Engineered AAV Capsid Achieves Robust Transduction in Non-Human Primate Central Nervous System After Low Dose Systemic Administration

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Introduction

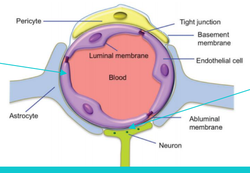
- Adeno-associated viral (AAV) vectors have transformative potential for treating neurological disorders.
- Limitations in effective coverage of the central nervous system (CNS) coupled with safety concerns due to high systemic exposure have hindered clinical translation.
- We previously reported discovery of a novel AAV capsid ATC-134 that achieves widespread CNS coverage in >50% of neurons, with durable expression and knockdown using a miRNA (miR) payload against Atxn2.
- Here, we report ATC-134 packaging a histone protein encoding payload achieved >90% neuronal transduction across Adult NHP CNS after IV dosing at a lower dose of 3e13 vg/kg.

Study Design

ATC-134 Capsid Packaging Protein (Histone) Cargo Driven by Ubiquitous CBh Promoter Was Evaluated in Adult NHPs

ATC-134 – A Novel BBB-Penetrant AAV Capsid

Neurotropic peptide for human BBB penetration



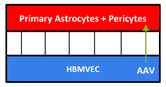
Backbone sequences for cell-type transduction and expression

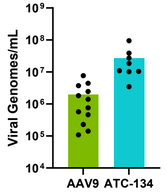
Vector	ROA	Dose (vg/kg)	N-value	In-life (days)	Analysis
ATC-134-H2B-HA	IV	3e13	2	28	Cargo: VG, mRNA, IHC

ATC-134 Successfully Transcytoses the Human BBB in a Synthetic Triculture Model

ATC-134, a Novel BBB-Penetrant AAV Capsid Transcytoses ~20-Fold More Efficiently Than AAV9 in a Synthetic Human BBB Model

AAV vectors (5×10^{10} viral particles/mL) were applied to the endothelial channel of a human SynBBB triculture microfluidic model under flow for 4 h, and transcytosed vector genome copies in the tissue chamber were quantified by qPCR.

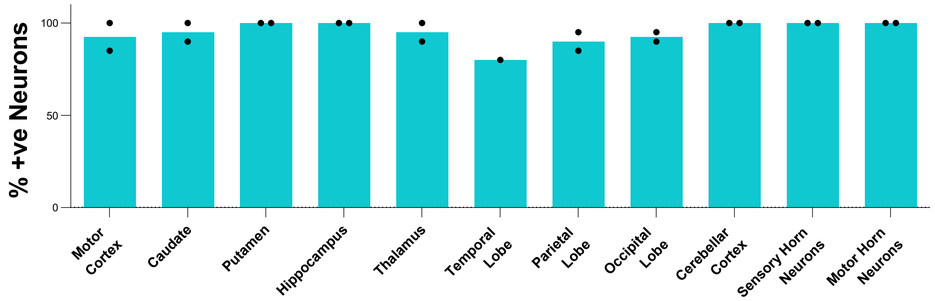




ATC-134 Shows Robust Transduction Across Multiple CNS Regions

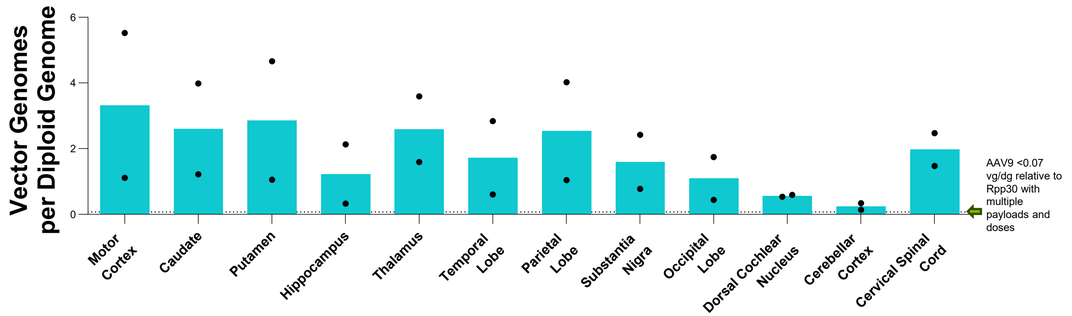
ATC-134-H2B-HA Dosed at 3e13 vg/kg Shows >90% Neuronal Transduction Across Multiple CNS Regions

Semiquantitative assessment of Immuno-histochemistry (IHC) reported as % HA-Tag positive neurons from ATC-134-H2B-HA treated NHP CNS



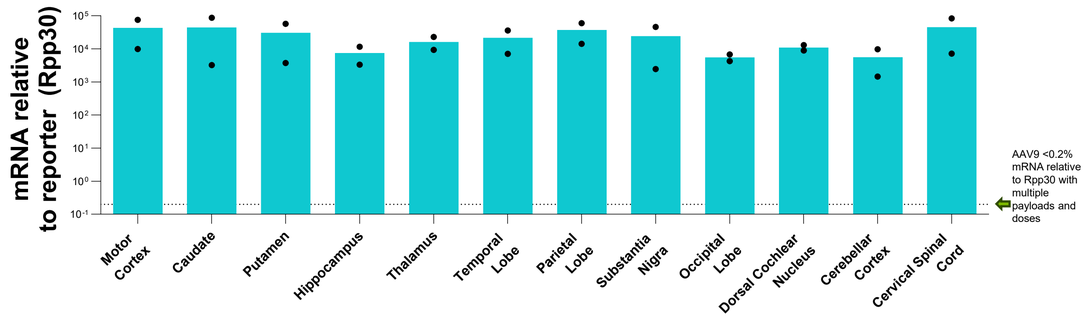
ATC-134-H2B-HA Dosed at 3e13 vg/kg Shows Greater Biodistribution Compared to AAV9 Across Multiple CNS Regions

Vector genome biodistribution quantified using digital droplet polymerase chain reaction (ddPCR) normalized to housekeeping gene Rpp30 in individual cortical and deep brain regions.



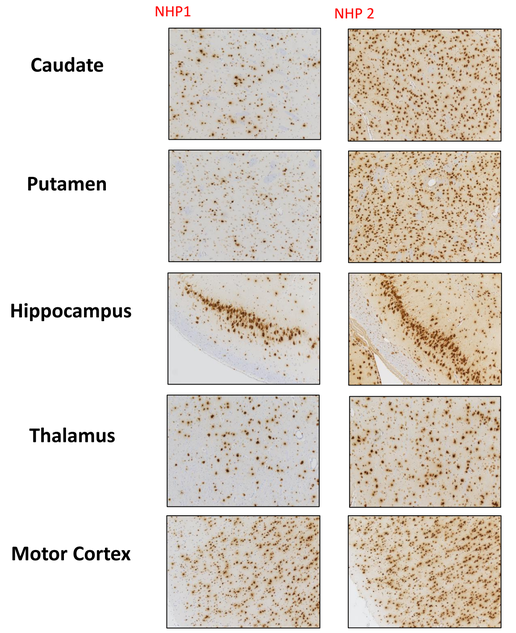
ATC-134-H2B-HA Dosed at 3e13 vg/kg Shows Increased RNA Expression Compared to AAV9 Across Multiple CNS Regions

Vector RNA expression quantified using reverse-transcriptase digital droplet polymerase chain reaction (RT-ddPCR) normalized to housekeeping gene Rpp30 in individual cortical and deep brain regions.



Robust and widespread CNS Transduction

ATC-134-H2B-HA Dosed at 3e13 vg/kg Shows Widespread Neuronal Transduction by Immunohistochemistry



Representative IHC images showing HA-Tag positive staining in neurons (dark brown) from ATC-134-H2B-HA treated brain.

Conclusions

- ATC-134 achieves near-complete (80-100%) CNS transduction following a single low-dose (3e13 vg/kg) systemic administration which supports its translational potential for neurological disease applications.
- ATC-134 shows higher CNS transduction and lower off-target (liver) distribution compared to AAV9 in NHPs.
- Protein cargo (H2B-HA) resulted in >100-fold increase in RNA expression and higher (>80-100%) neuronal expression compared to previously reported miRNA cargo at similar or lower doses.
- ATC-134 achieves CNS transduction efficiency that meets or exceeds benchmarks reported for next-generation BBB-penetrant AAV capsids, reinforcing its potential as a best-in-class vector.

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