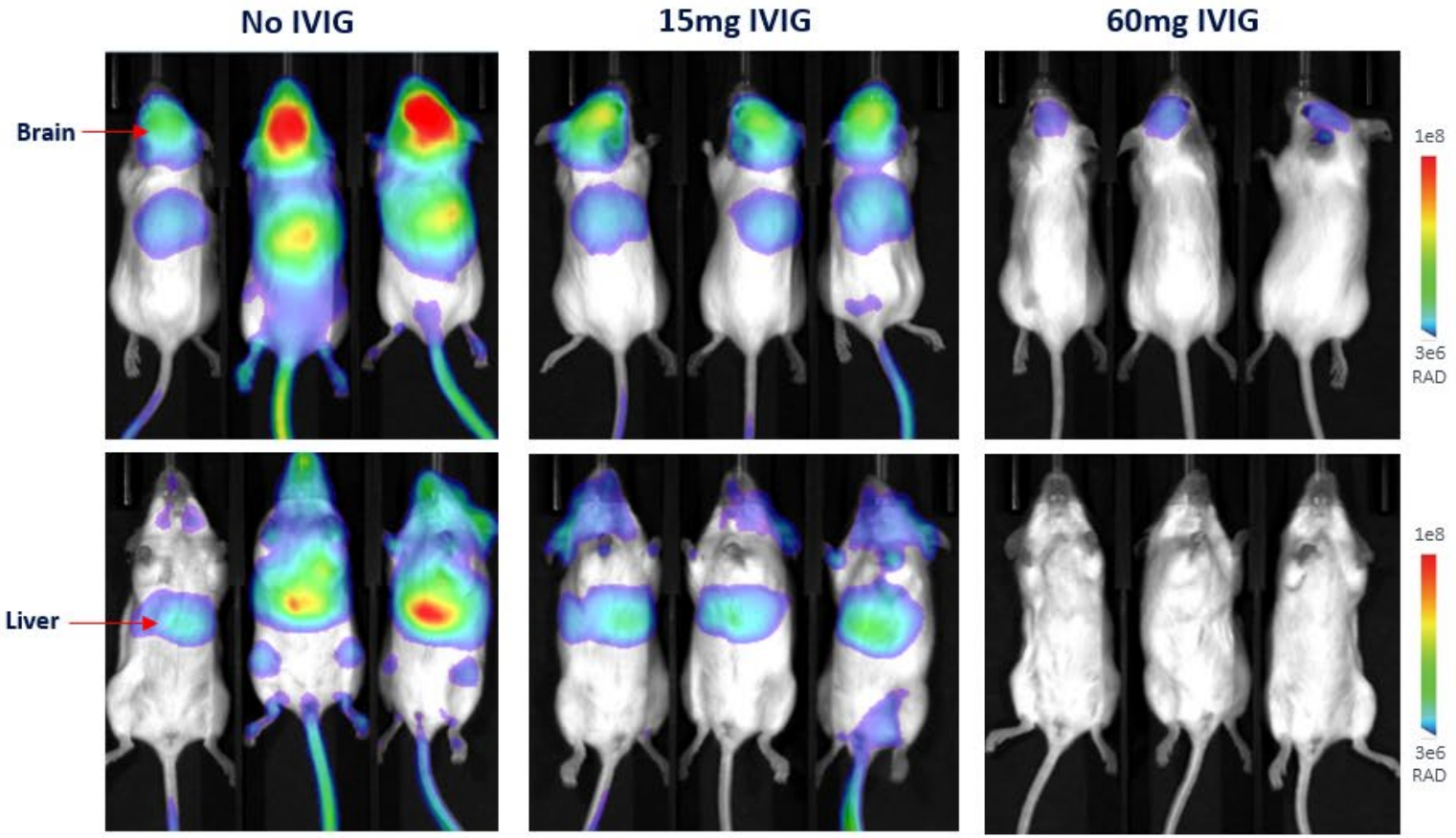
Stealth CNS capsid

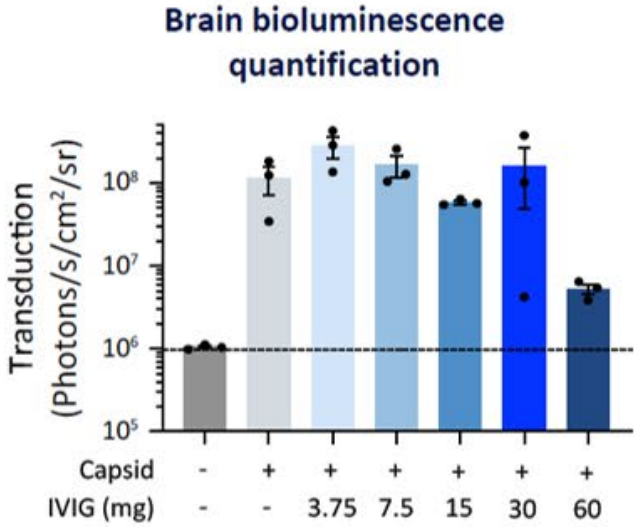


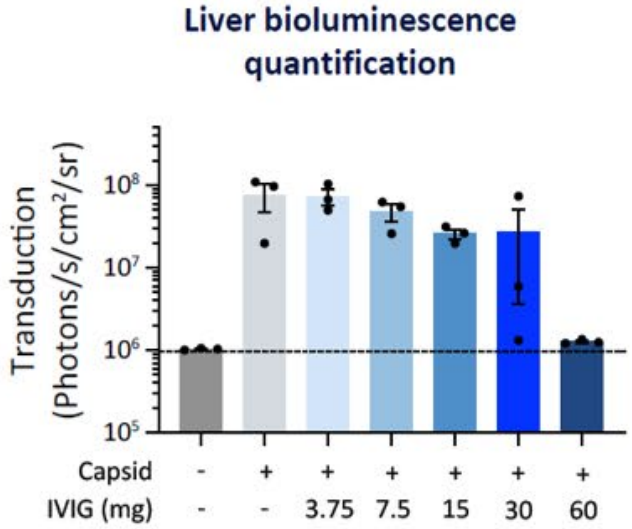
Patients eligible for AAV gene therapy

Development of a mouse passive immunization model with human IVIG





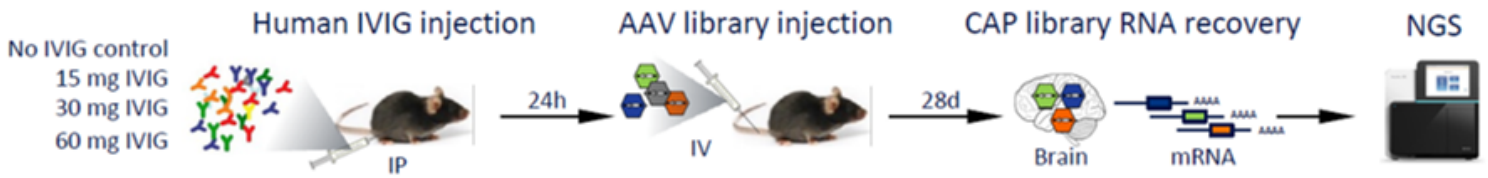




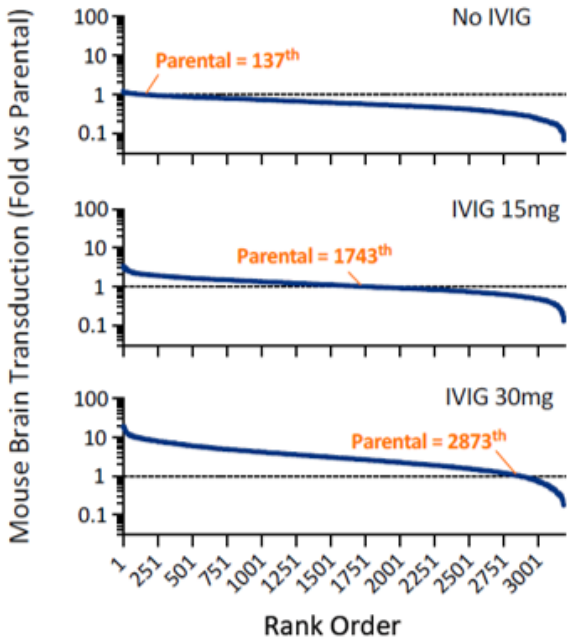
Screen for IVIG-evading variants that retain brain transduction in mouse

voyager therapeutics

Library screening strategy



Variants outcompete parental capsid in presence of IVIG



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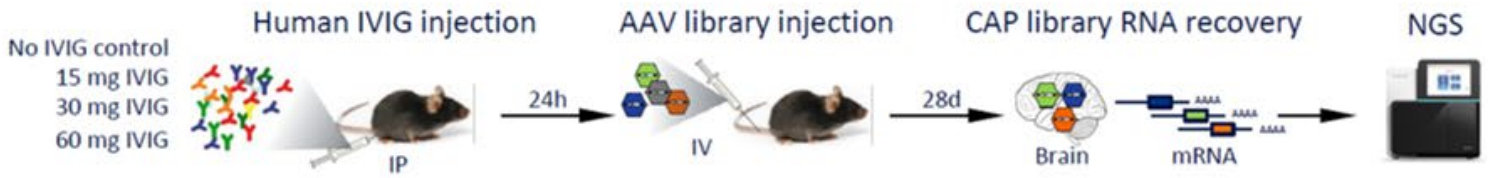

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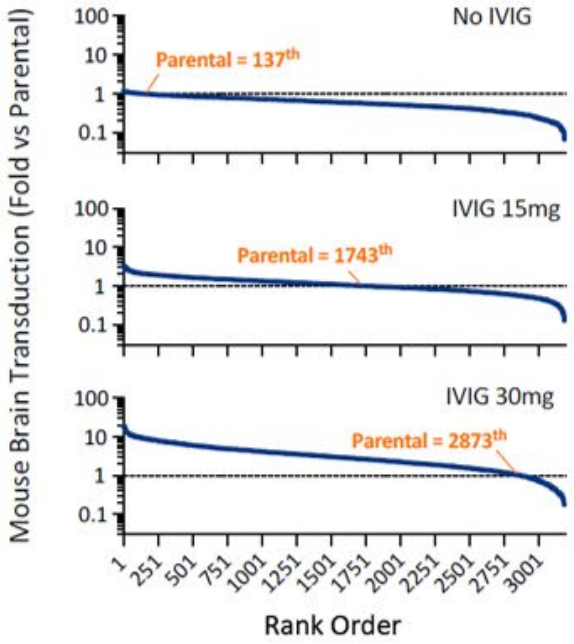
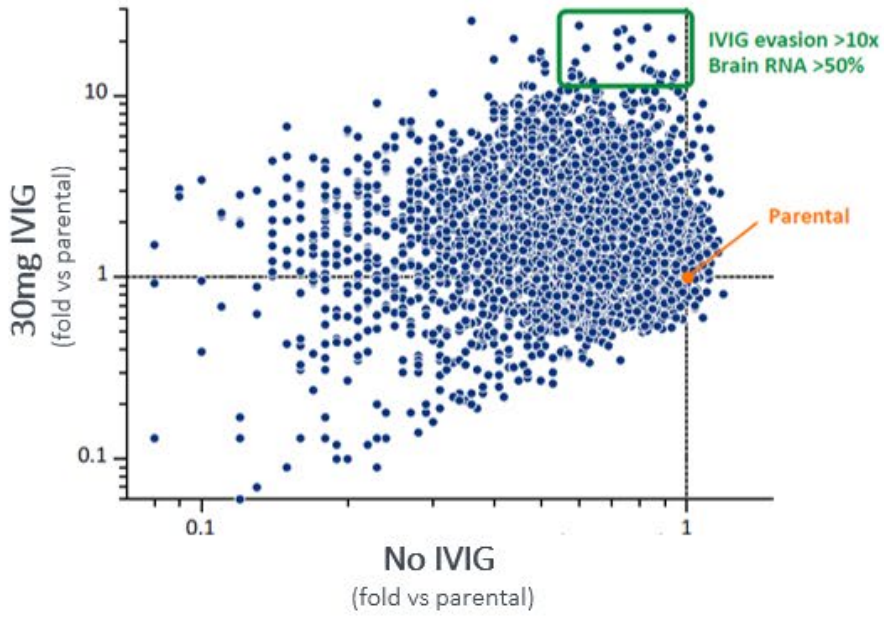
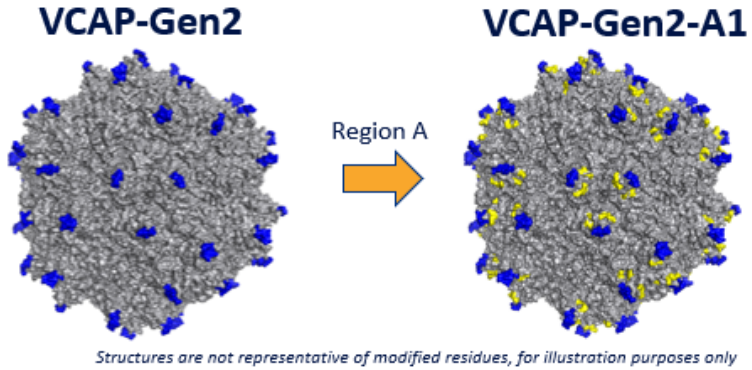


Selection of variants evading IVIG while retaining CNS transduction



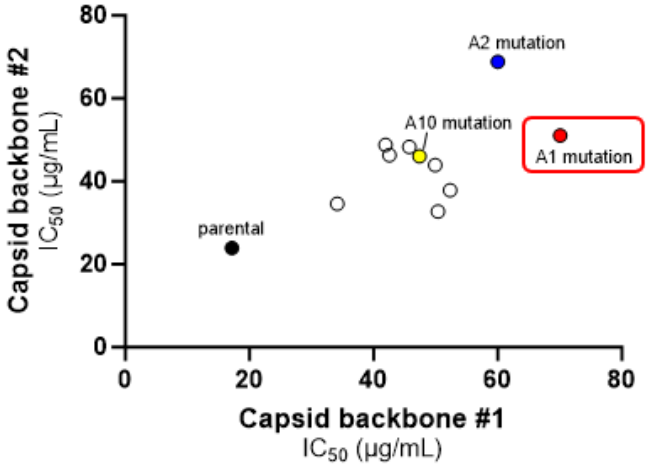
VCAP-Gen2-A1 evades human neutralizing antibodies and retains brain transduction in mouse



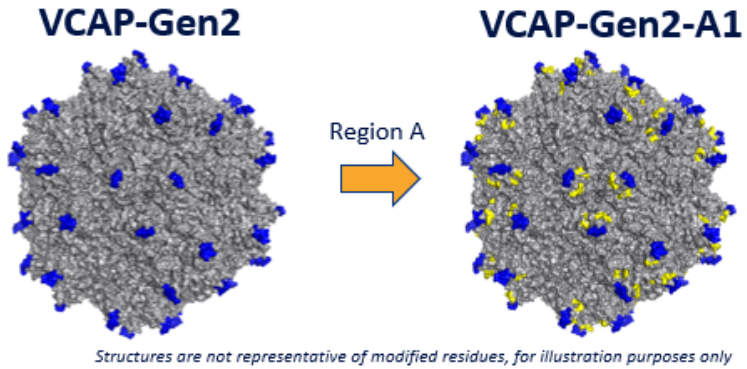
Structures are not representative of modified residues, for illustration purposes only

VCAP-Gen2-A1 is a derivative of VCAP-Gen2 with antibody-evading mutations in region A

Human IVIG evasion *in vitro*



VCAP-Gen2-A1 evades human neutralizing antibodies and retains brain transduction in mouse



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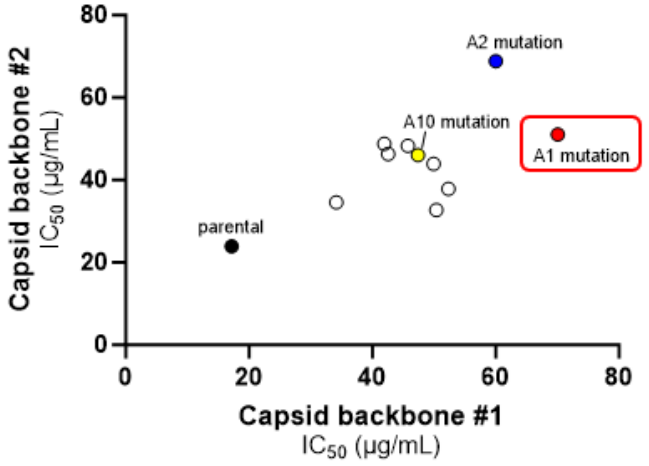
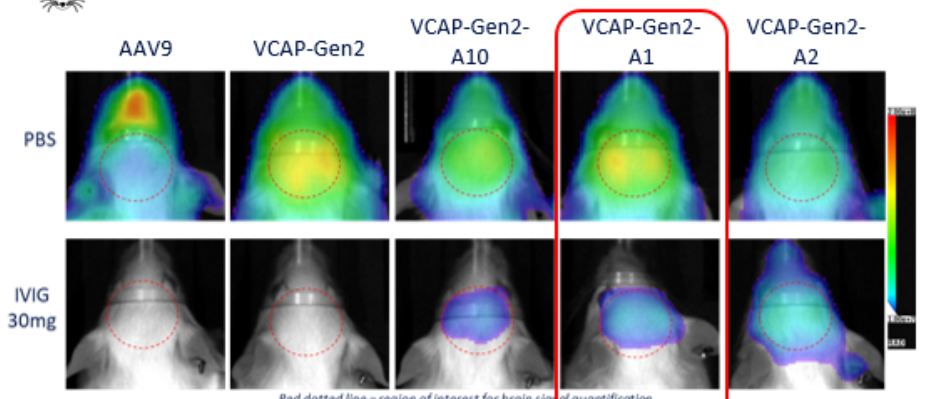
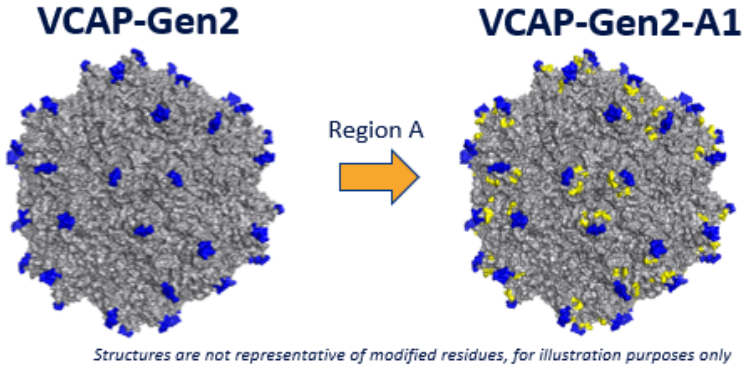


Mouse brain transduction & IVIG evasion



	AAV9	VCAP-Gen2	VCAP-Gen2-A10	VCAP-Gen2-A1	VCAP-Gen2-A2
Brain	-	+++	++	+++	+
IVIG evasion	-	-	+	++	+++

VCAP-Gen2-A1 evades human neutralizing antibodies and retains brain transduction in mouse



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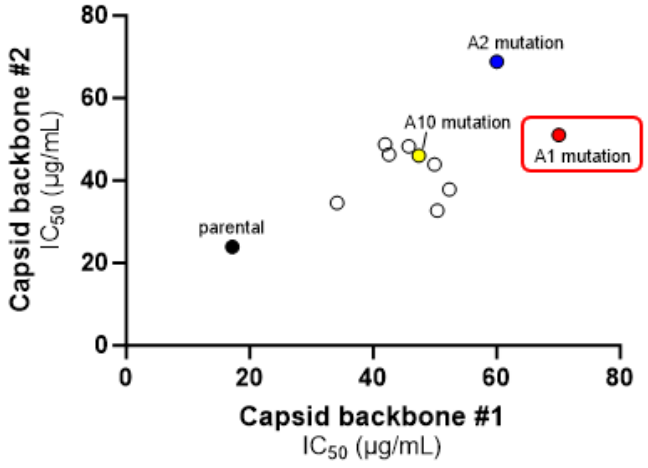
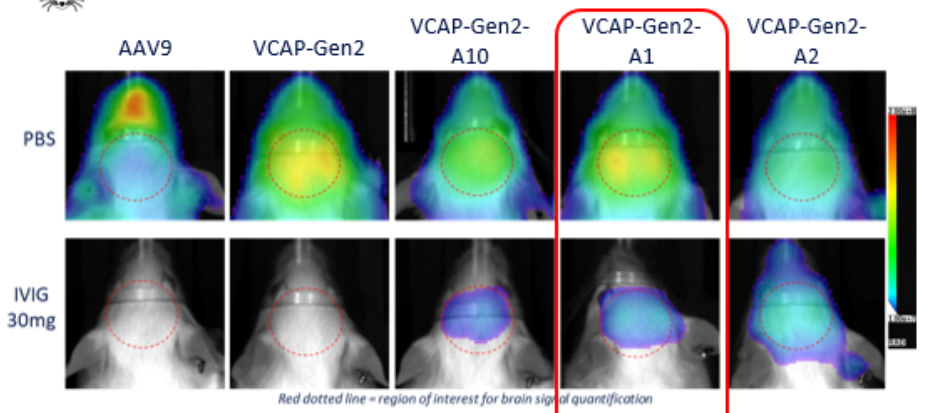
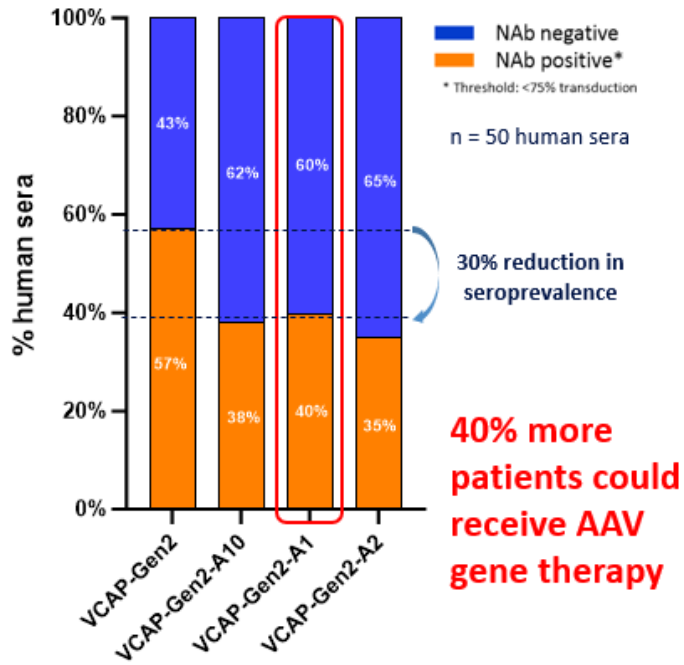


Mouse brain transduction & IVIG evasion



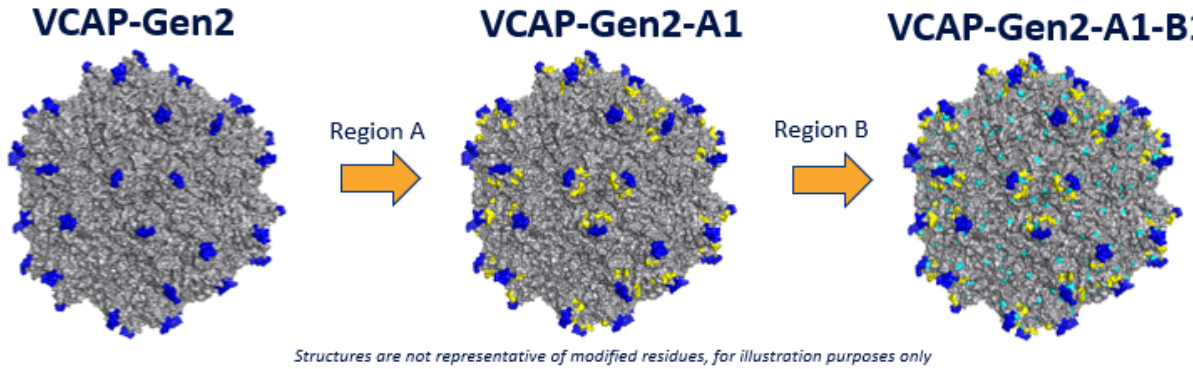
	AAV9	VCAP-Gen2	VCAP-Gen2-A10	VCAP-Gen2-A1	VCAP-Gen2-A2
Brain	-	+++	++	+++	+
IVIG evasion	-	-	+	++	+++

Human serum evasion *in vitro*



40% more patients could receive AAV gene therapy

VCAP-Gen2-A1-B1 further evades human antibodies with minimal impact on brain transduction



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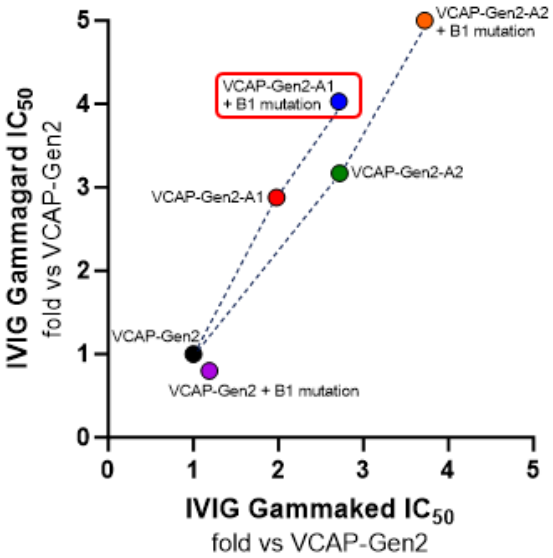
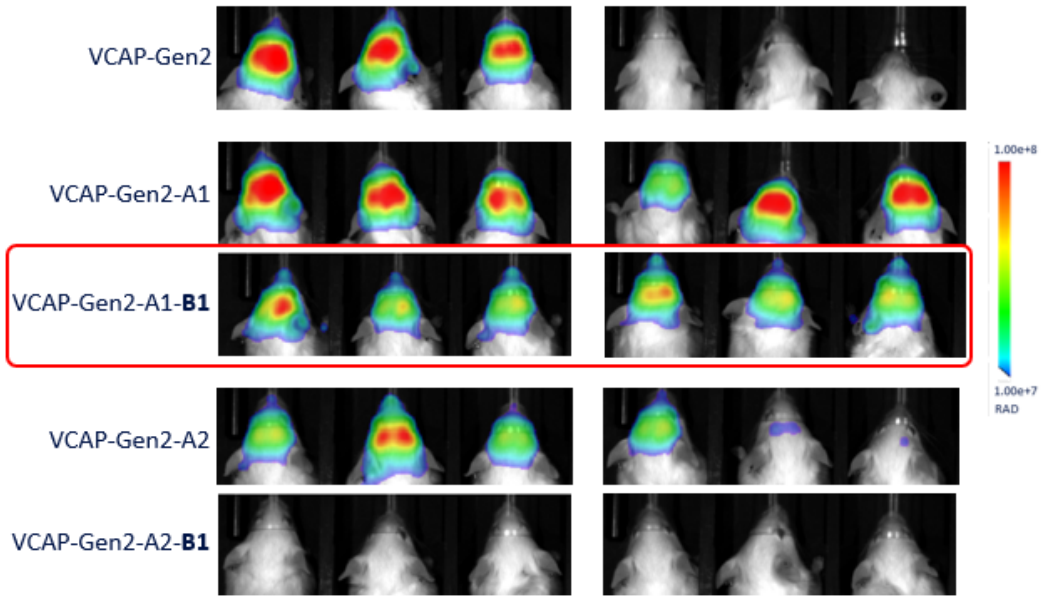
VCAP-Gen2-A1-B1 is a derivative of VCAP-Gen2-A1 with mutations in region B

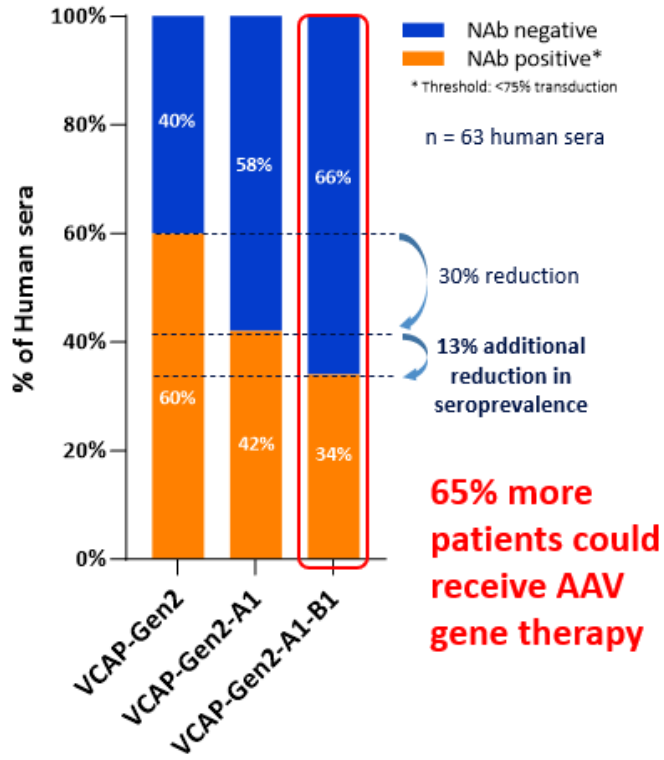
Human IVIG evasion *in vitro*



Mouse brain transduction & IVIG evasion



Human serum evasion *in vitro*



65% more patients could receive AAV gene therapy

Evaluation of VCAP-Gen2-A1 & VCAP-Gen2-A1-B1 in NHP

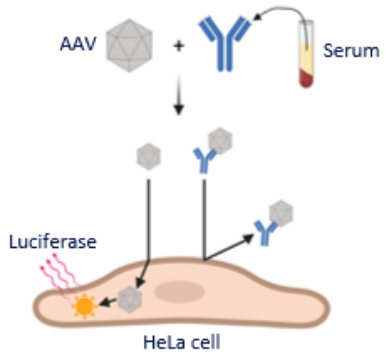
voyager therapeutics

Key questions:

- Do VCAP-Gen2-A1 & VCAP-Gen2-A1-B1 retain **brain transduction & cellular tropism** of the parent capsid VCAP-Gen2 in NHP?
- Can these variants transduce NHP brain in the **presence of pre-existing antibodies**?

Transduction inhibition profile in cyno. serum

Transduction inhibition assay



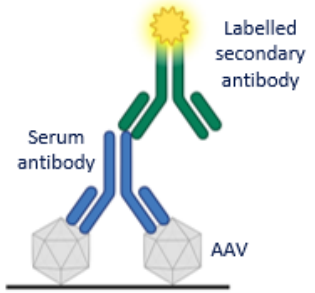
	Animal	AAV9
		1:8 dilution
NAb negative	Animal 1 (M)	472%
NAb negative	Animal 2 (F)	406%
NAb negative	Animal 3 (M)	334%
NAb positive	Animal 4 (M)	7%

Values represent % transduction vs no serum control

Positive
Intermediate
Negative

Total antibody (TAb) profile

ELISA assay

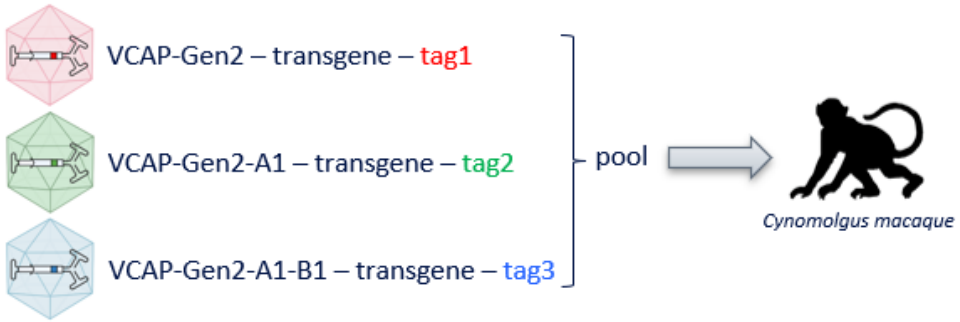


Animal	AAV9
	1:25 dilution
Animal 1 (M)	0.82
Animal 2 (F)	1.02
Animal 3 (M)	0.84
Animal 4 (M)	1.05

Values represent OD_{450nm}

Positive
Intermediate
Negative

Multiplexed capsid evaluation in NHP



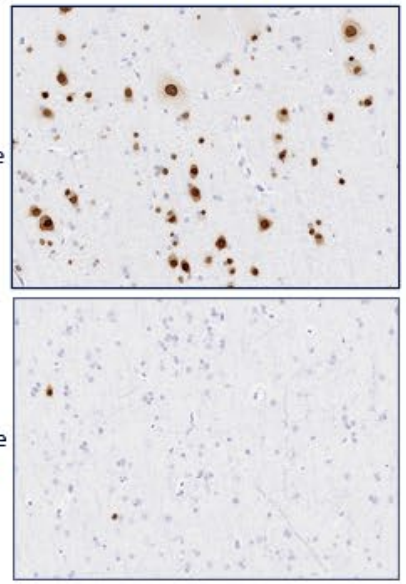
VCAP-Gen2-A1 transduces NHP brain in an animal with pre-existing antibodies

Motor cortex IHC DAB staining

VCAP-Gen2

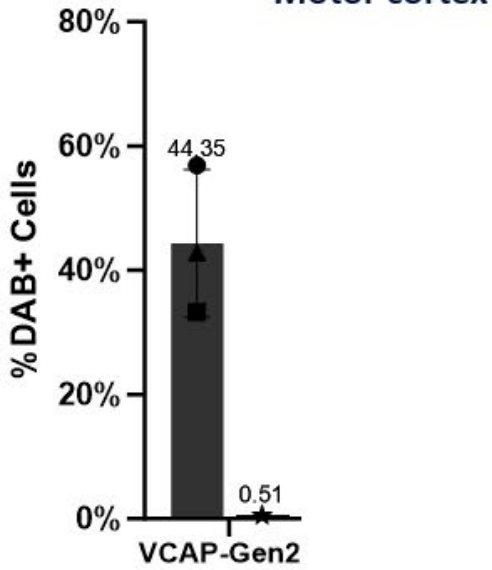
NAb negative cyno

NAb positive cyno



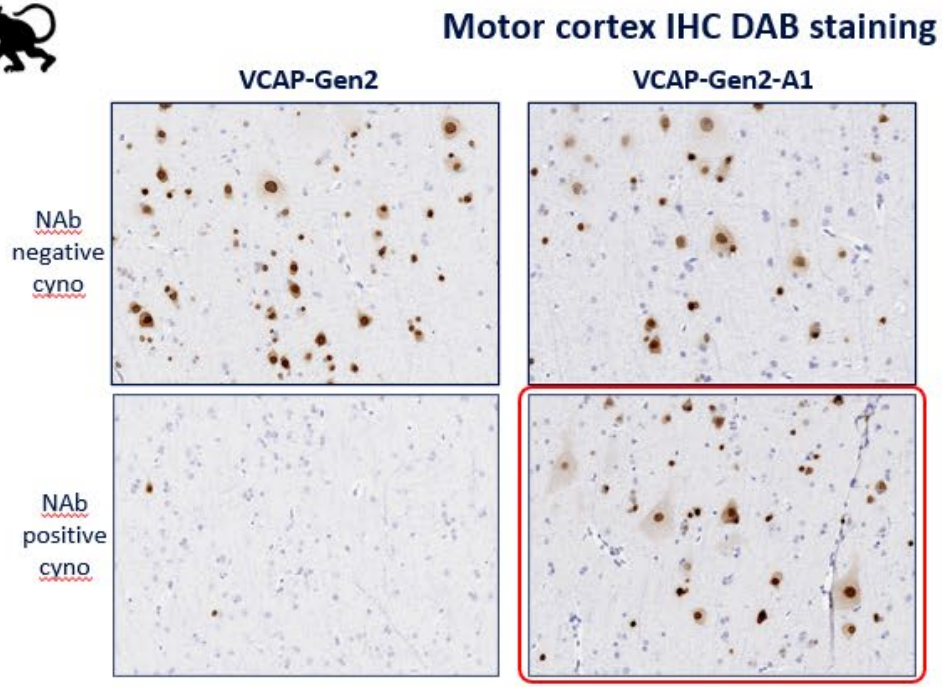
Chromogenic:
Tag + Tag -

Motor cortex



pre-existing NAbs - +

VCAP-Gen2-A1 transduces NHP brain in an animal with pre-existing antibodies



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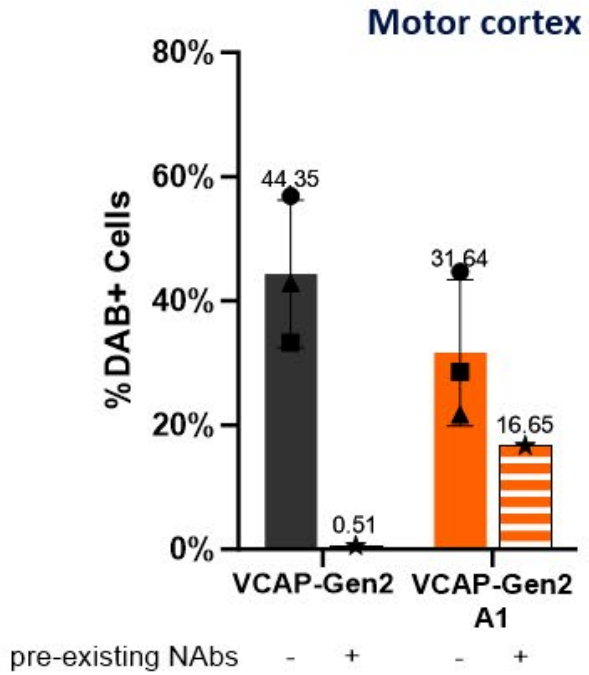
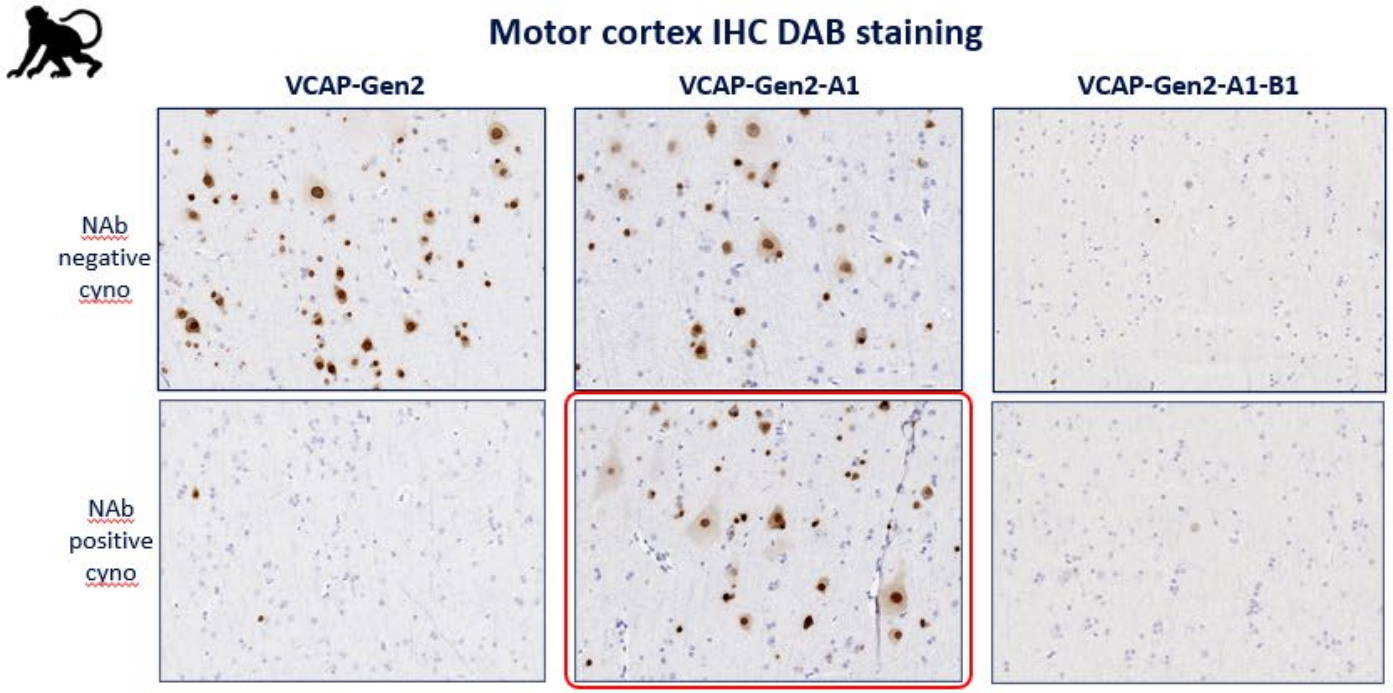
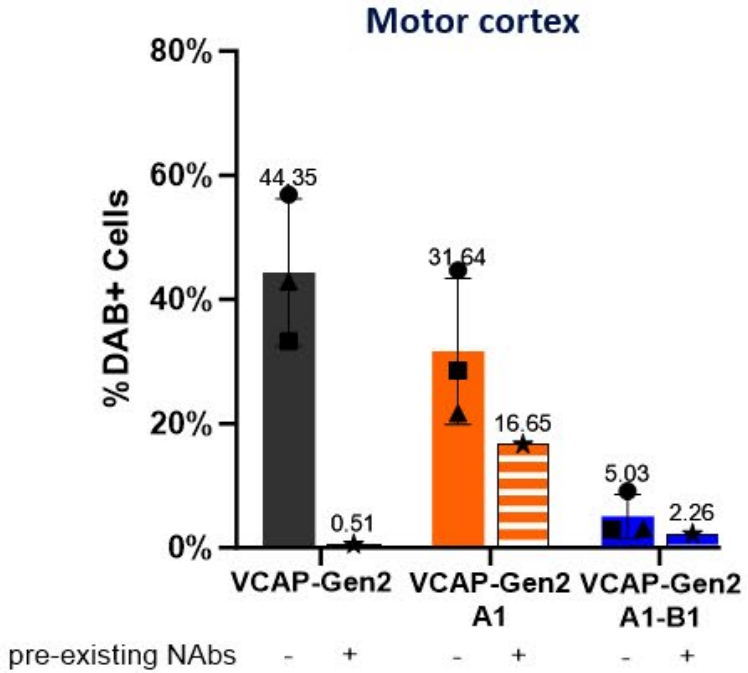


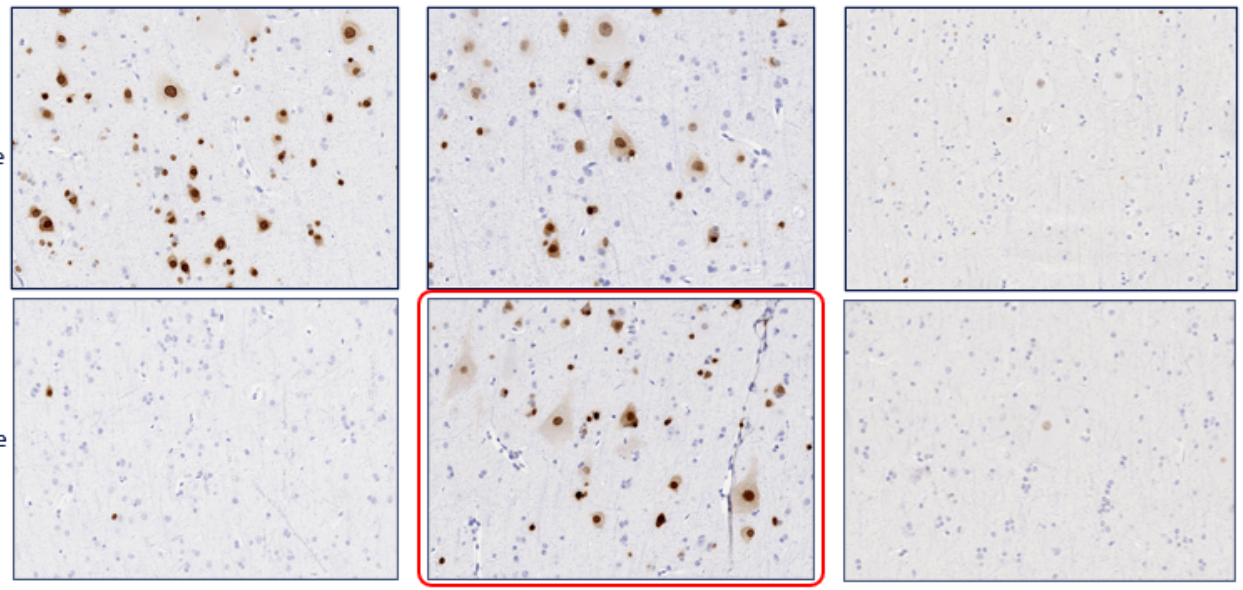
VCAP-Gen2-A1 transduces NHP brain in an animal with pre-existing antibodies





VCAP-Gen2-A1 transduces NHP brain in an animal with pre-existing antibodies

Motor cortex IHC DAB staining



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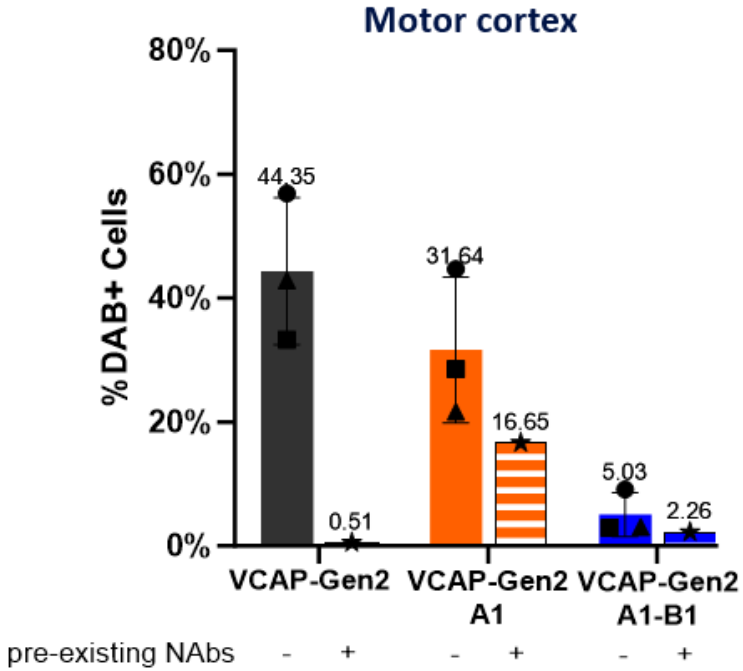
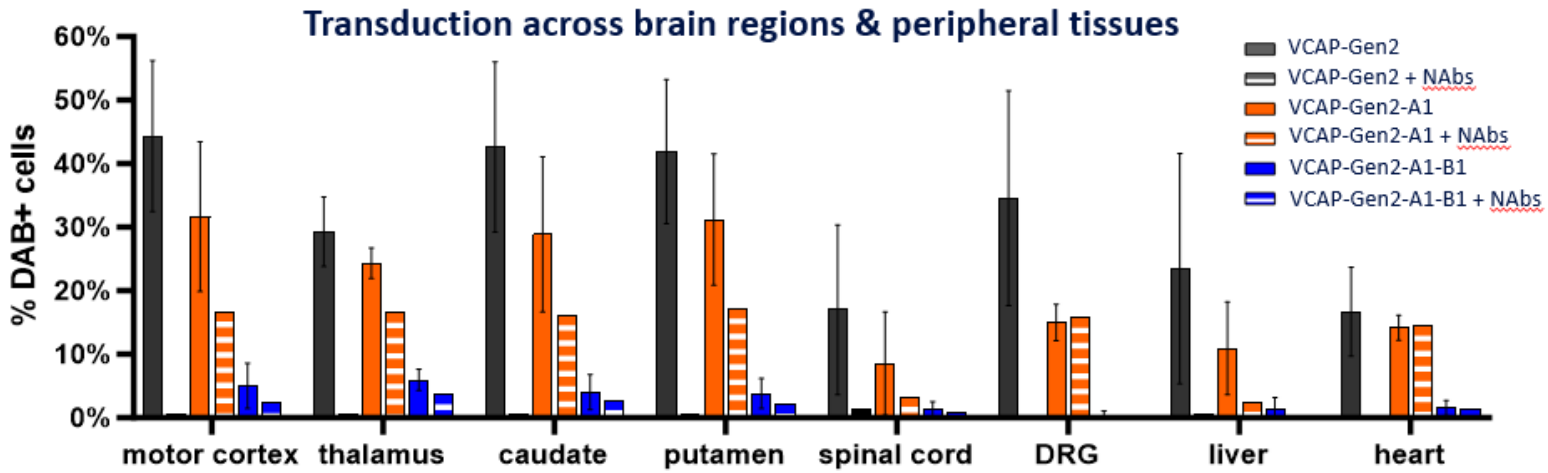
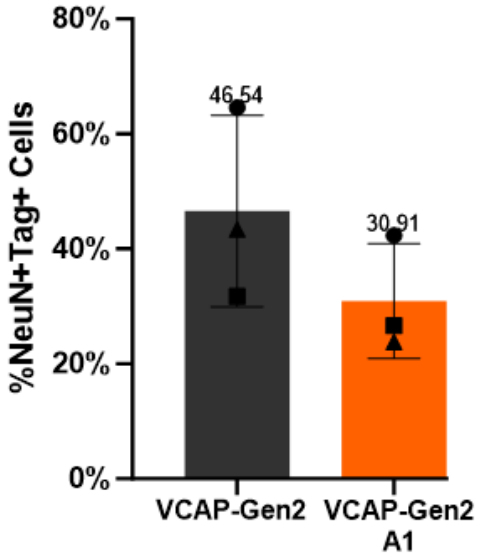


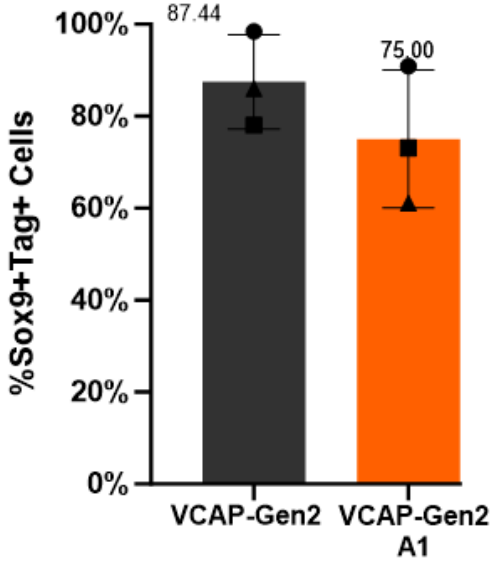


VCAP-Gen2-A1 retains brain cellular tropism of its parent VCAP-Gen2

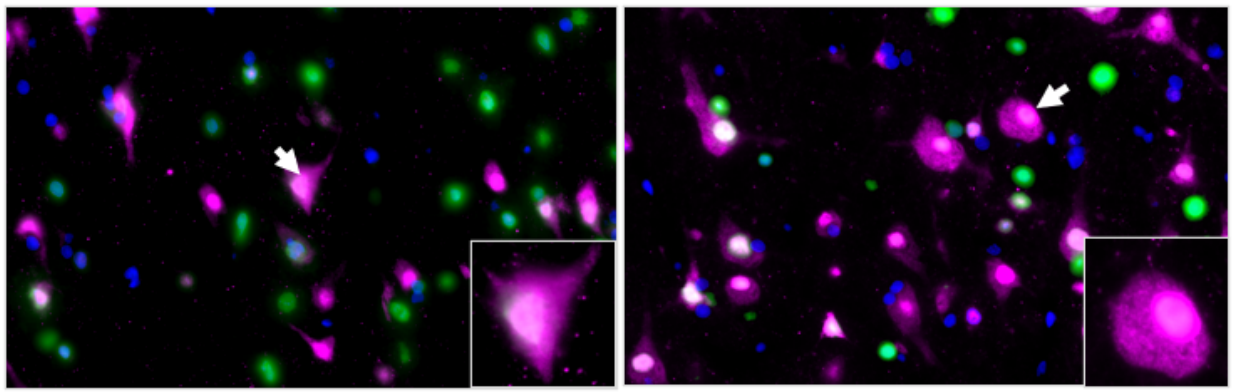
Neurons (motor cortex)



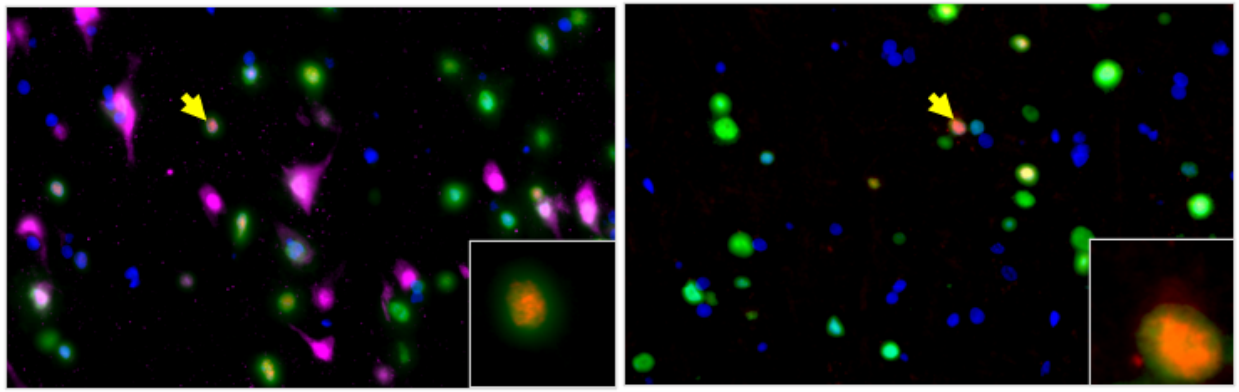
Astrocytes (motor cortex)



VCAP-Gen2 | VCAP-Gen2-A1

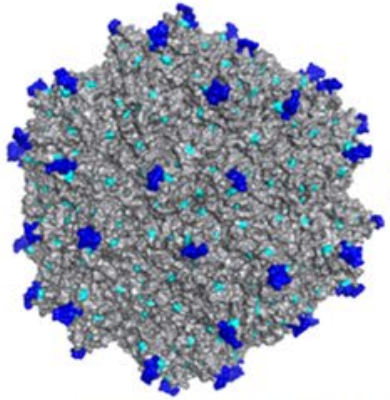


VCAP-Gen2 | VCAP-Gen2-A1



DAPI Transgene-tag – FITC NeuN – Cy5 Sox9 - TRITC

Leveraging machine learning to identify improved mutations in region B



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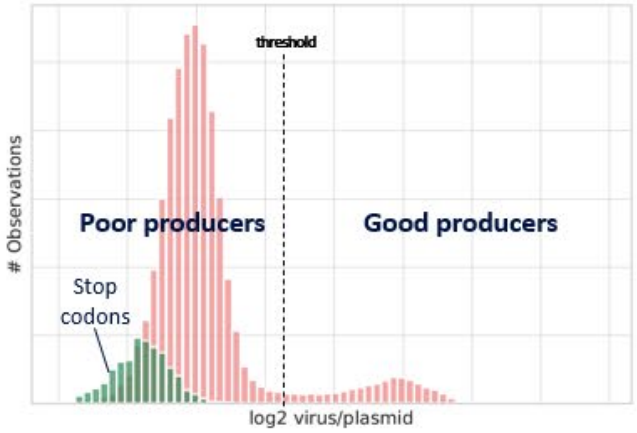
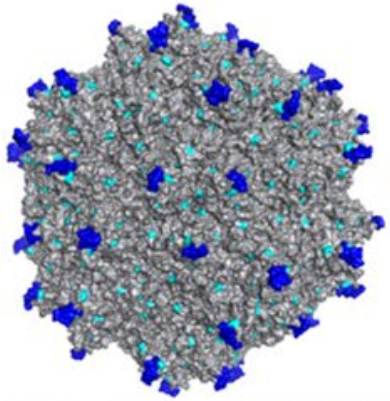
Region B is important for AAV capsid assembly, making it difficult to mutate

Virus production is a bottleneck for region B



Leveraging machine learning to identify improved mutations in region B

voyager therapeutics



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Region B is important for AAV capsid assembly, making it difficult to mutate

For more details on ML approach, see **poster #1911** by **Dan Cox** Thursday, 15th May, 5:30pm, Hall I2

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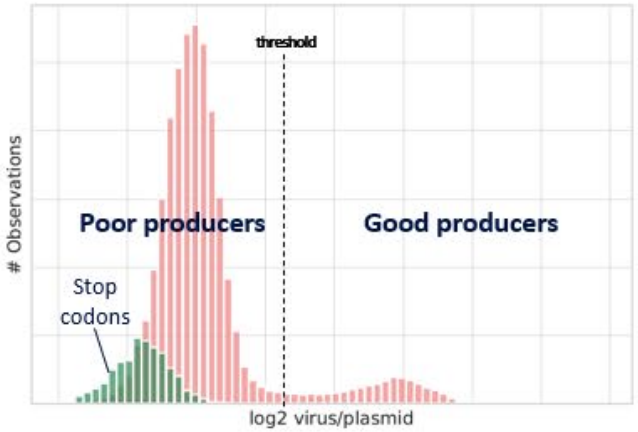
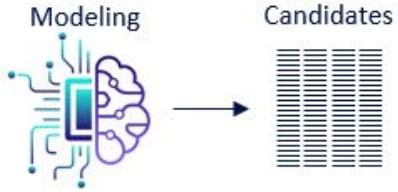
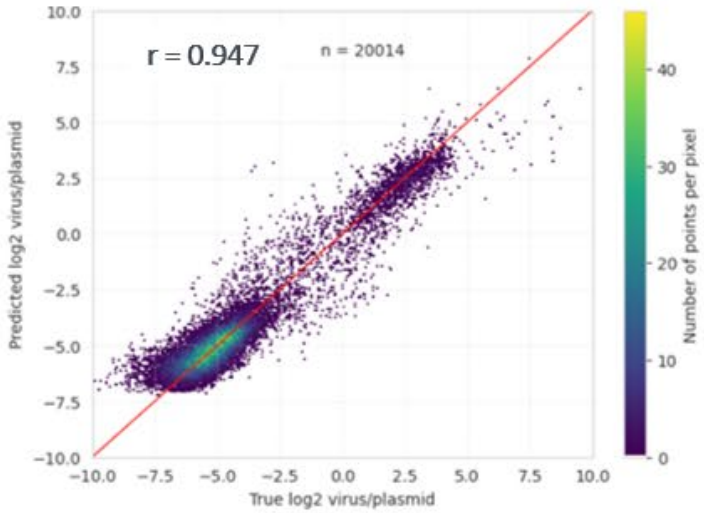
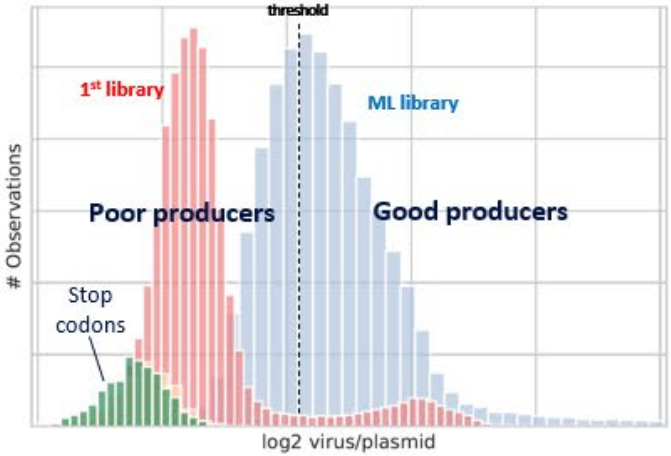


Machine learning



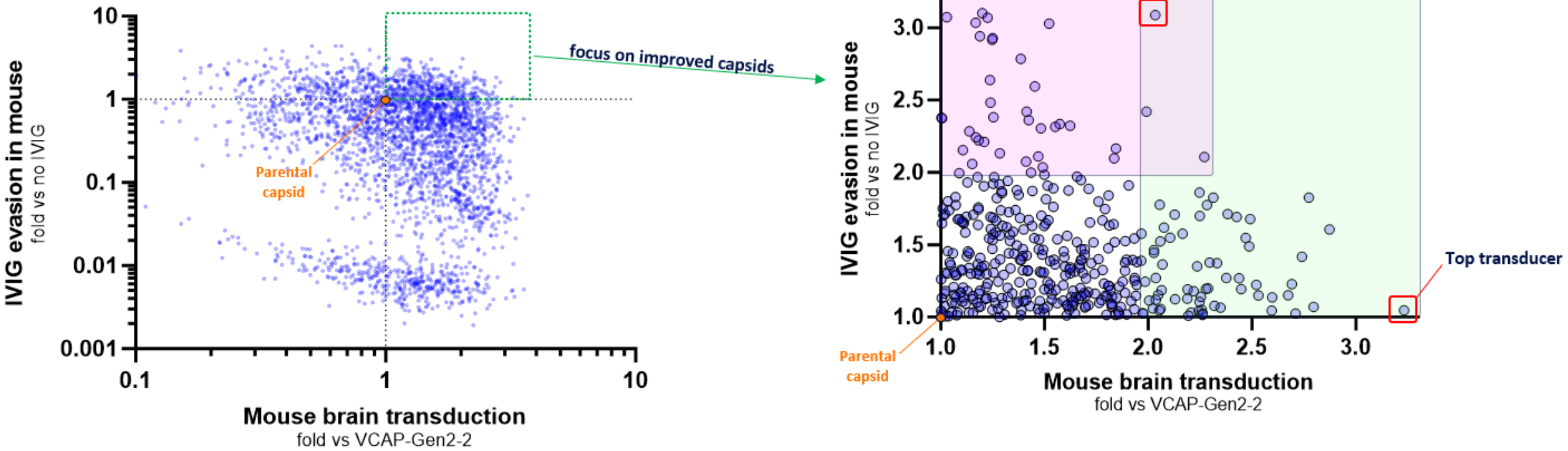


Machine learning increases capsid fitness

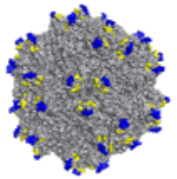


Top ML candidates for region B are improved for both NAb evasion and brain transduction in mouse

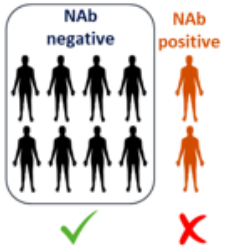
Mouse brain transduction & human IVIG evasion



Summary



- **VCAP-Gen2-A1** is a **3rd generation TRACER AAV capsid** with a combination of high brain transduction and antibody evasion



- VCAP-Gen2-A1 could **allow 40% more patients to receive AAV gene therapy**

- VCAP-Gen2-A1 **transduces NHP brain in the presence of natural pre-existing NAbs**

- Machine Learning – based approach identified additional mutations in a different capsid region that **improve both brain transduction & antibody evasion**

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Questions?

voyager therapeutics