Reduction of ATXN2, a therapeutic target for sporadic ALS, in non-human primates using a novel, intravenously delivered AAV capsid

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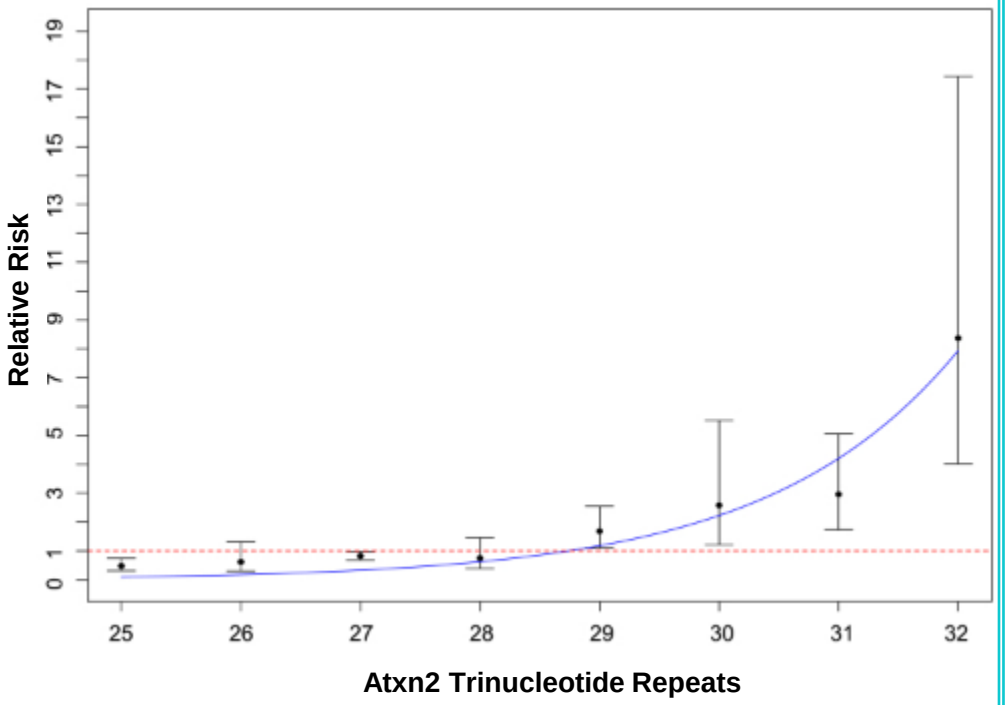
Disclosures

- I am an employee of Affinia Therapeutics

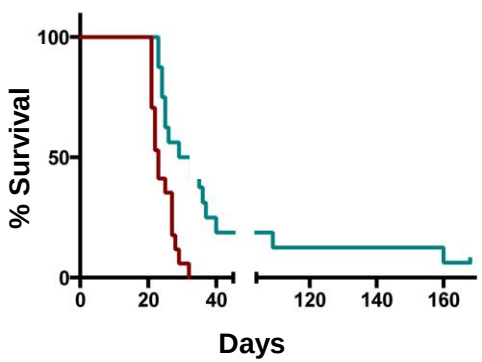
Ataxin-2 reduction as a therapeutic approach for sporadic ALS

Increased ATXN2 trinucleotide repeats increase ALS risk

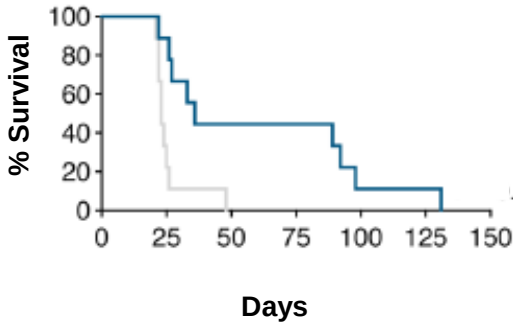


Meta-analysis of 15 published studies with ~11,000 ALS and ~15,500 control cases

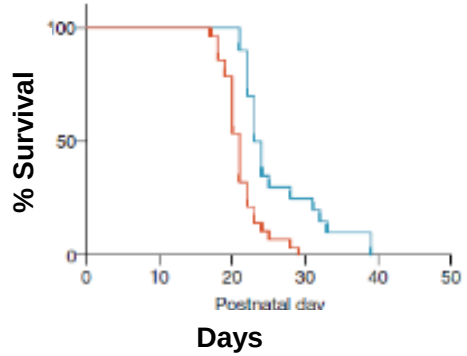
ATXN2 reduction in TDP43 mice extends their lifespan



ASO



CRISPR



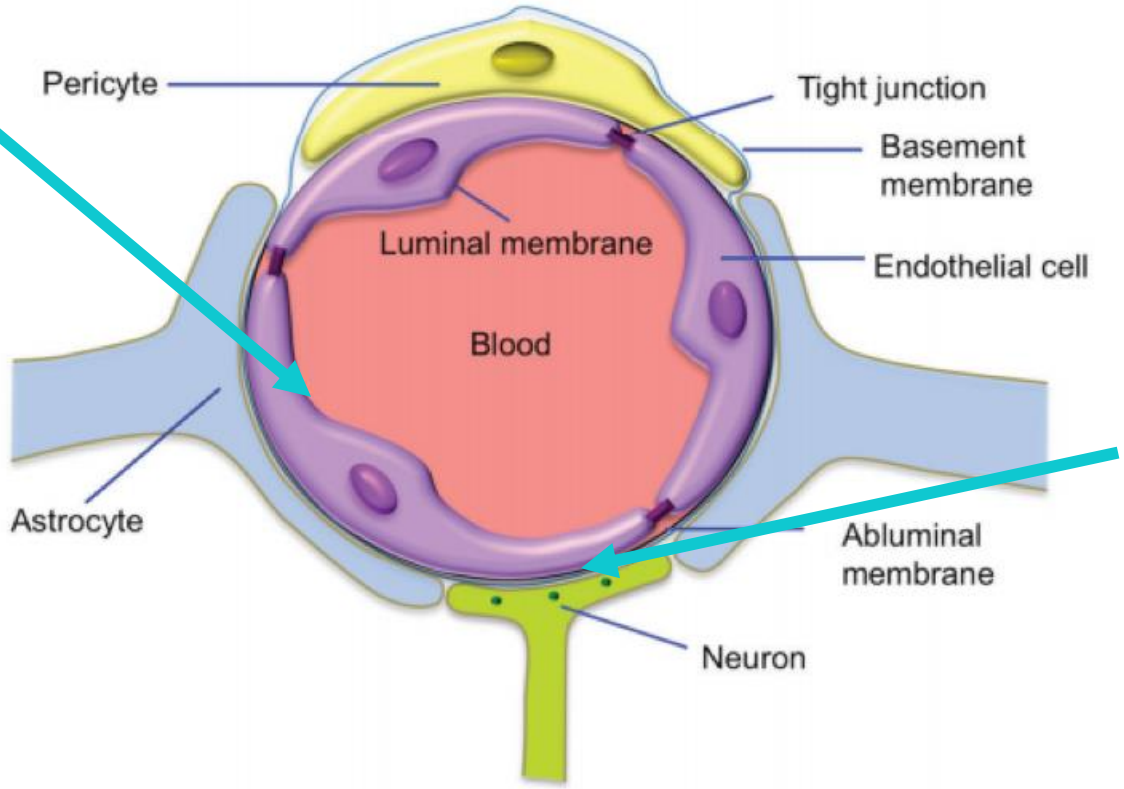
KO

Becker et al. Nature 2017; Elden, Nature, 2010; Neuenschwander, JAMA Neurol, 2014; Sproviero, Neurobiol Aging, 2017; Amado et al. ASGCT 2023; Zeballos et al. Nat Comm 2023

Rationally designed CNS capsids for BBB penetration

Neurotropic peptide for human BBB penetration

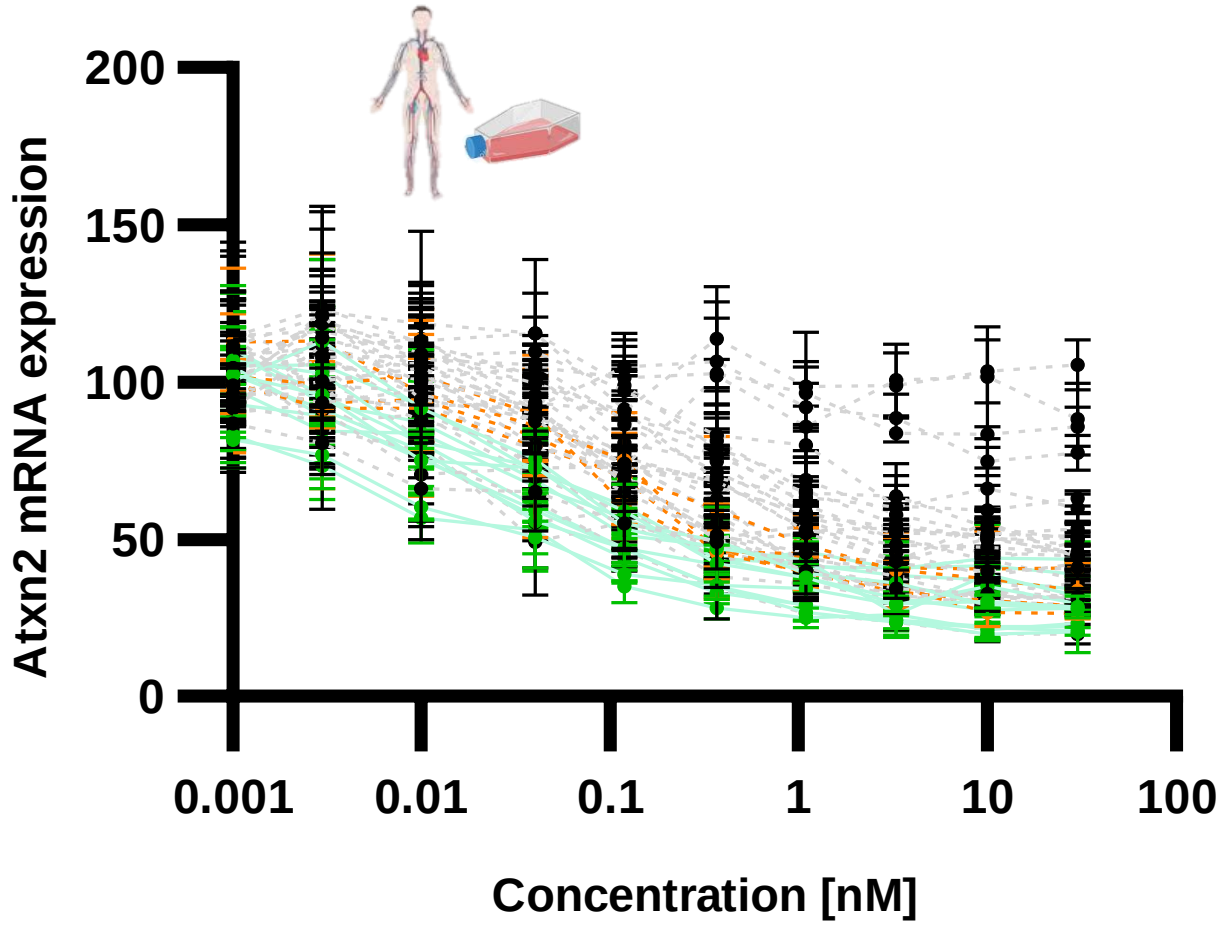
- IV delivery leverages blood flow throughout the brain to cortical and deep brain regions
- CNS peptides bind receptors on brain endothelial cells that likely allow transcytosis through the endothelial cells with potential for reduced dose secondary to CNS tropism
- Understand receptor expression across species



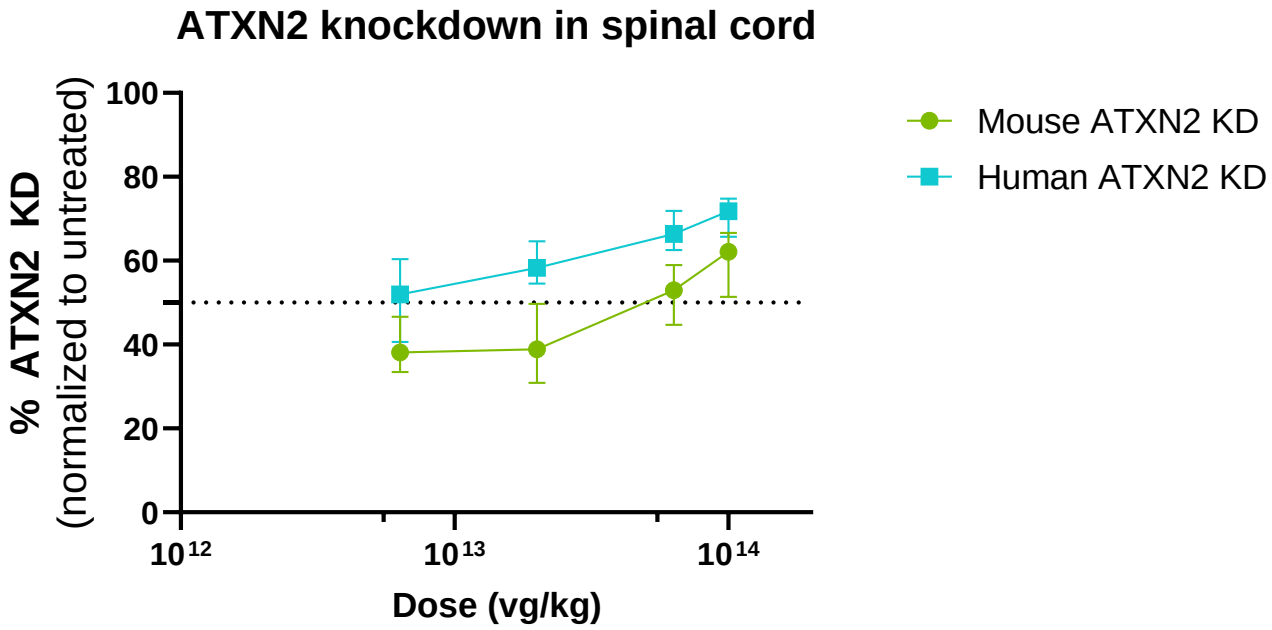
Backbone sequences for cell-type transduction and expression

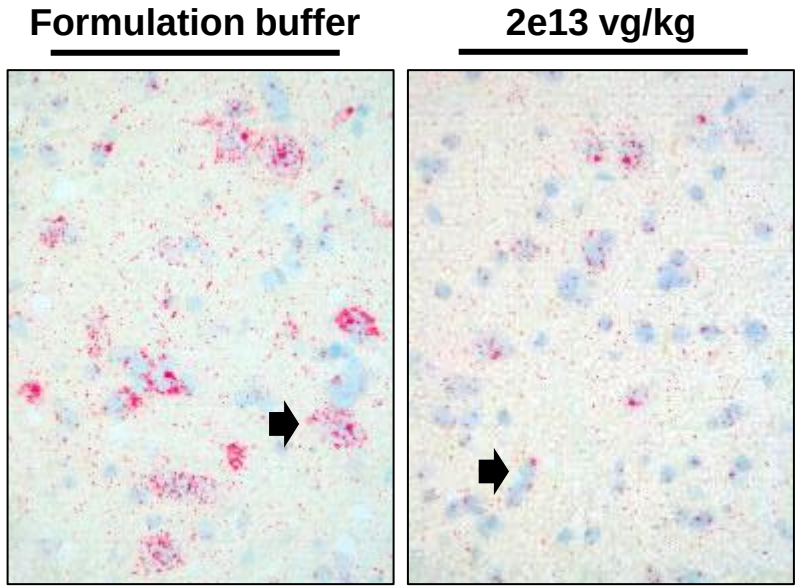
- AAV backbone sequences to target neurons and other cell types of interest, once across the BBB

Multiple siRNAs reduce ATXN2 mRNA in cultured cells



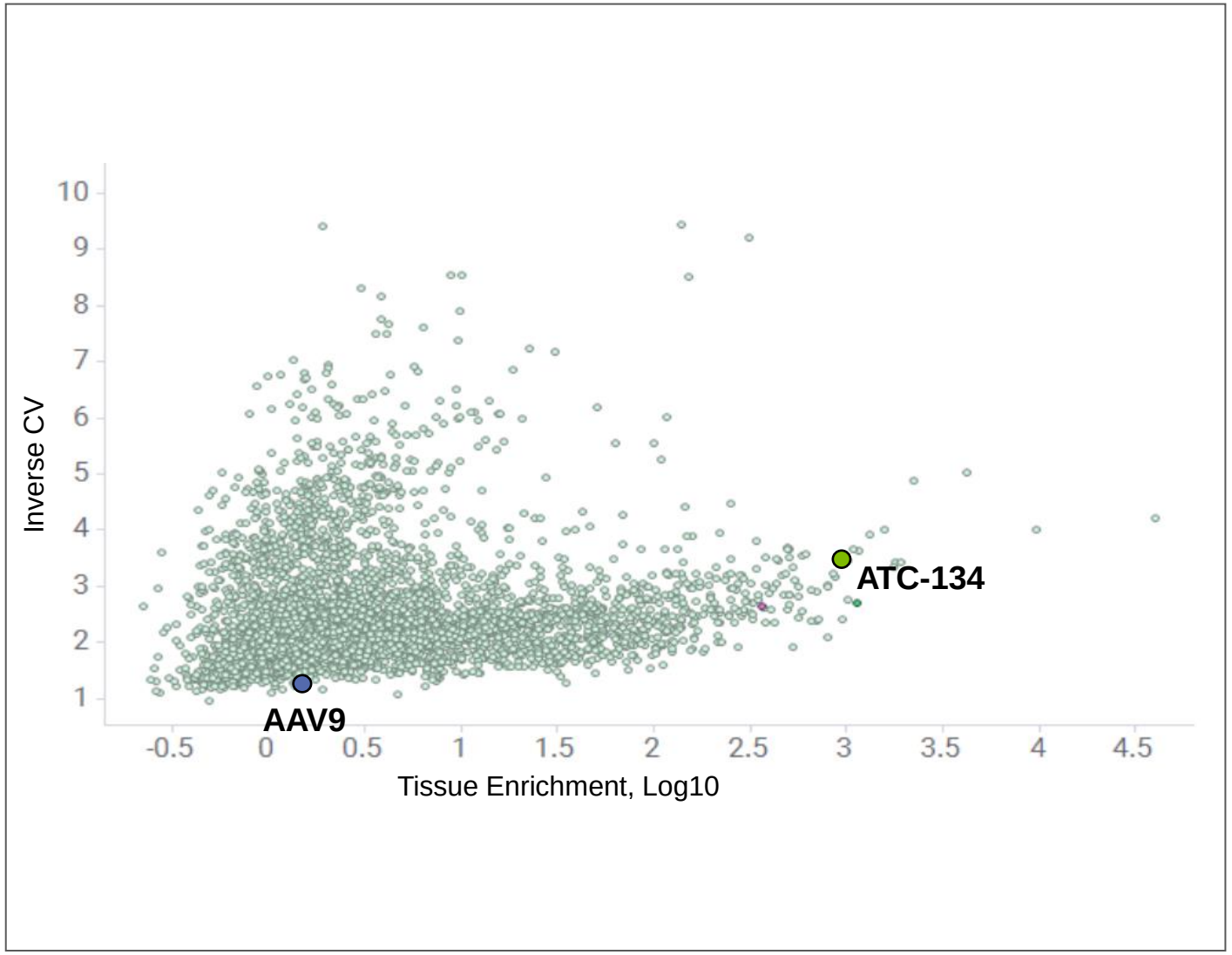
ATXN2 miRNA reduces human and mouse ATXN2 mRNA in mouse spinal cord





hATXN2 mRNA (ISH)
Hematoxylin (nuclei)

ATC-134 was identified in a pooled study in NHP based on superior CNS tropism vs. AAV9



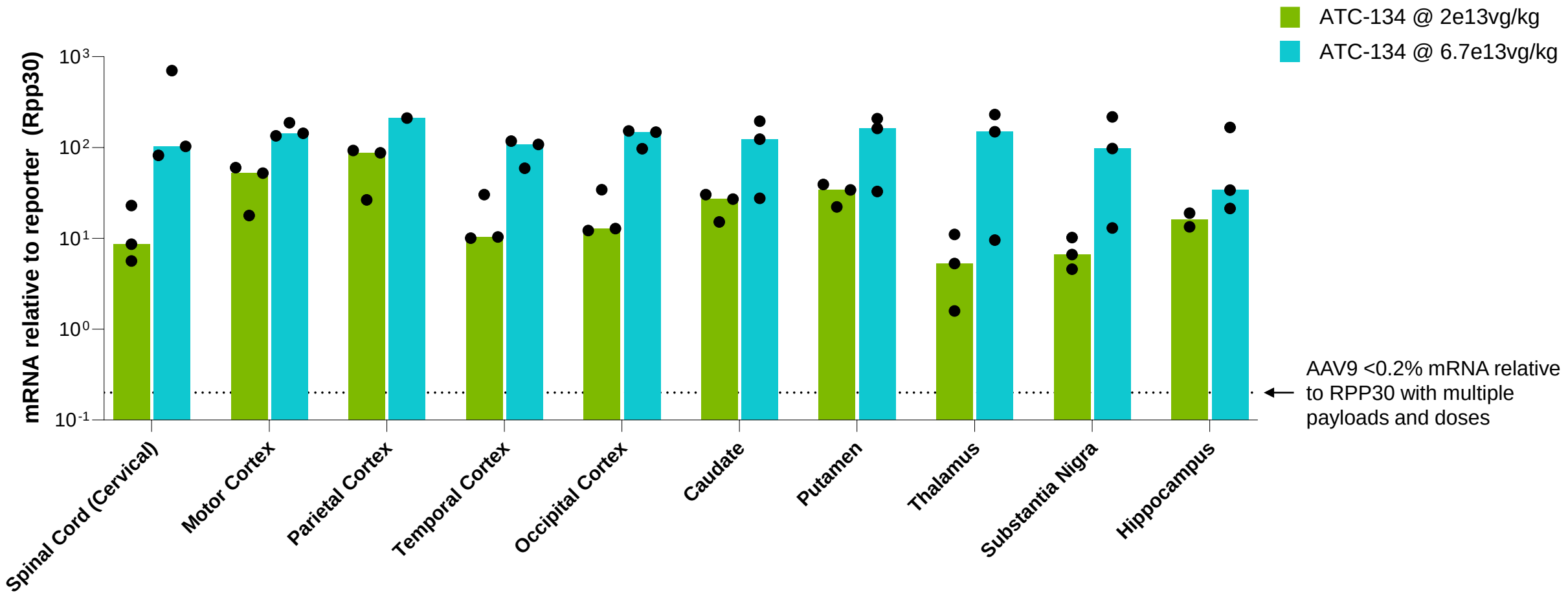
A single-clone NHP validation study for ATC-134 at two doses with Atxn2 miRNA cargo

Group	Vector	ROA	Dose (vg/kg)	N-value	In-life (days)	IS	Analysis
1	ATC-134-CBh.ATXN2.miRNA	IV	2e13	3	60	No	Primary: Cargo mRNA, H&E, Atxn2 mRNA, ISH
2	ATC-134-CBh.ATXN2.miRNA	IV	6.7e13	3	60	No	

NHP species: cynomolgus macaques

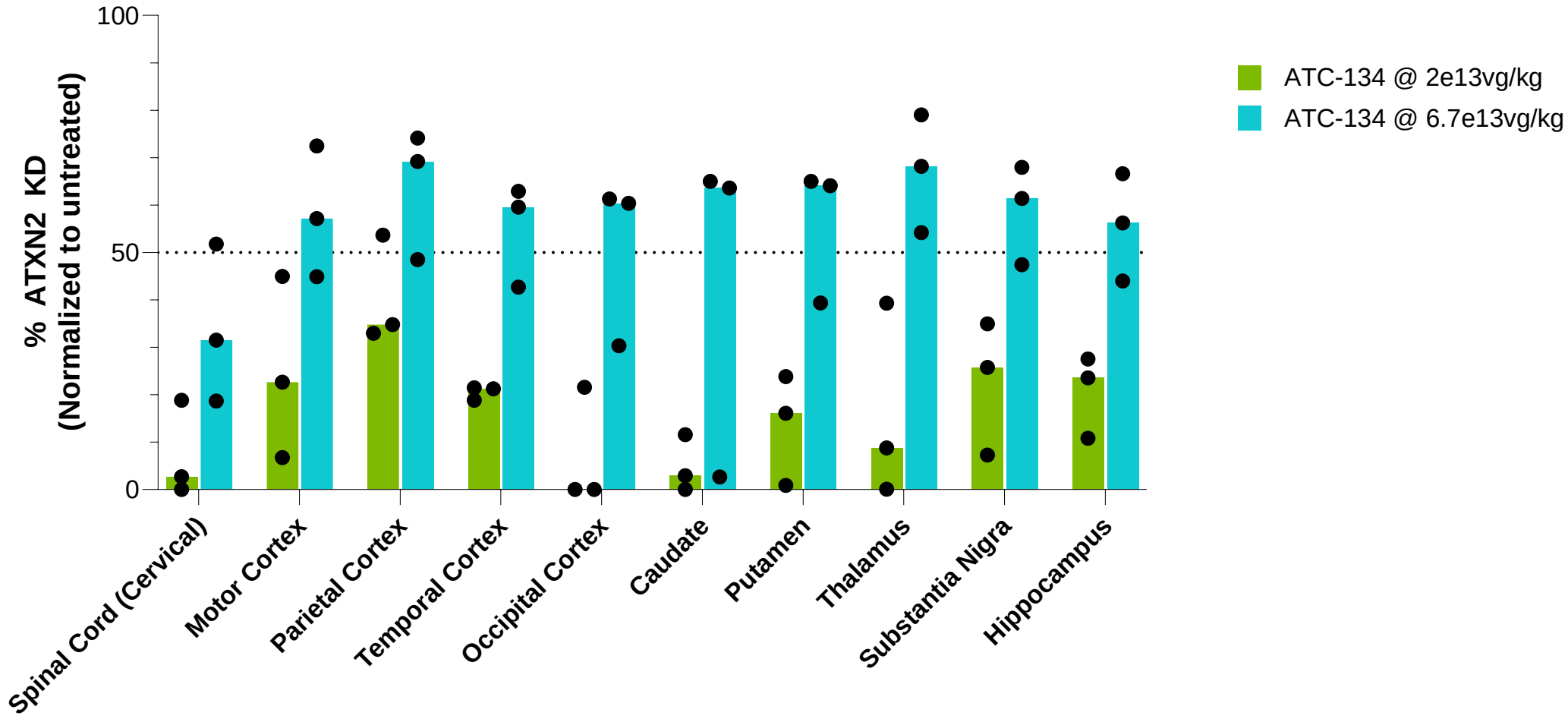
Expression (RNA): dose dependent increase across multiple regions

Single clone NHP study
RNA



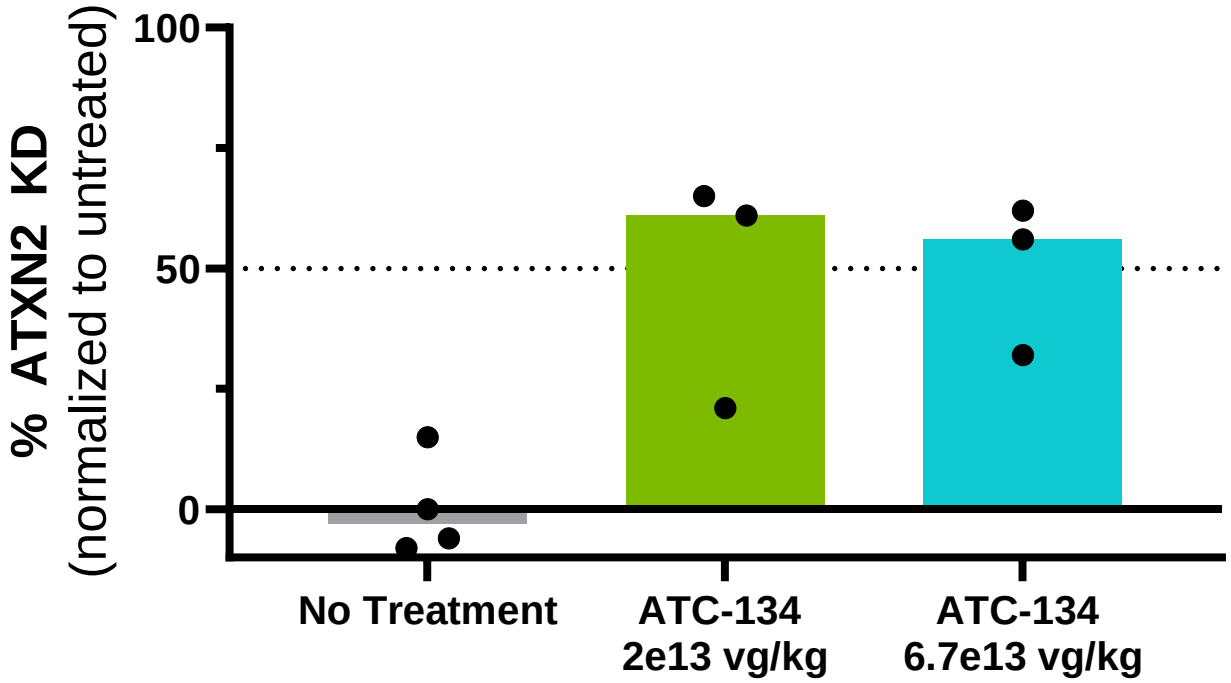
ATXN2 knockdown: miR with ATC-134 capsid induces >50% knockdown in NHP across multiple regions

Single clone NHP study
ATXN2

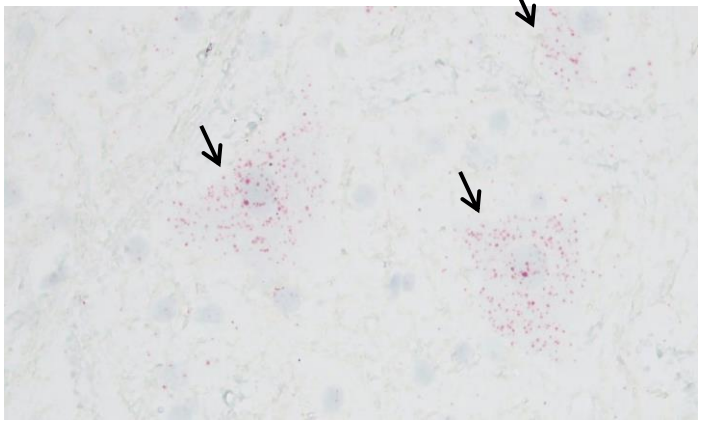


>50% ATXN2 knockdown in lower motor neurons of the spinal cord as quantified by ISH

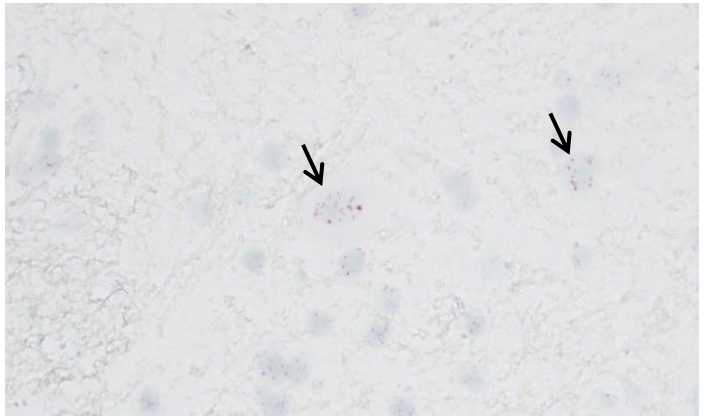
Single clone NHP study
ATXN2



No Treatment



Treatment with ATC-134-ATXN2 miR (6.7e13 vg/kg)

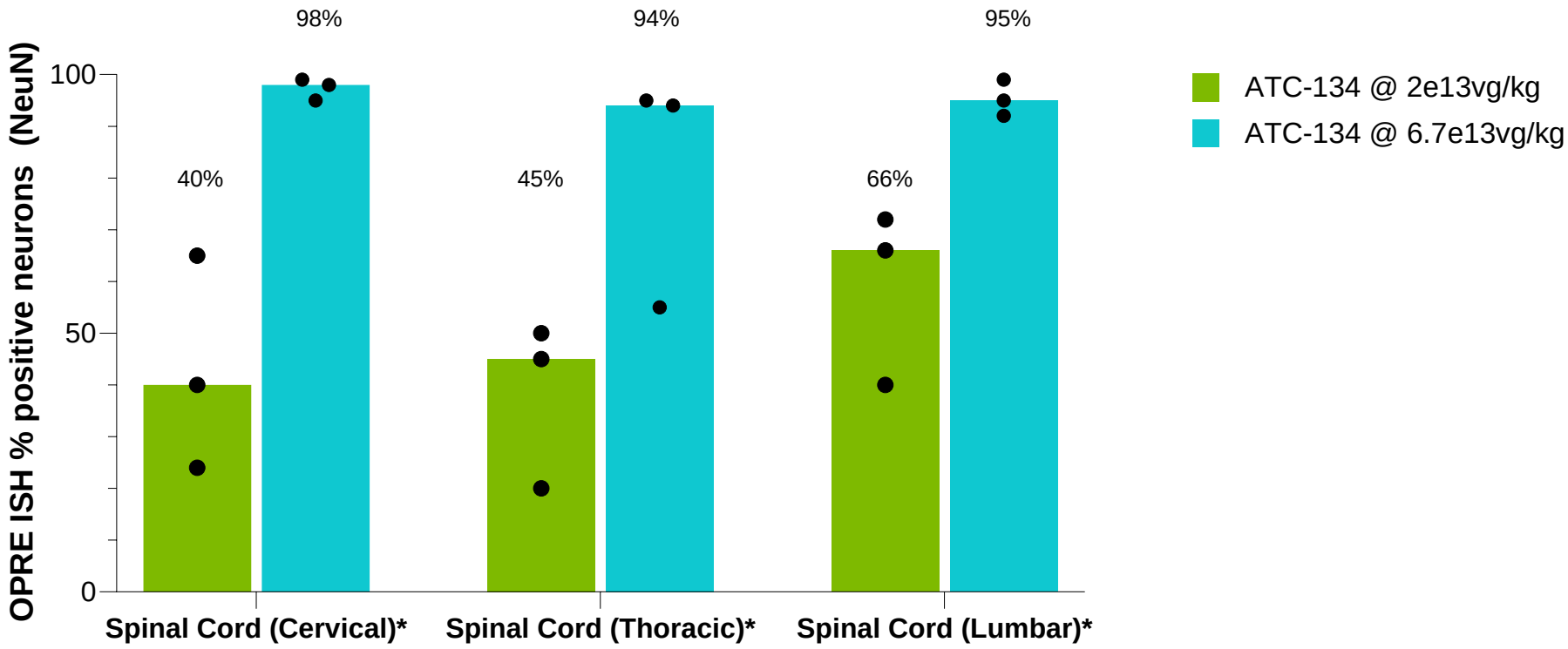


Pink= ATXN2 ISH

ISH: In-situ hybridization

>50% neurons transduced at the 6.7e13 vg/kg dose, lower motor neurons of the spinal cord shown

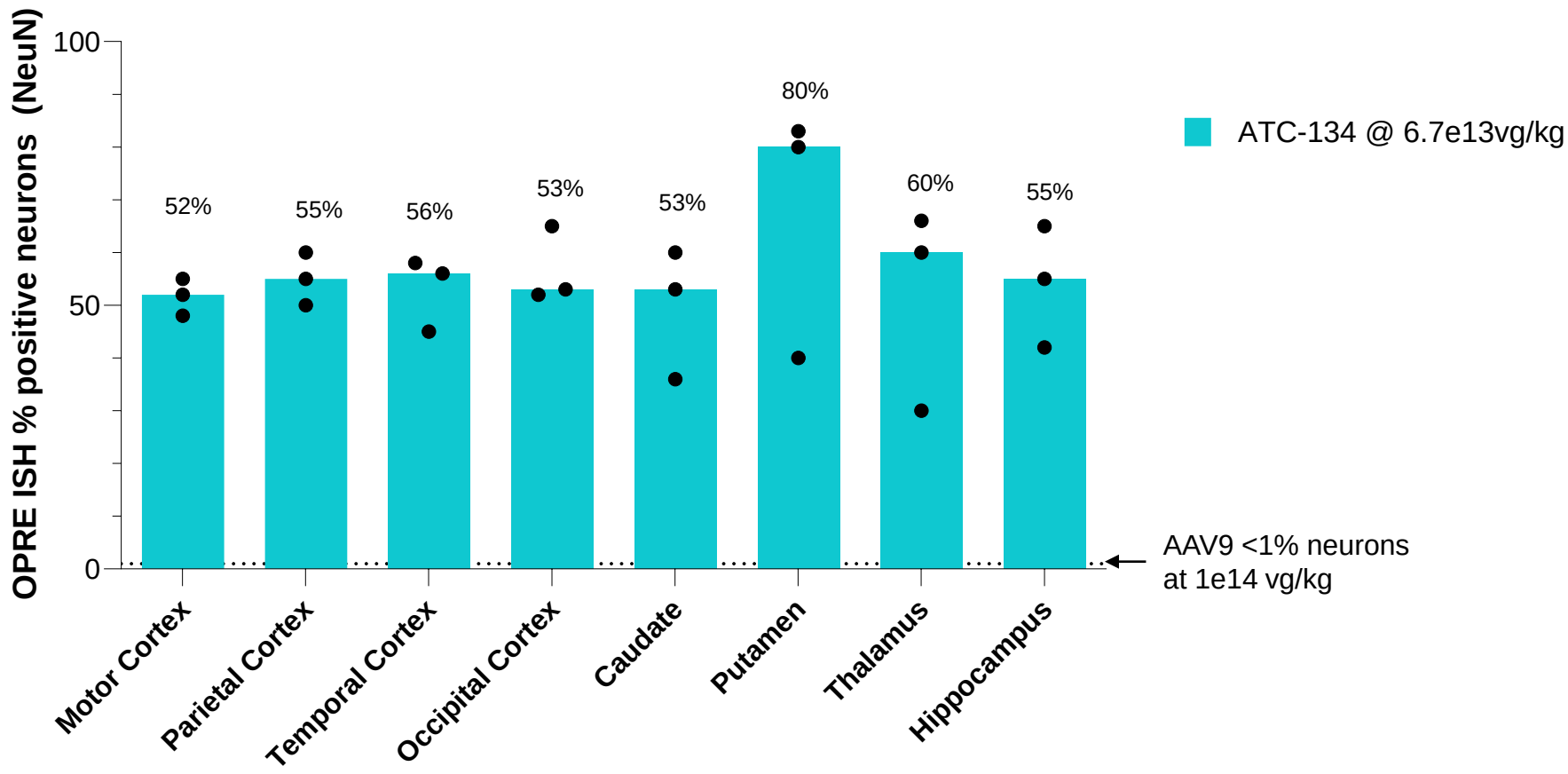
Single clone NHP study
% neurons



*Lower motor neurons

>50% neurons transduced at the 6.7e13 vg/kg dose, cortical and deep-brain regions shown

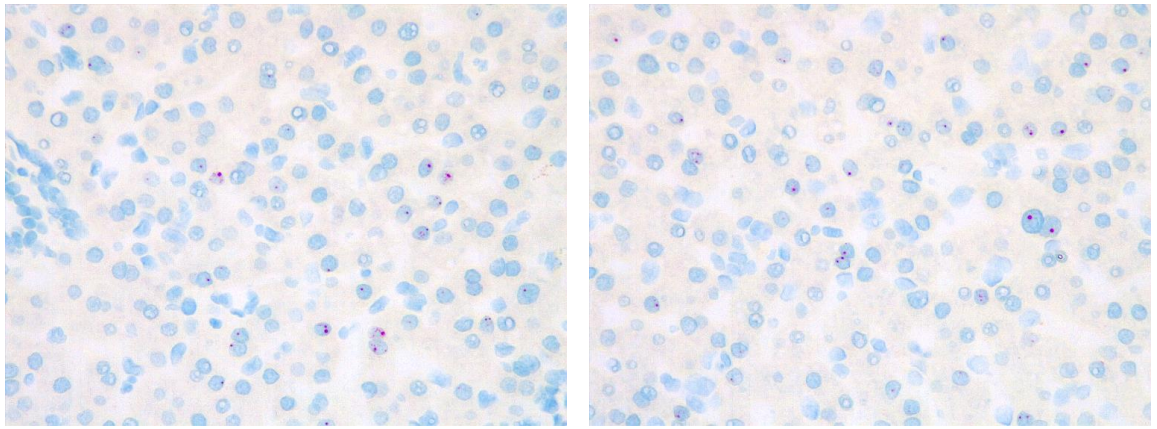
Single clone NHP study
% neurons



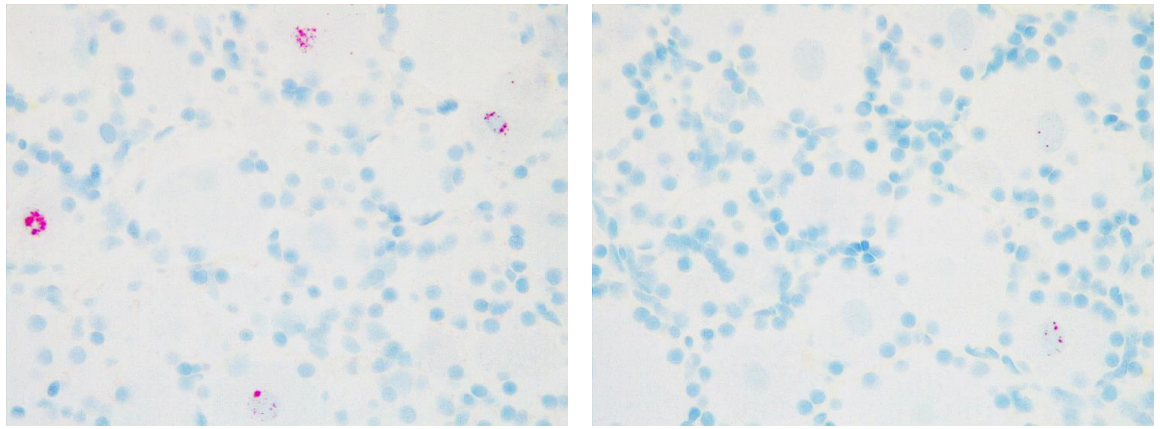
Minimal transduction in liver and DRG at 6.7e13 vg/kg of ATC-134

Single clone NHP study
ISH

Liver



DRG



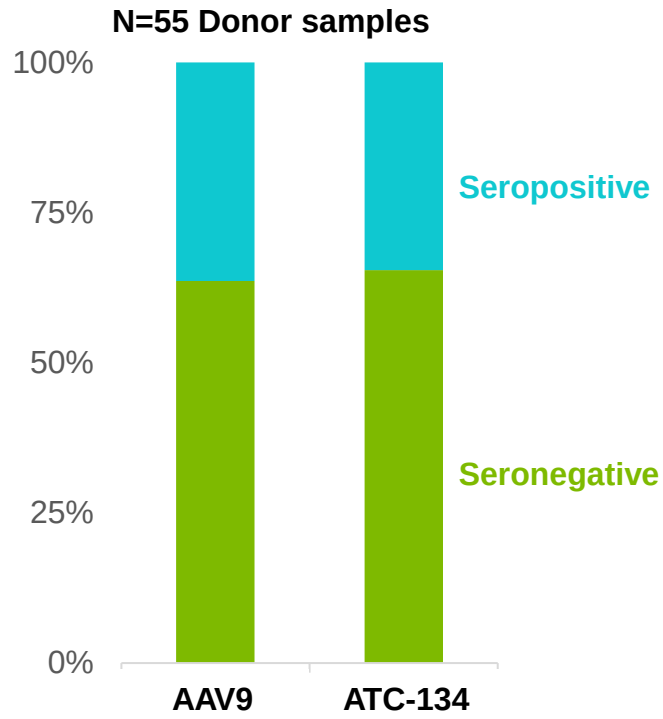
Pink= transgene ISH

Favorable manufacturing and immuno-phenotype attributes

Yield and quality attributes

	ATC-134
Upstream Harvest Yield (vg/L)	2.3e14
Capsid Purity (% by ce-SDS)	82.95%
HCP (ng/mL)	<LLOQ
pDNA (copies / 1e13 vg)	2.38e11
HcDNA (pg / 1e13 vg)	1636
AUC (% Full / Partial +Empty)	91.6 / 8.4
Aggregation (% monomer by DLS)	98.7

Preexisting immunity



Preexisting immunity data shown at 1:5 serum dilution

ATC-134 capsid induces robust ATXN2 reduction in NHPs with potential for broader utility for CNS diseases

- Function: >50% ATXN2 mRNA knockdown across multiple CNS regions
- Distribution: >50% neuronal transduction in cortices, deep-brain and spinal cord
- Exposure: Dose-dependent increase in mRNA expression of therapeutic miRNA
- Safety: No adverse safety events observed to date; minimal transduction in liver and DRGs

Acknowledgements

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