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Iterative Evolution of Cross-Species BBB-Penetrant Capsids

In Vivo Gene Therapy & Genome Editing Summit

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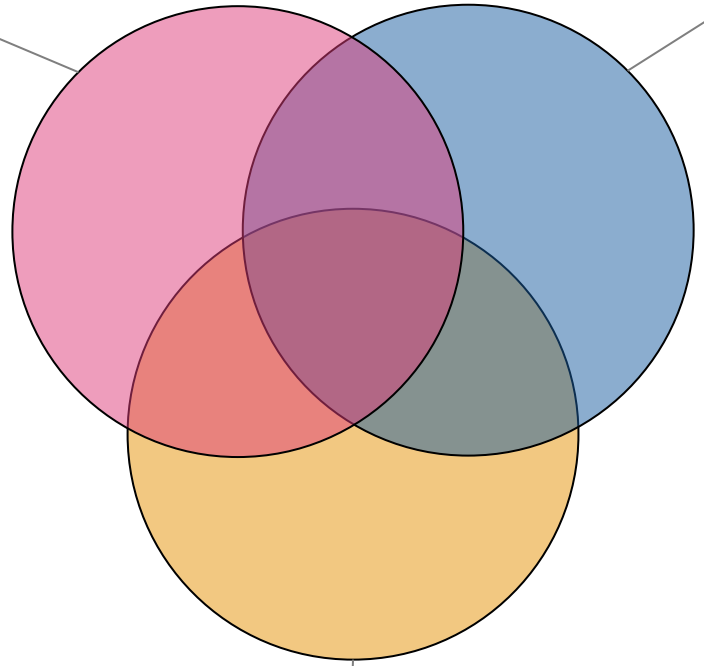
Mathieu Nonnenmacher | Voyager Therapeutics

Forward-Looking Statements

This presentation contains forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995 and other federal securities laws. The use of words such as “may,” “will,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “target,” “future,” “potential,” or “continue,” and other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements include, among other things, statements about Voyager’s ability to utilize its TRACER-derived capsids in its own product development programs and to progress its own product development programs, including identifying a lead clinical candidate for each program; Voyager’s ability to utilize receptors to its TRACER-derived capsid families to enable rational capsid design and speed the evolution of those capsid families; and opportunities to establish human proof of concept and translation of pre-clinical data into humans for Voyager’s TRACER-derived capsids through Voyager’s and its collaborators’ and partners’ product development programs. These forward-looking statements are only predictions, and Voyager may not actually achieve the plans, intentions, or expectations disclosed in the forward-looking statements. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that Voyager expected. Such risks and uncertainties include, among others, the continued development of various technology platforms, including Voyager’s TRACER capsid discovery platform; Voyager’s scientific approach and program development progress, and the restricted supply of critical research components; the ability to attract and retain talented contractors and employees, including key scientists and business leaders; the ability to create and protect intellectual property; the sufficiency of cash resources; the possibility and the timing of the exercise of development, commercialization, license and other options under the Pfizer and Novartis license option agreements and other collaborations; the ability of Voyager to negotiate and complete other licensing or collaboration agreements on terms acceptable to Voyager and third parties; the success of programs controlled by third party collaboration parties in which Voyager retains a financial interest, and the success of Voyager’s product candidates. These statements are also subject to a number of material risks and uncertainties that are described in Voyager’s most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission, as updated by its subsequent filings with the Securities and Exchange Commission. Any forward-looking statement speaks only as of the date on which this presentation was posted to Voyager’s website. Voyager undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

Voyager Criteria for a Successful Clinical Candidate

Target Tissue and Cellular tropism
- Significant increase over natural capsids
- >50-75% target cells at medium dose
- Liver detargeting
- Acceptable DRG transduction



Evidence supporting human translation
- cross-species equivalence
- human cell culture model
- Receptor identification

Scalable Manufacturing
- similar to parental capsids
- low aggregation
- compatible with existing process

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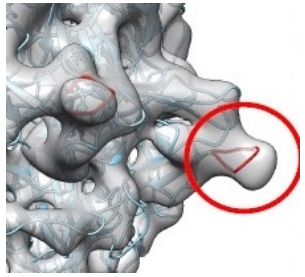
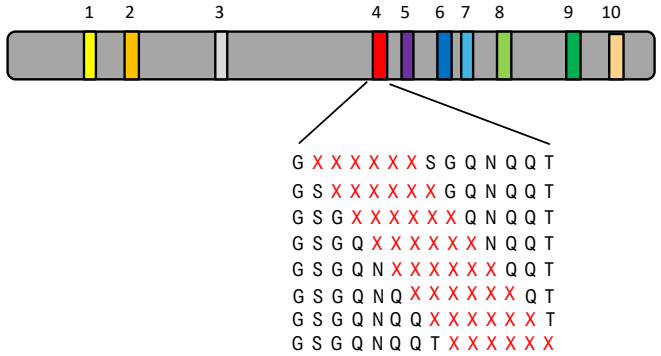
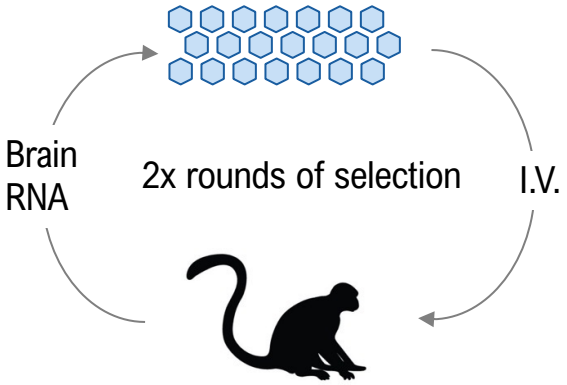
Discovery of Cross-Species Capsids VCAP-101/102

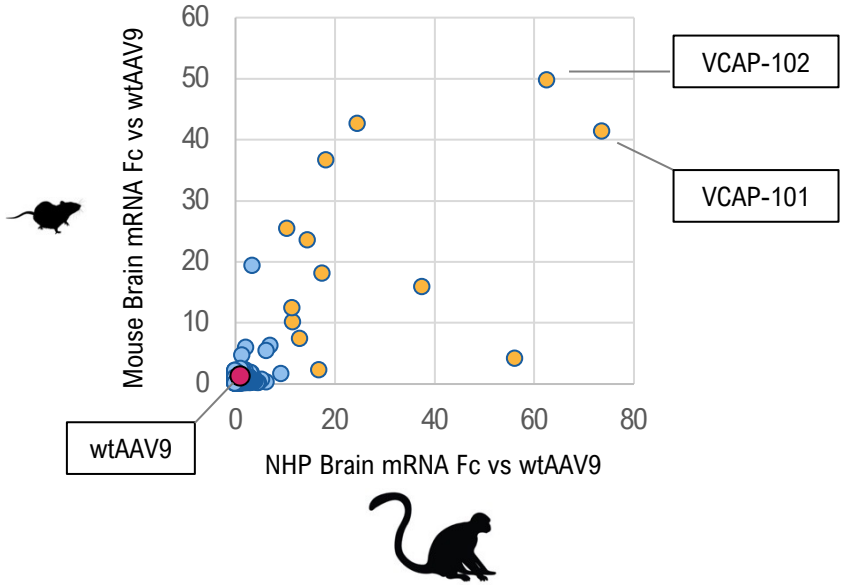
Scanning of capsid surface sites for peptide insertion



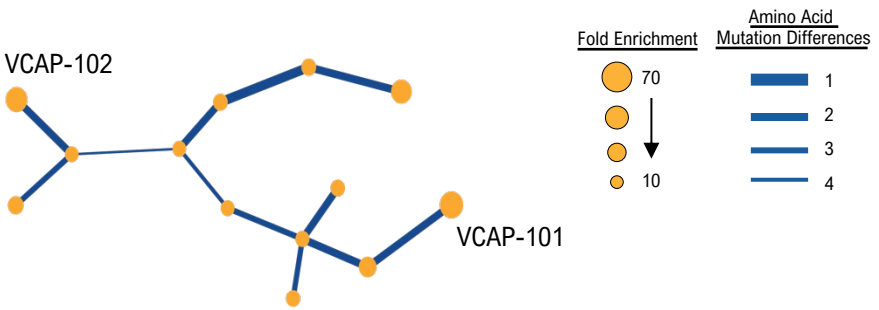
VR4 display Library



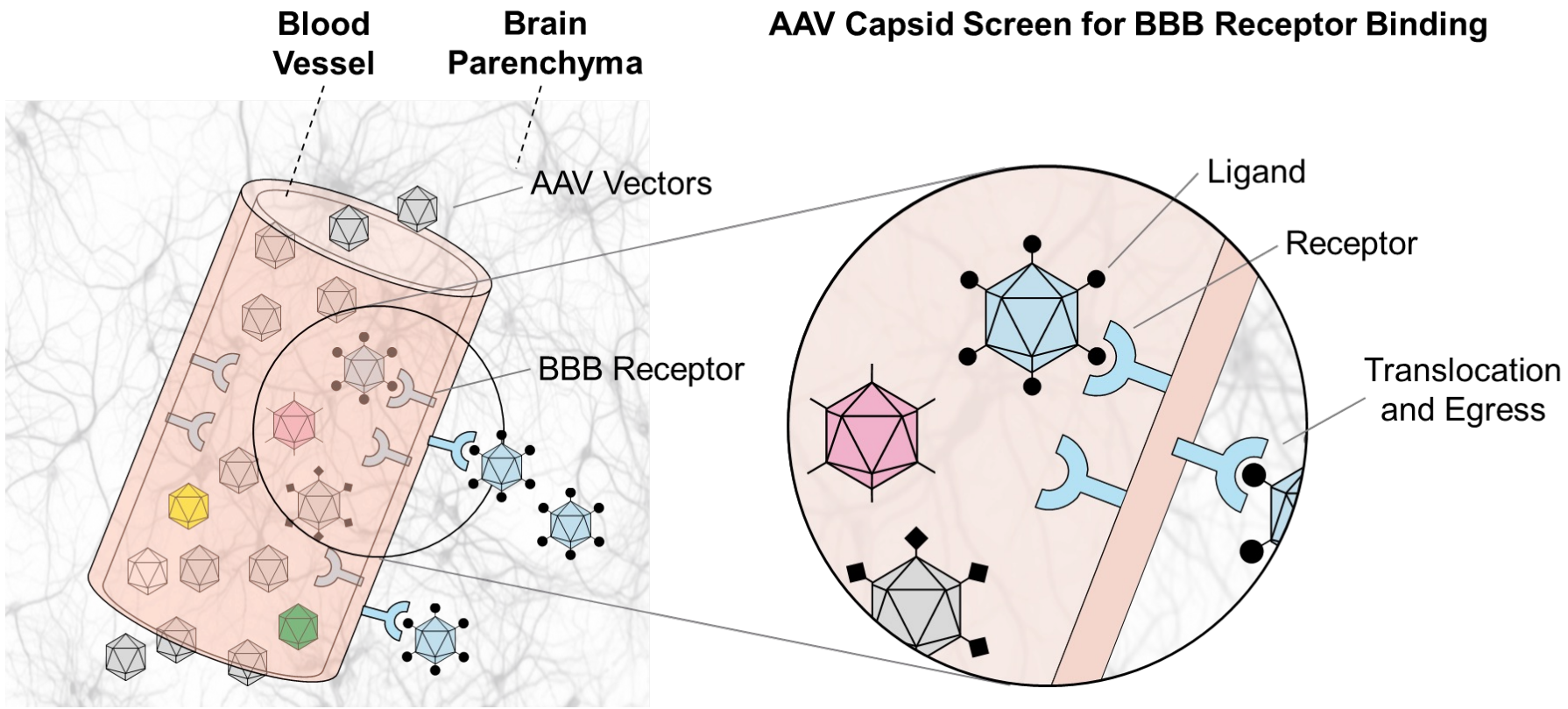




Network Clustering of Hits with FC/wtAAV9 > 10:



Receptor/Ligand Paradigm in BBB-penetrant Capsid Engineering



Known AAV-Receptor interactions:

- VCAP-101/102 – RX (Voyager)
- PHP.B-Ly6A (Deverman, Wilson)
- 9P39-Ly6C1 (Deverman)
- 9P31-CA4 (Gradinaru)

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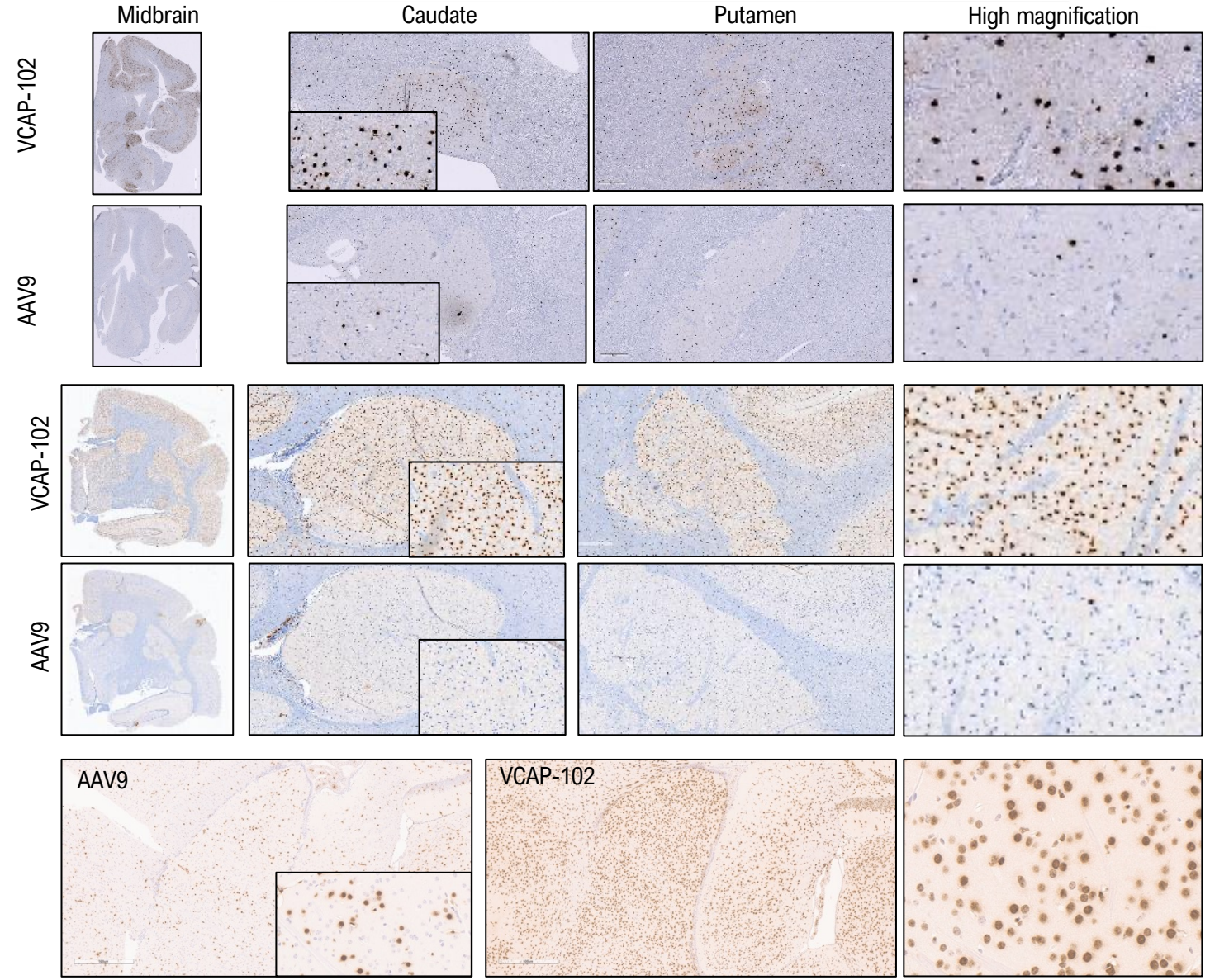
Characterization of a Cross-Species Capsid : VCAP-102 in AGM, Marmoset and Mouse



AGM
1e13 VG/kg
scH2B

~ 40X

Marmoset
2e12 VG/kg
scH2B

~ 400X

Mouse
5e13 VG/kg
scH2B

~ 40X

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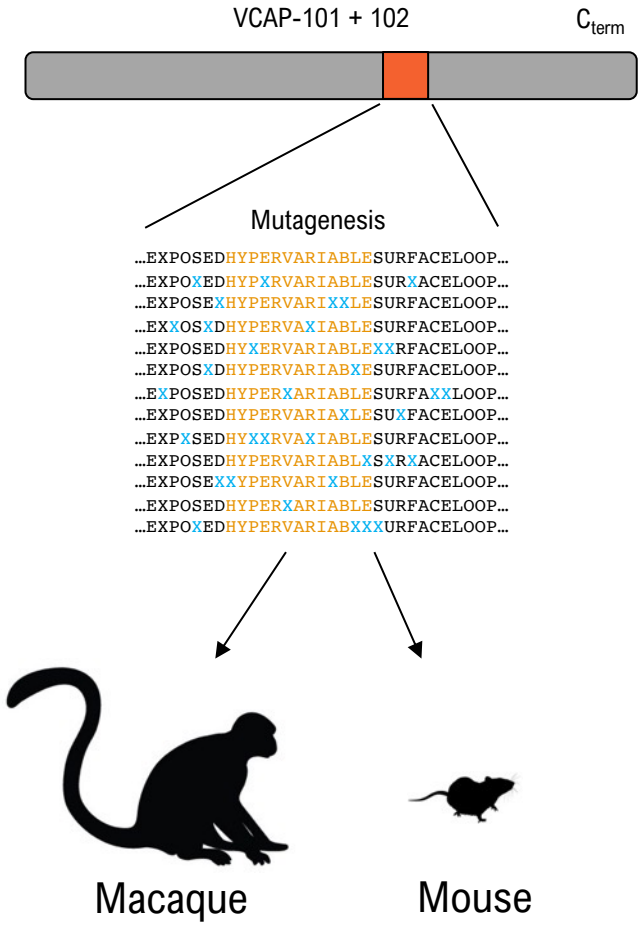
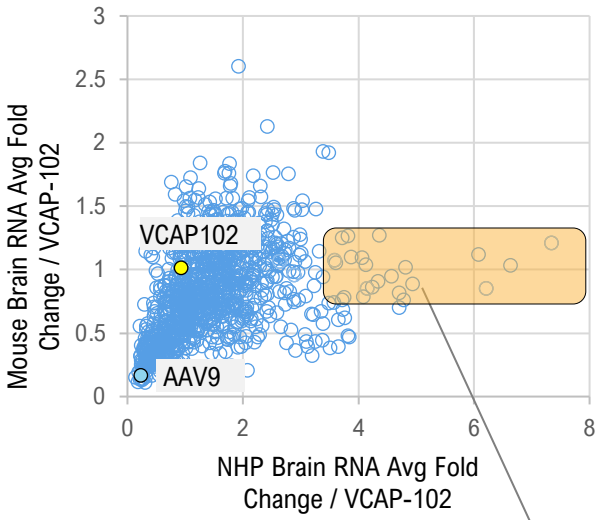
Gen2 Variant Engineering by Saturation Mutagenesis

Fitness Maturation

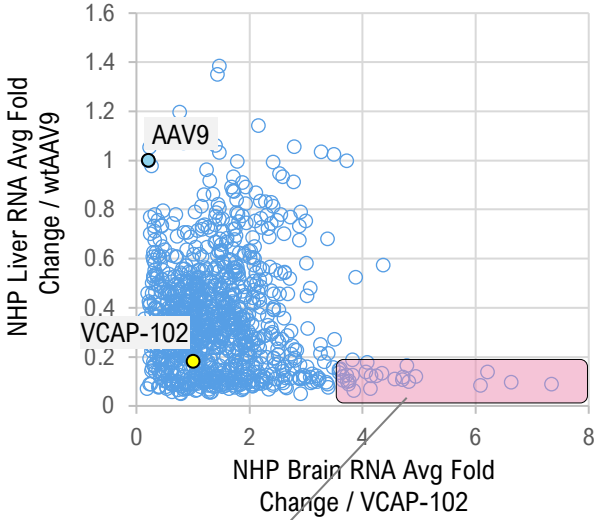


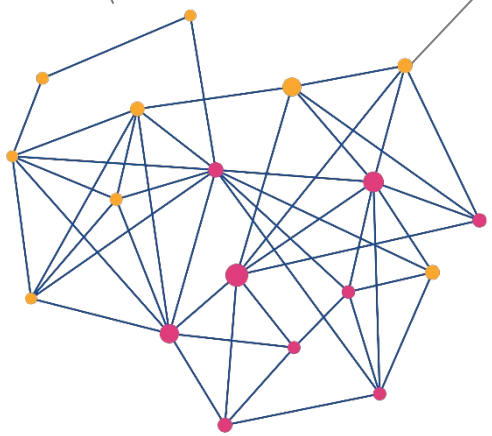
Gen2 Candidates Selection

Brain Transduction



Liver Detargeting





>10 capsids for NHP validation

Multiplexed Capsid Evaluation in NHP – Multi-Tag Approach

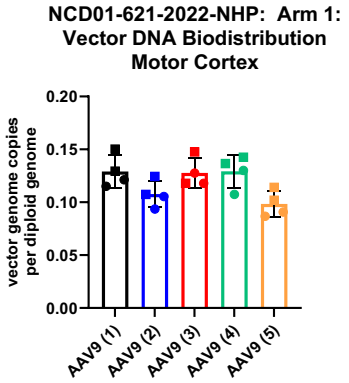
AAV9-Tg1
AAV9-Tg2
AAV9-Tg3
AAV9-Tg4
AAV9-Tg5

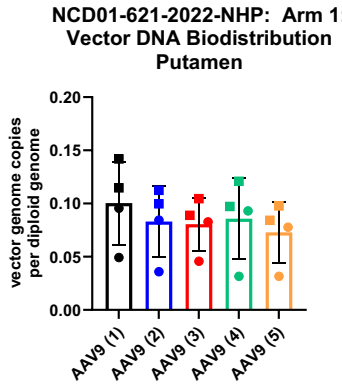
3 x Cyno

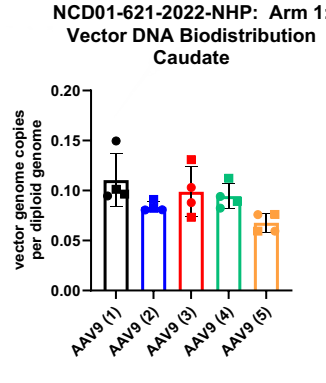
VG biodistribution

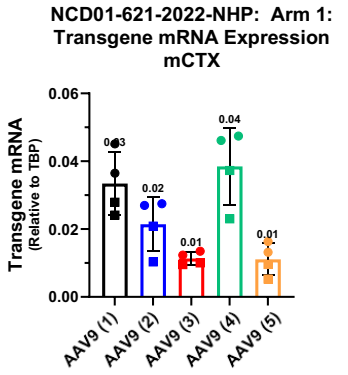
mRNA Expression

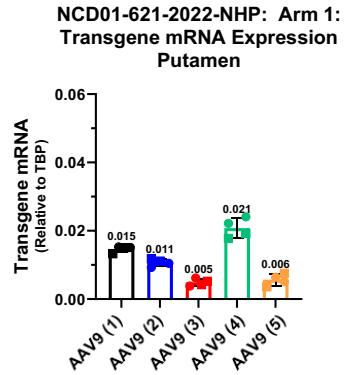
% transduced cells
(IHC – Halo)

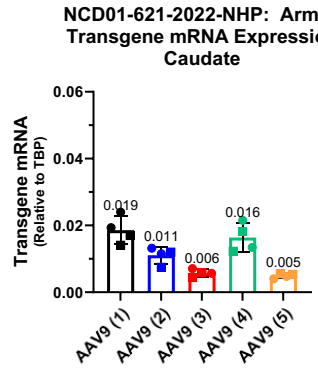


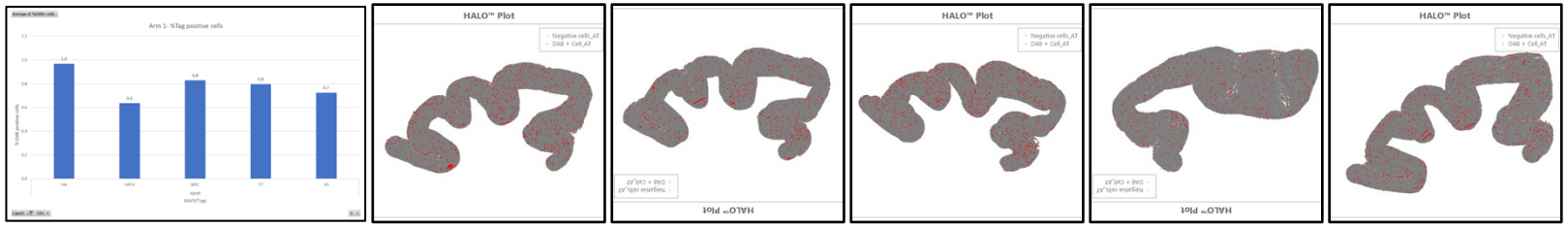






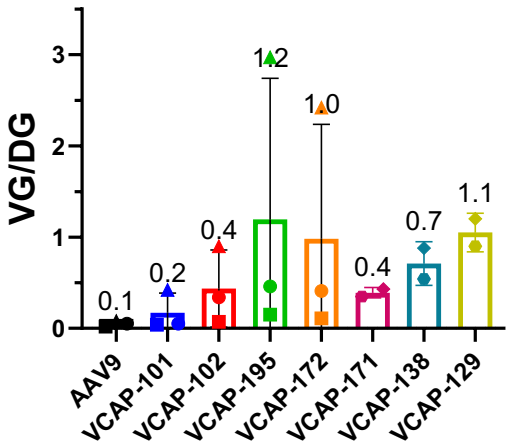


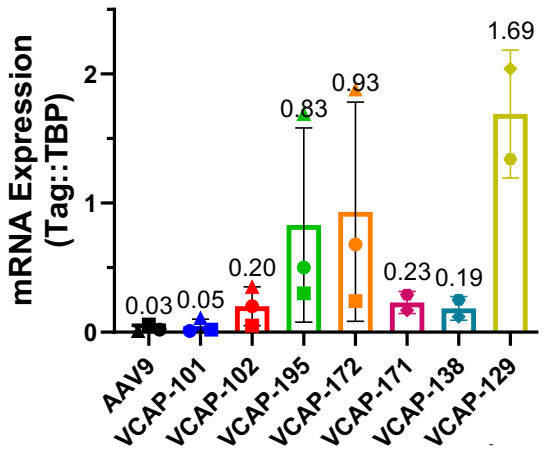


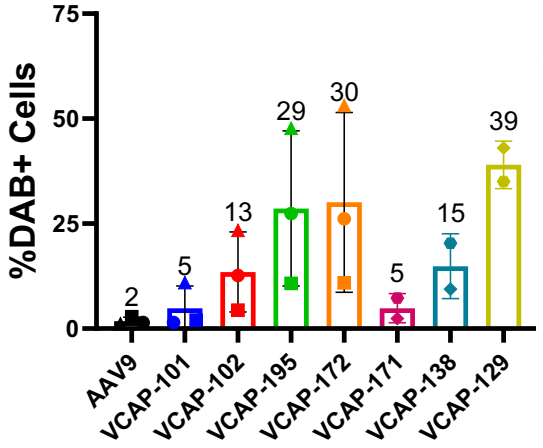


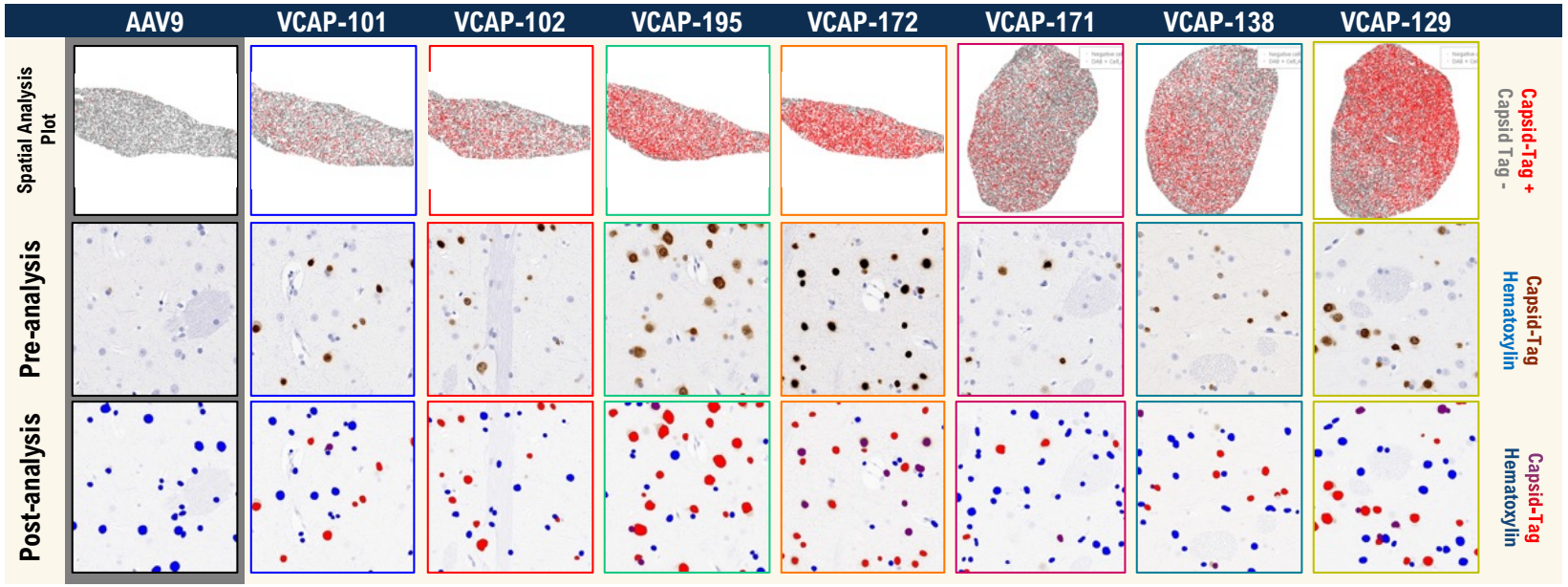
Vector Genome, mRNA Expression and % Cells in NHP Putamen

Up to 30% Cells Transduced in the Putamen at an IV dose of 4E12 vg/kg

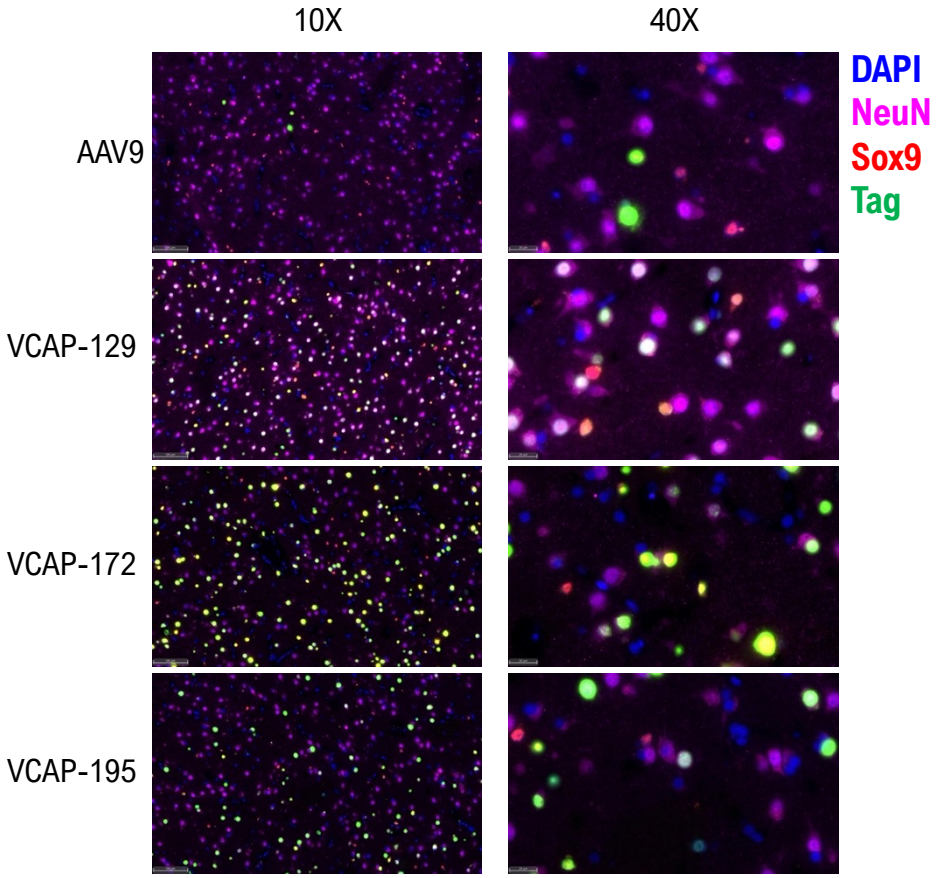


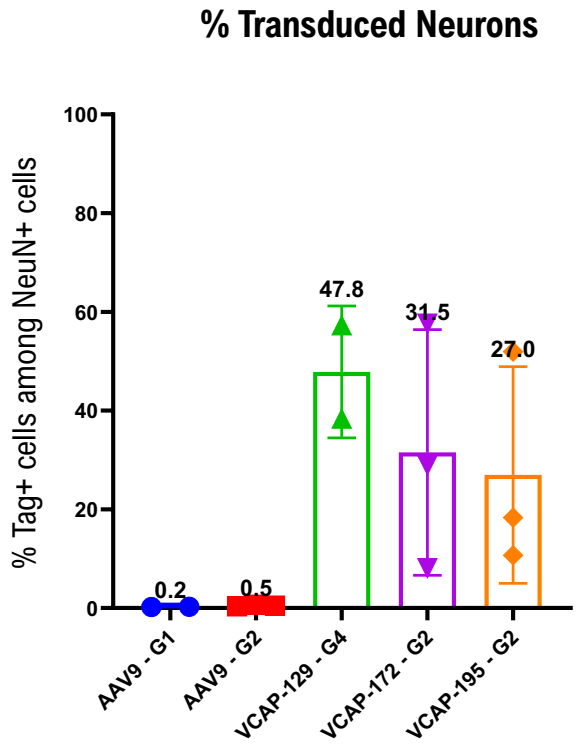


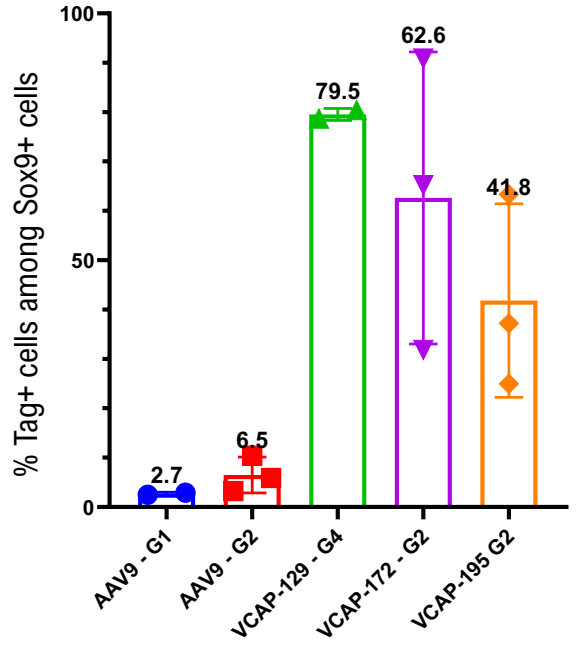




Neuron / Astrocyte Transduction by Gen2 Capsids in NHP Putamen







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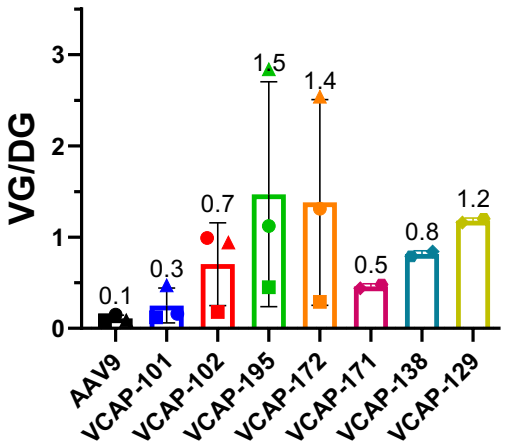
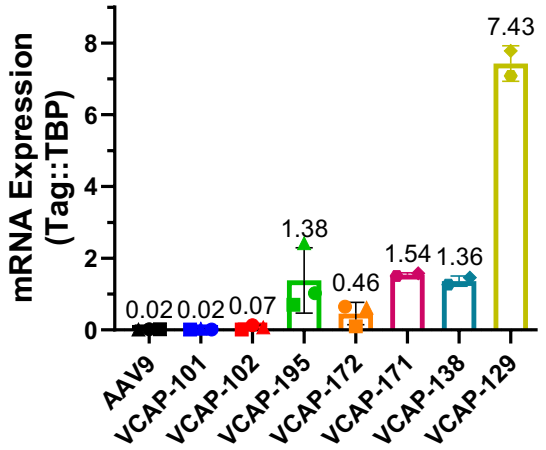
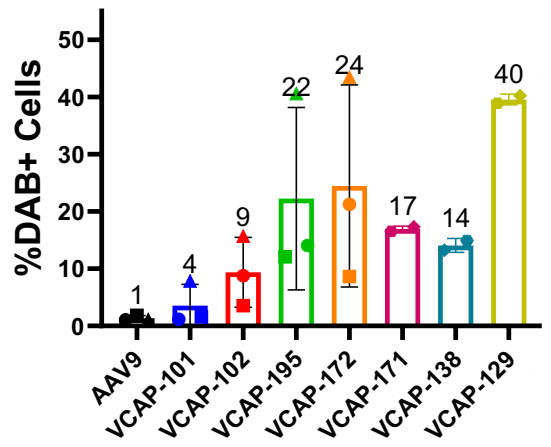
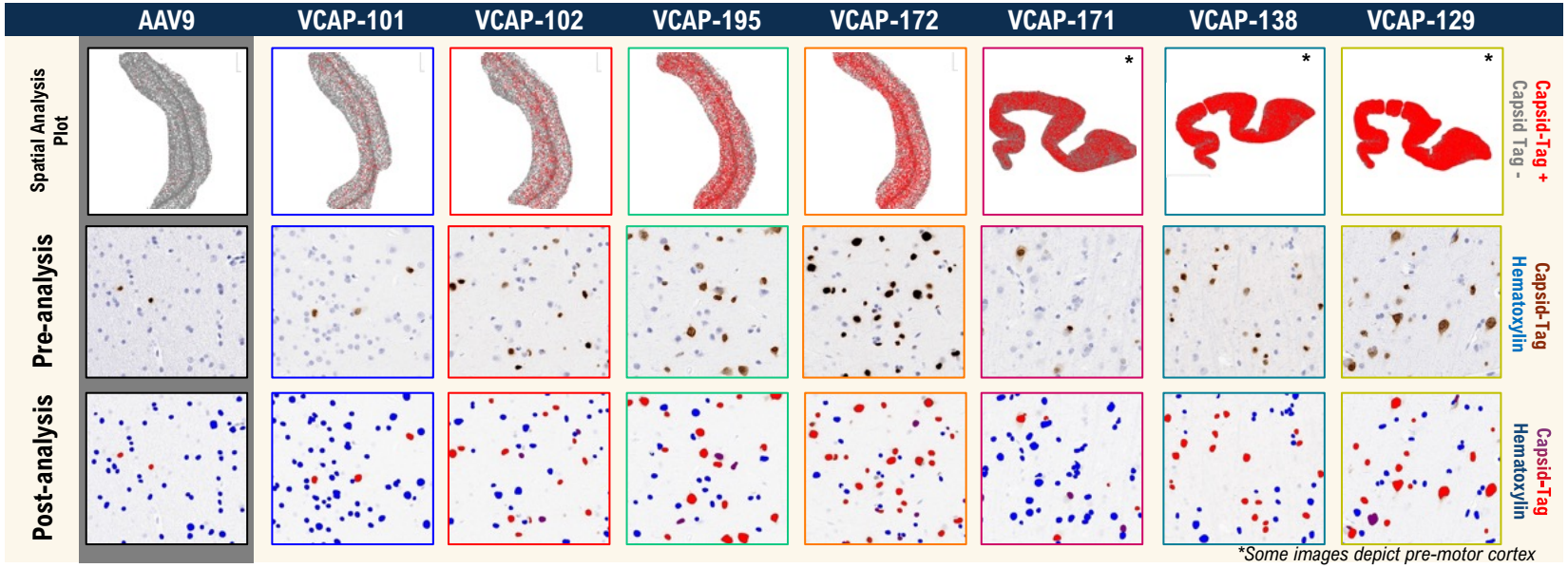
Vector Genome, mRNA Expression and % Cells in NHP Motor Cortex*

Up to 40% Cells Transduced in the Motor Cortex at an IV dose of 4E12 vg/kg









*Some images depict pre-motor cortex

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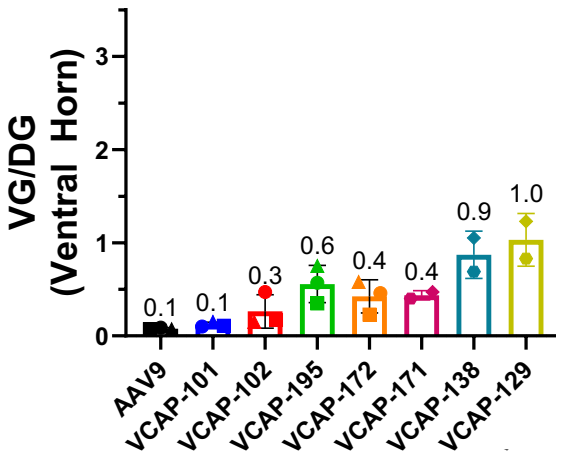
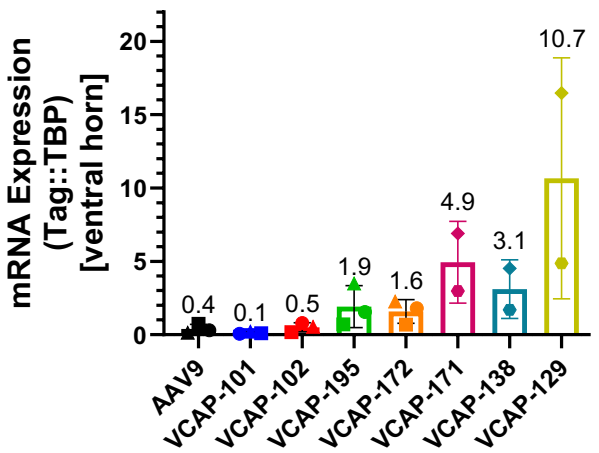
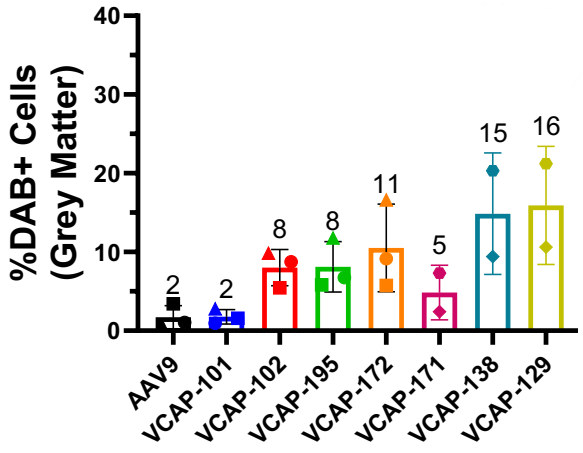
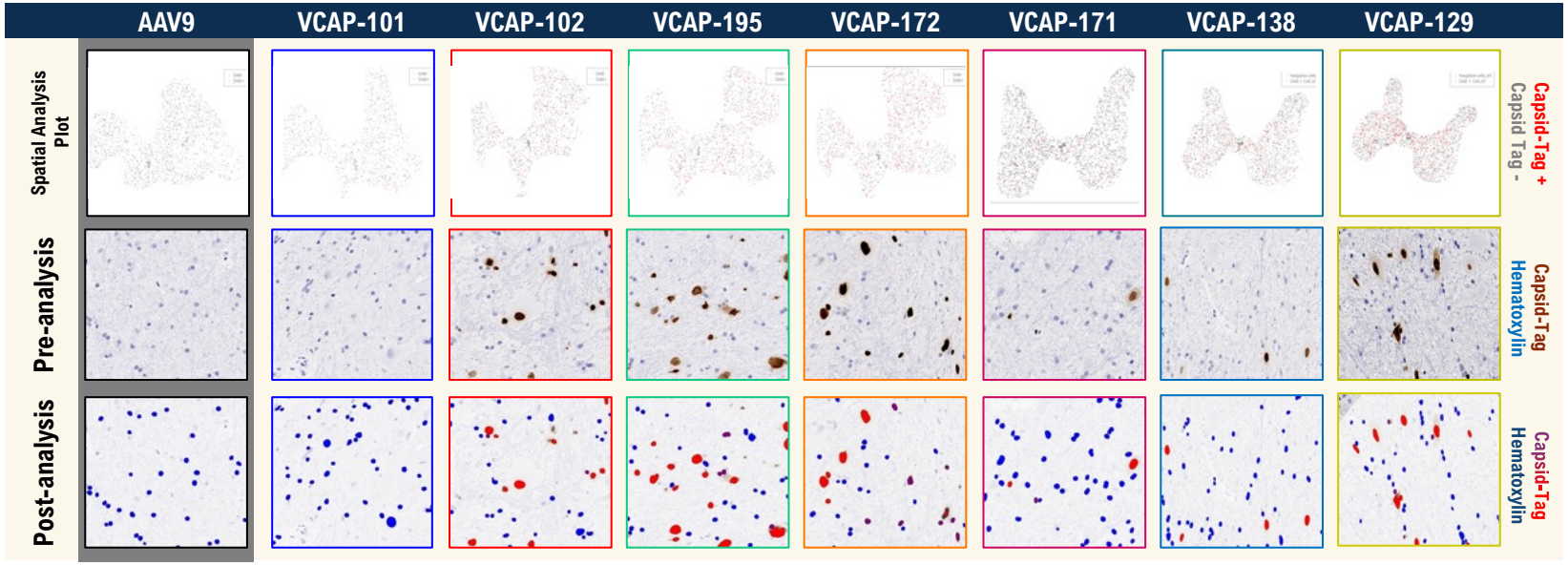
Vector Genome, mRNA Expression, and % Cells in NHP Cervical Spinal Cord

Improved Delivery relative to AAV9 and VCAP102 at an IV dose of 4E12 vg/kg

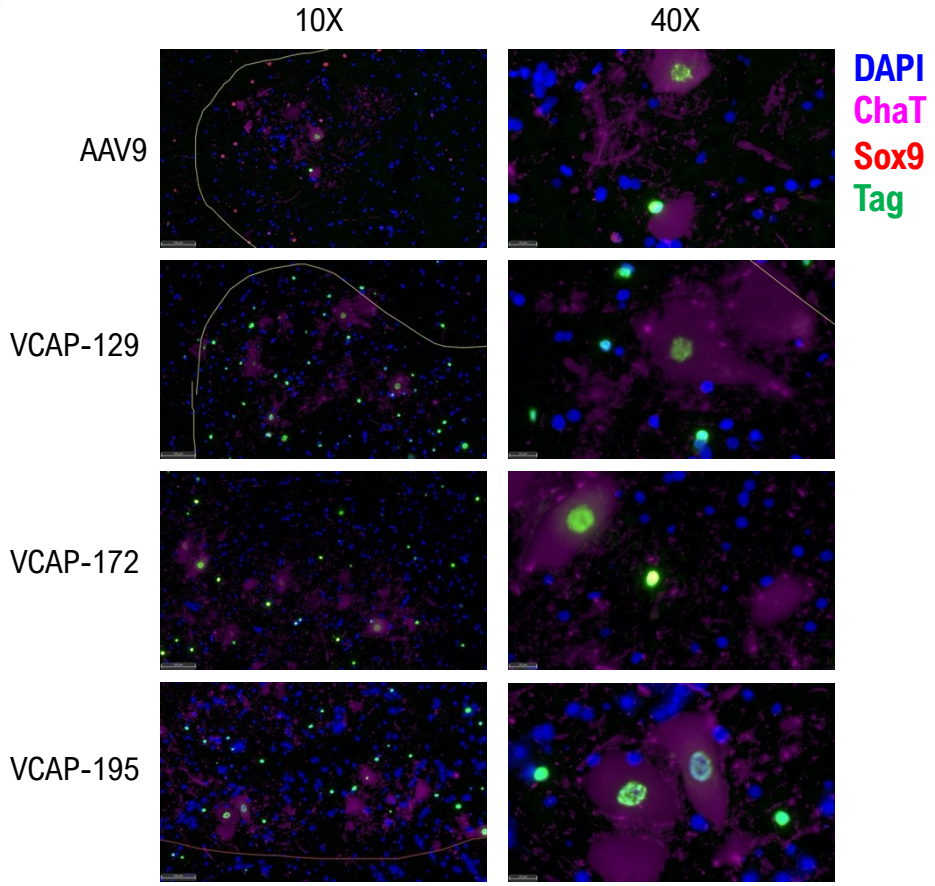


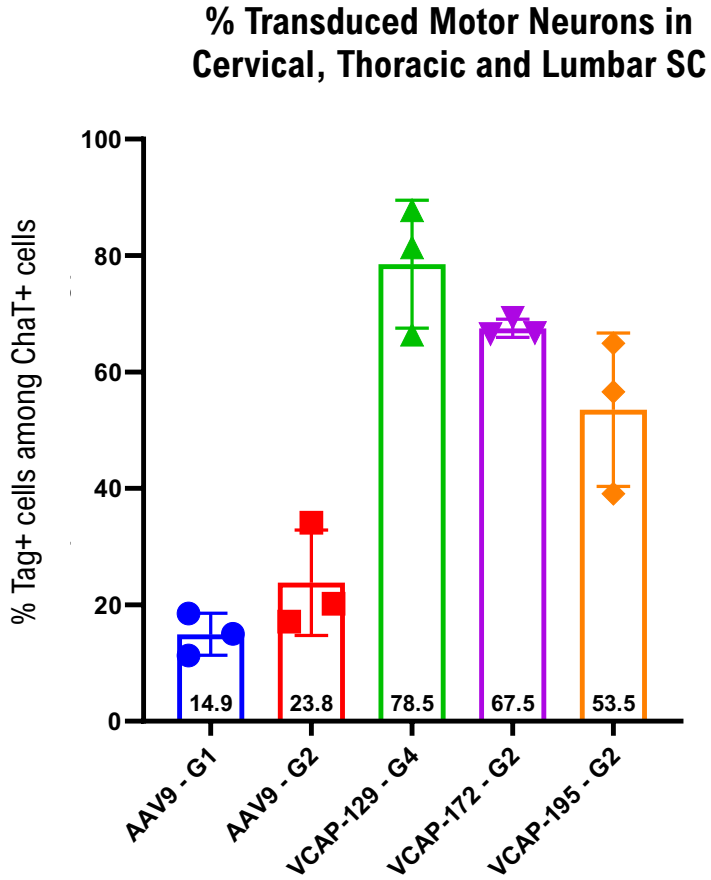




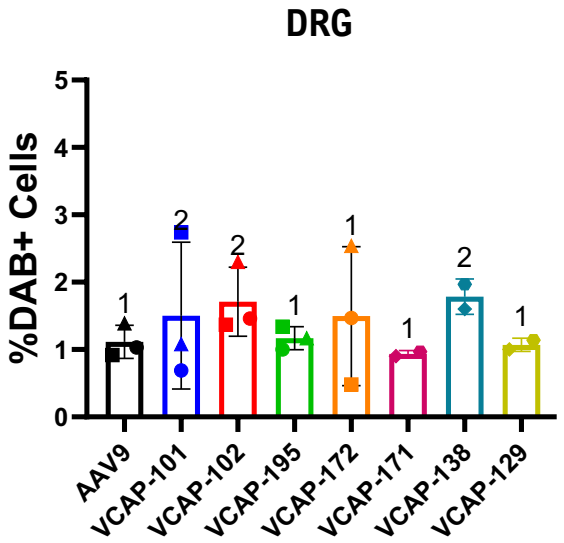


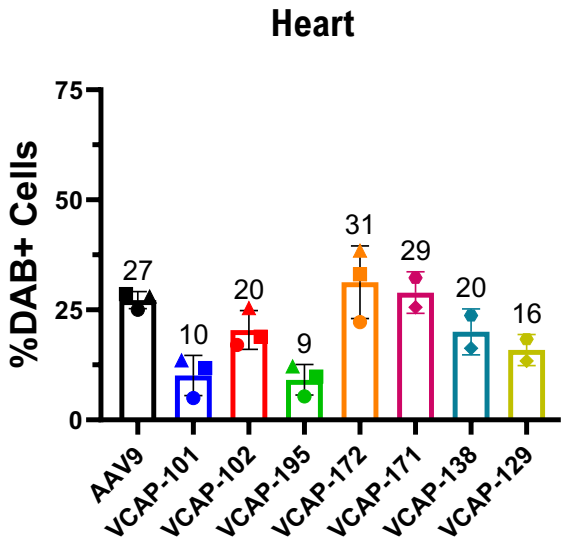
Motor Neuron Transduction by Gen2 Capsids in NHP Spinal Cord

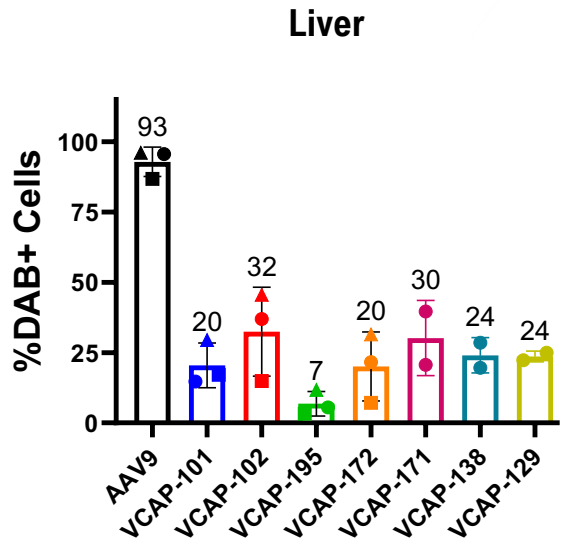


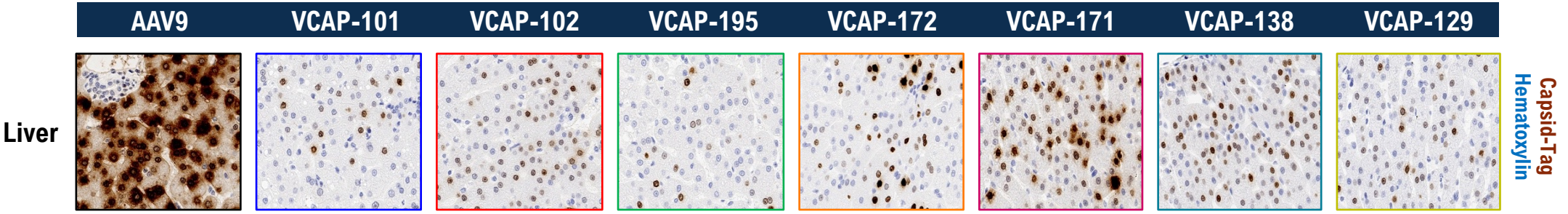


Transduction in NHP Peripheral Tissues - % Positive Cells









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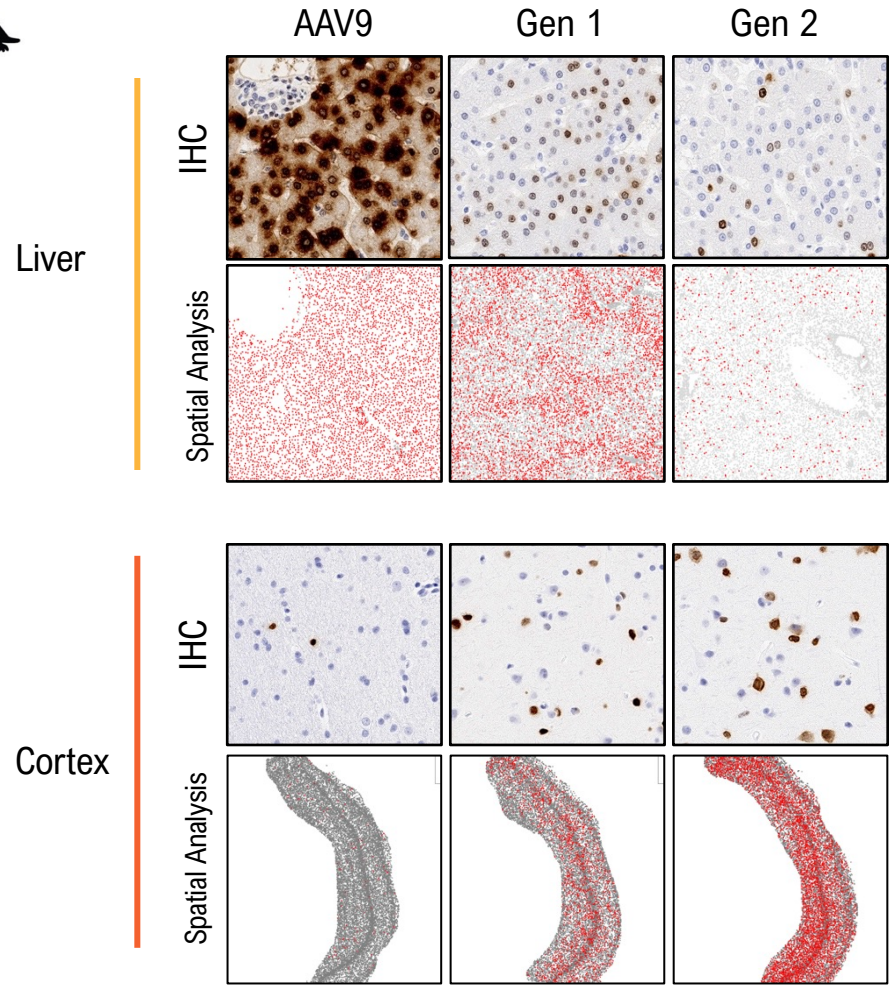
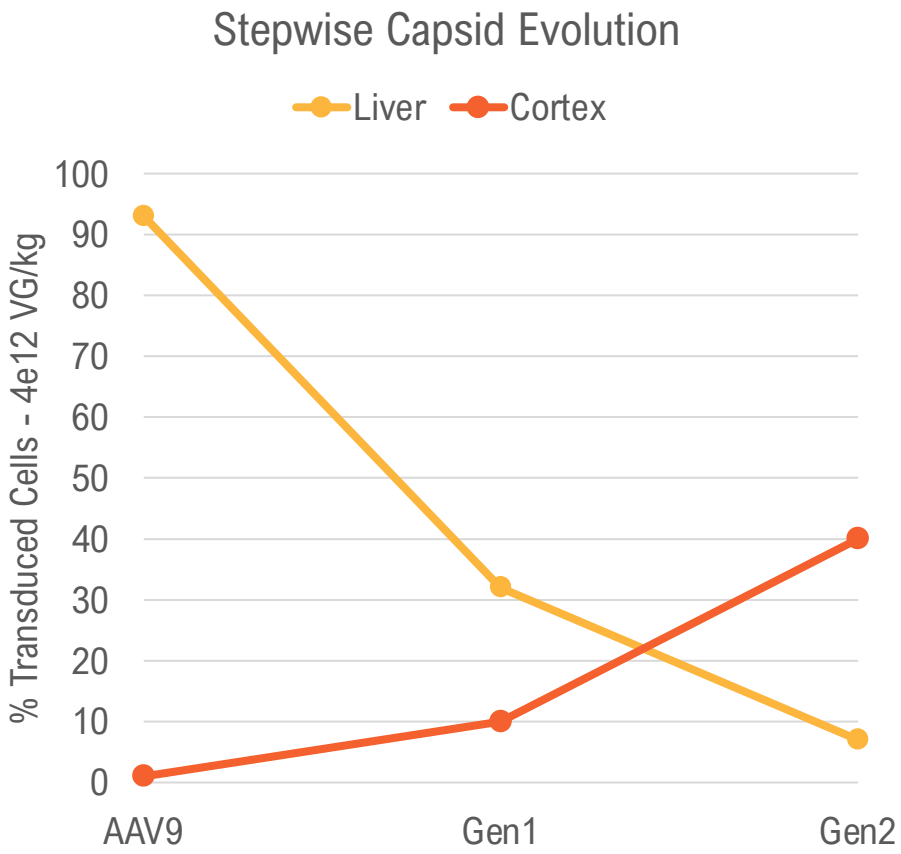
Stepwise Capsid Evolution : NHP Results





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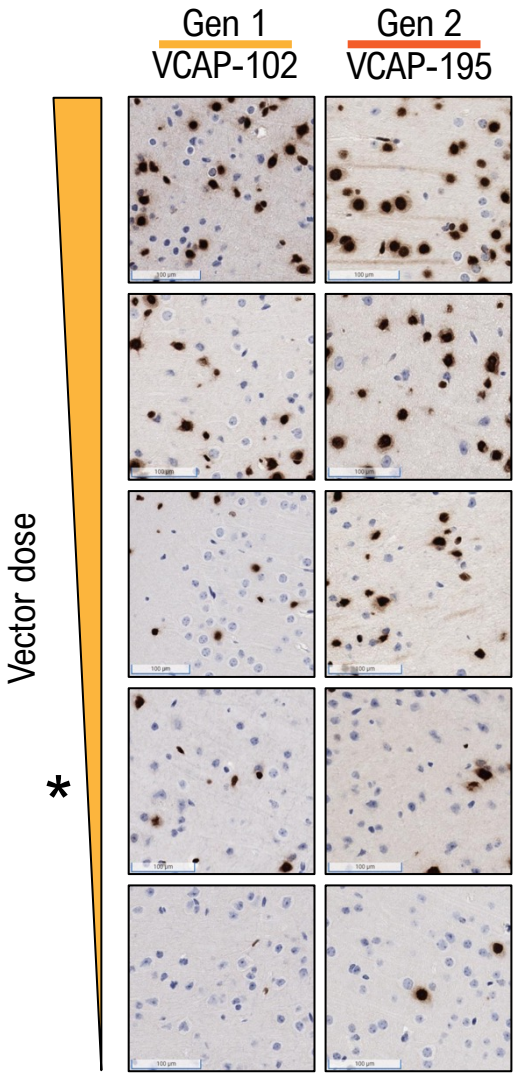
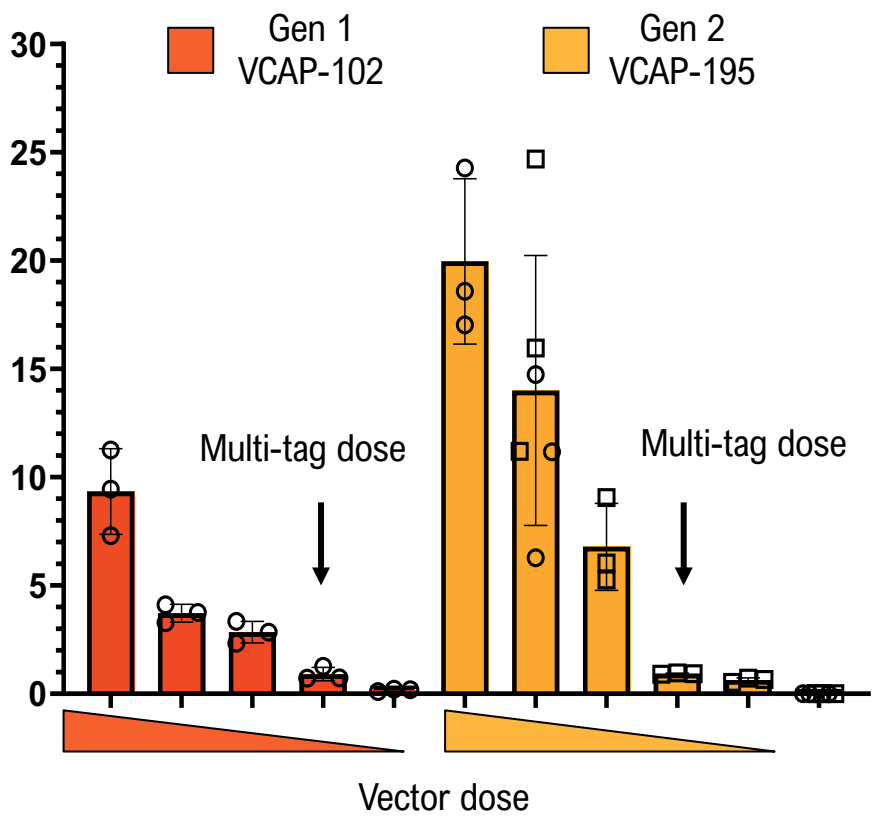
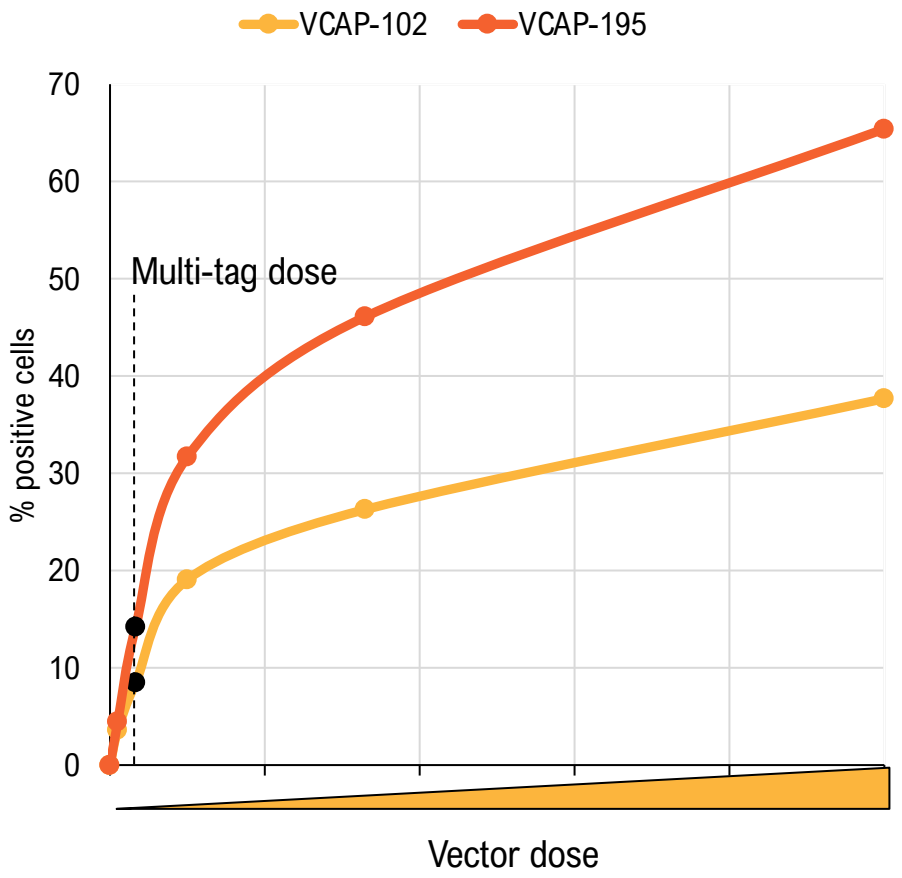
Dose-Response of Gen1 vs Gen2 Capsids in Mouse



Brain Transgene mRNA Expression



Dose-response in mouse cortex



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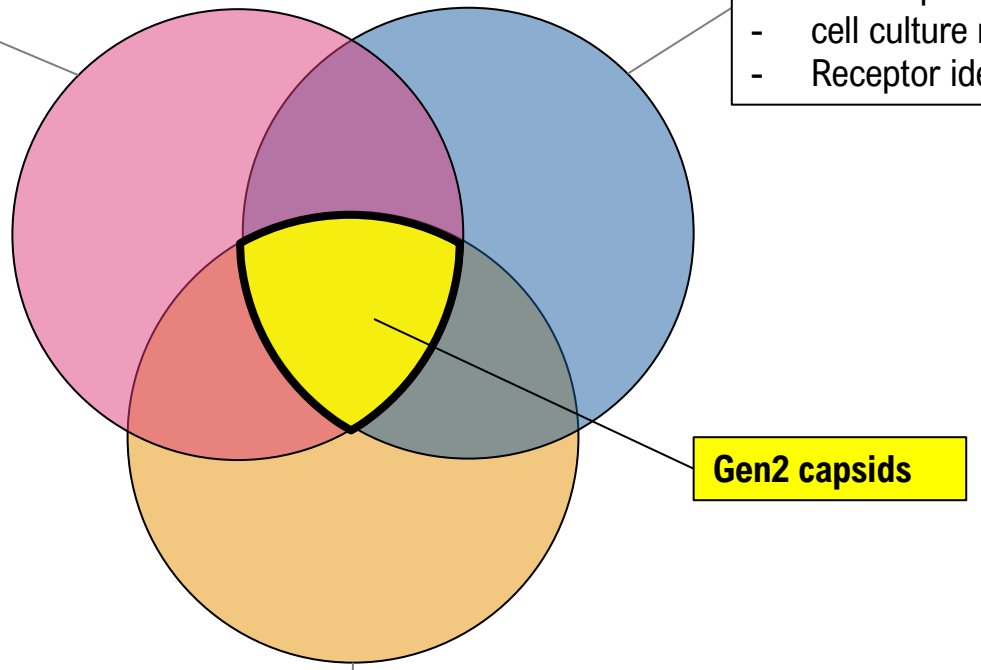
Voyager Criteria for a Successful Clinical Candidate

Target Tissue and Cellular tropism
- Significant increase over natural capsids
- >50-75% target cells at medium dose
- Liver detargeting
- Acceptable DRG transduction

Evidence supporting human translation
- cross-species equivalence
- cell culture model
- Receptor identification



Gen2 capsids

Scalable Manufacturing
- comparable to parental capsids
- low aggregation
- compatible with existing process

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Acknowledgements

- **VCAP-102 Evolution**
  - **Tyler Moyer**
  - Kristin Graham
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  - Joice Zhou
  - Jeyashree Natasan
  - Dhiral Shah
  - **Matt Child**
  - Roop Kaur
  - Zachary Thorpe
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  - **Nilesh Pande**
  - Alexa Tsolias
  - Amy Bruce
  - Rong Zhao
  - Hamza Khalid
  - Wenya Wang
- **Bioanalytics**
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  - Joe Clement
  - Alexis Bloedel
  - Rebecca Spellman
  - Camila Arce

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