AVIADOBIO
Chasing Cures. Delivering Hope.™

vMiX: A Modular AAV-Delivered miRNA Platform For Precise, Durable Gene Silencing Across Indications

Romain Joubert, AviadoBio

Cell, 12–13 November 2026

Disclosures

- Romain Joubert is an employee of AviadoBio Ltd and holds equity in the company. No other relevant financial relationships to disclose.
- Named as inventor on patents related to the vMiX™ platform.
- AVB-406 has not been approved by any regulatory authority.

vMiX™ Platform

One-time Gene Silencing

A modular platform adaptable to any disease where RNA silencing offers therapeutic value

vMiX™ (viral miRNA expression)



ONE-TIME GENE SILENCING

Efficient and safe miRNA gene silencing

TISSUE-TARGETED AAV CAPSIDS

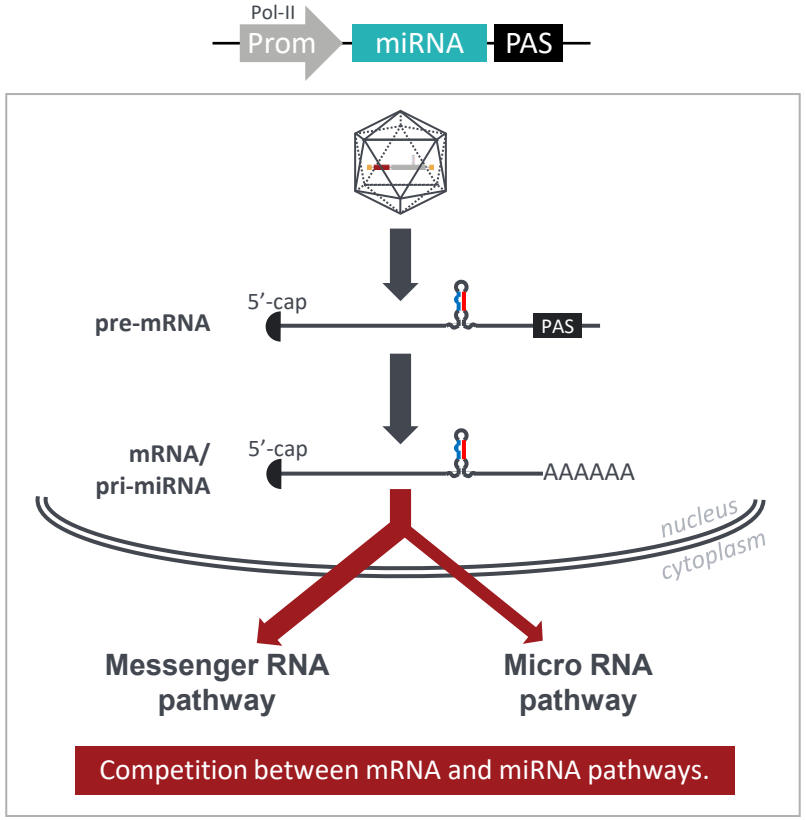
One-time intravenous dosing

TISSUE/CELL SPECIFIC REGULATION

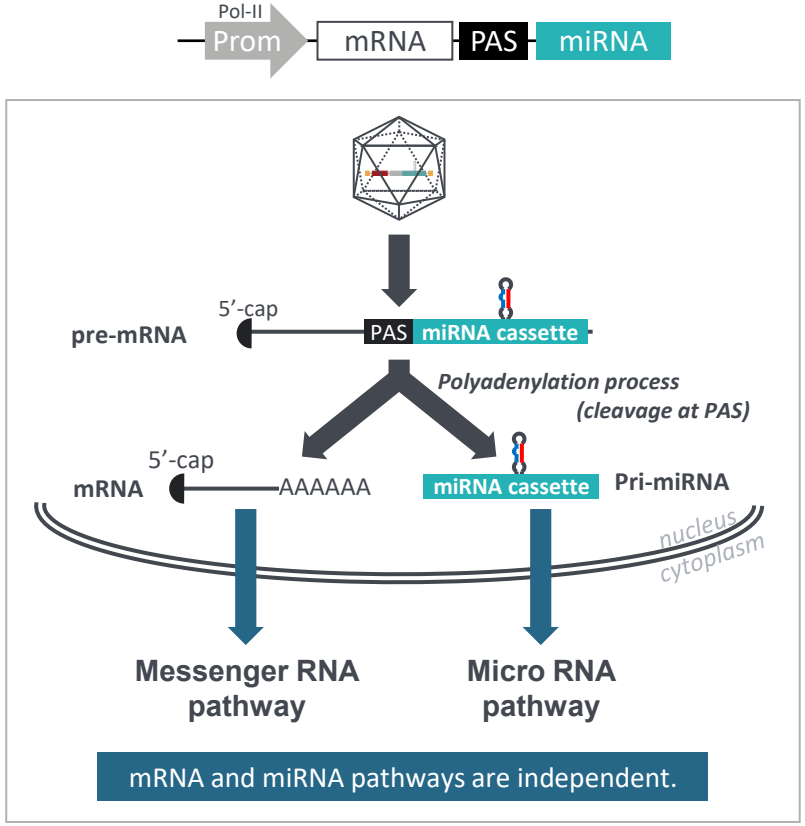
Precise and potent, with minimal off-target activity

vMiX™ decouples miRNA and mRNA processing to maximise silencing efficiency

Conventional mRNA-based design

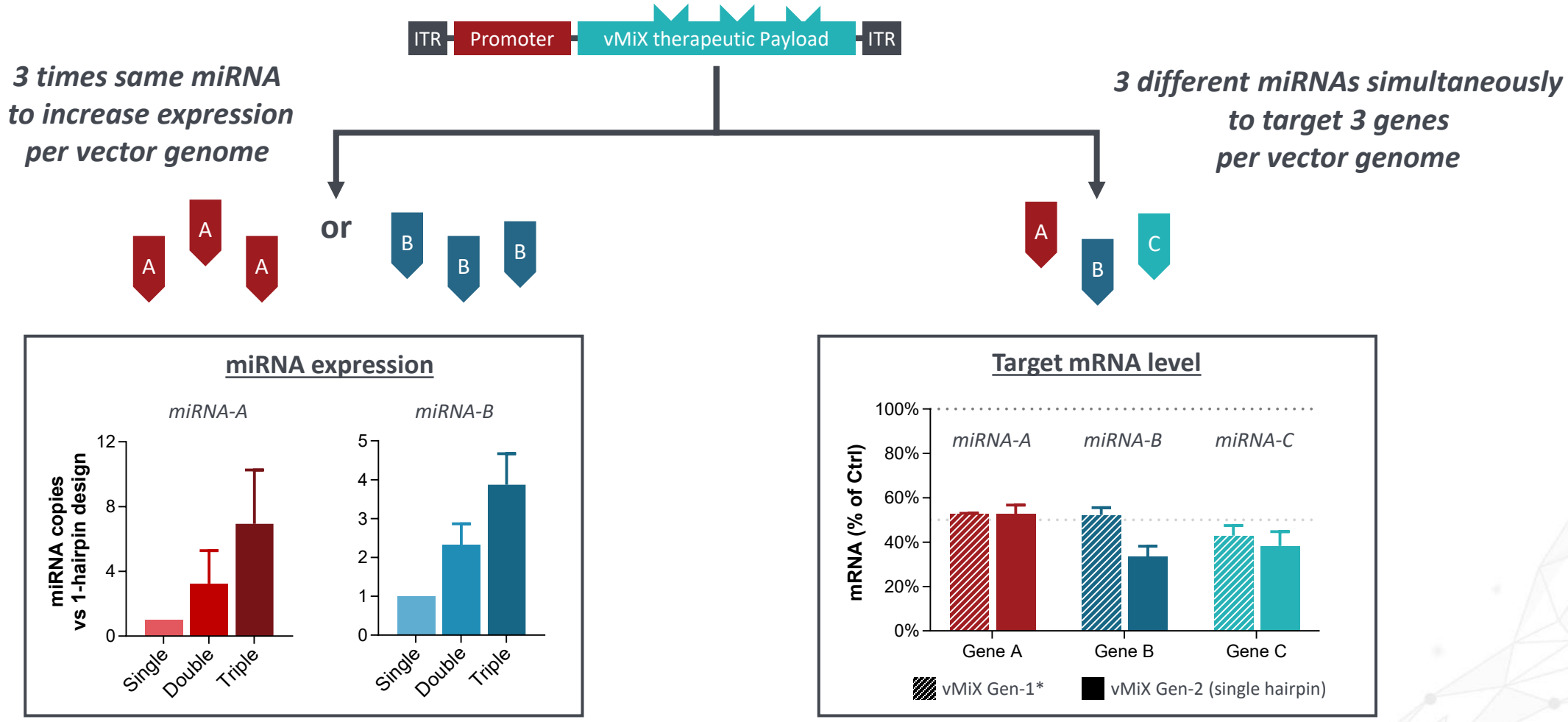


vMiX™ design



Unlike conventional designs, vMiX™ decouples miRNA and mRNA pathways at polyadenylation, preventing competition and enhancing silencing potency

vMiX™ has the potential to silence up to 3 targets simultaneously

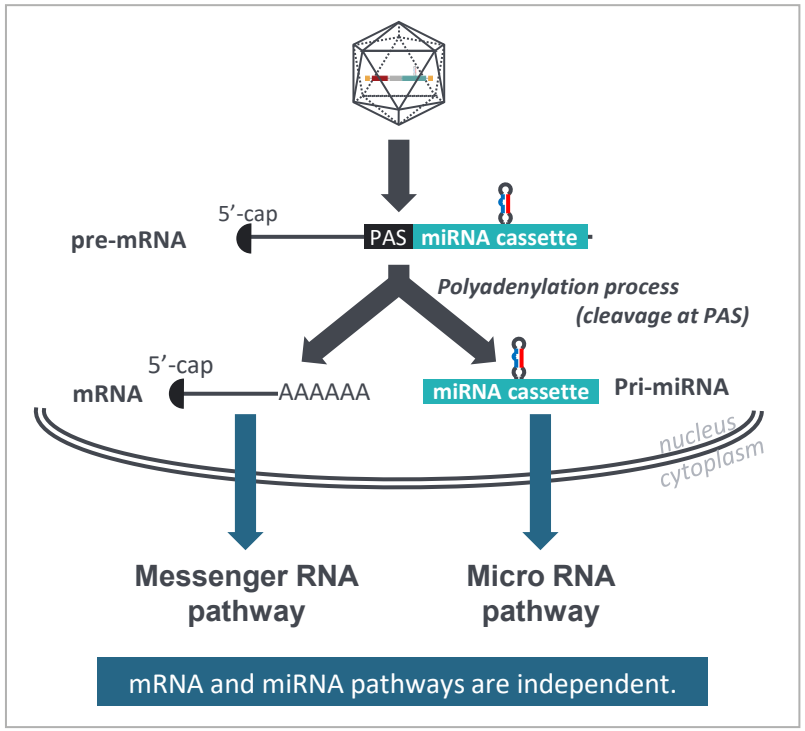


(vMiX Gen-1 has only 1 miRNA hairpin per payload)*

One vector, one promoter, two functions: vMiX™ enables simultaneous gene silencing and transgene expression

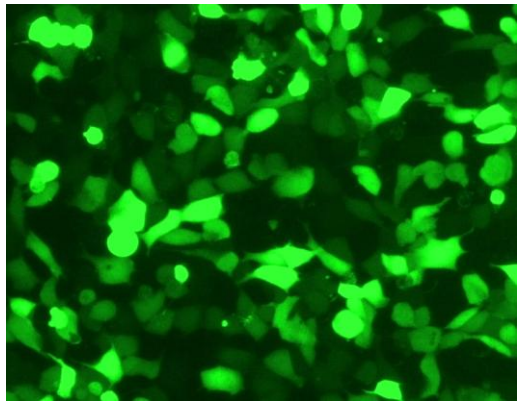
vMiX™ design



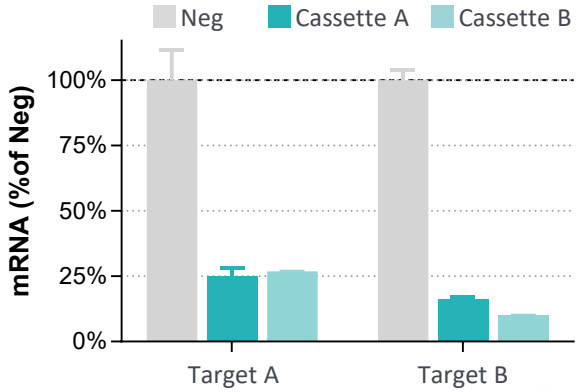




emGFP expression



Silencing



Across three vMiX™ cassette designs, knockdown was maintained while the co-encoded protein was still expressed, showing that the same payload can silence a gene and supply a replacement protein.

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AVB-406

AAV gene silencing
MAPT to treat Alzheimer's disease and other tauopathies

TARGET

Toxic **accumulation of mutant and/or hyperphosphorylated tau** drives neuronal death in primary and secondary tauopathies.

RNA-level silencing of *MAPT* gene enables reduction of all toxic protein species agnostic to pathology compartment or location.

PAYLOAD

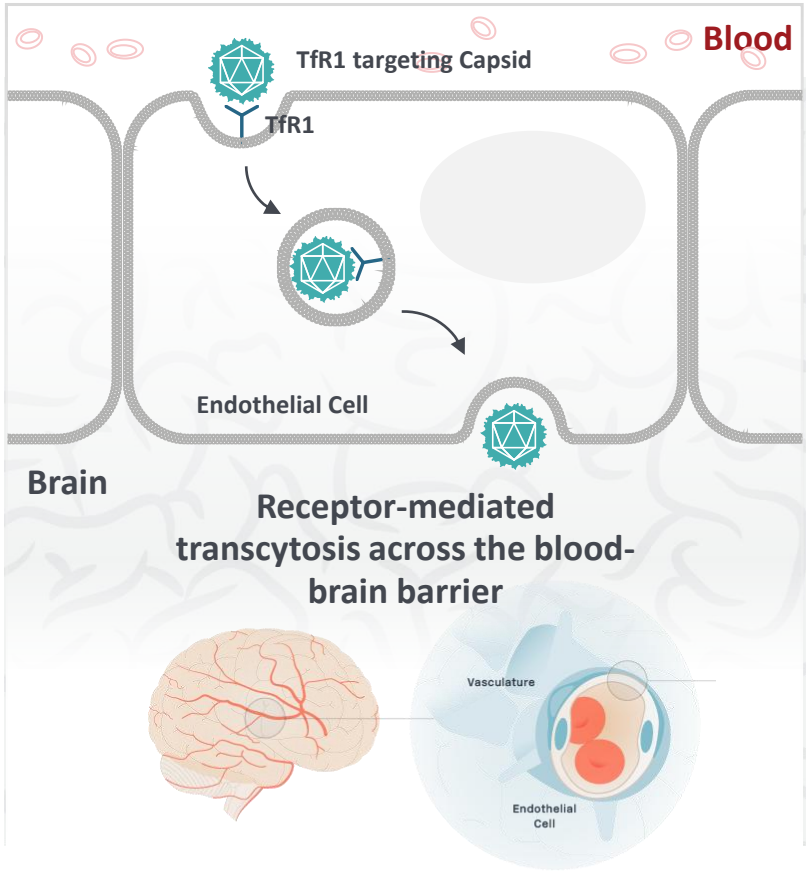


vMiX™ a one-time RNA silencing platform engineered for best-in-class specificity, potency, and neuron-selective regulation.

DELIVERY

One-time IV dosing of a **novel capsid targeting human TfR1 (CapX™)**, supporting broad CNS biodistribution with reduced peripheral exposure.

AVB-406 delivery: human TfR1 targeting capsid enables one-time IV dosing with a clear translational path



BBB receptor: human TfR1[1]

- Receptor-mediated transcytosis across the BBB
- Highly conserved, ubiquitously expressed on BBB; validated clinically by TfR1 shuttle programmes (JCR, Denali, Roche)

Delivery properties[1,2]

- Broad, brain-wide CNS transduction after IV delivery
- Access to deep structures (cortex, hippocampus, striatum)
- Reduced liver transduction relative to AAV9

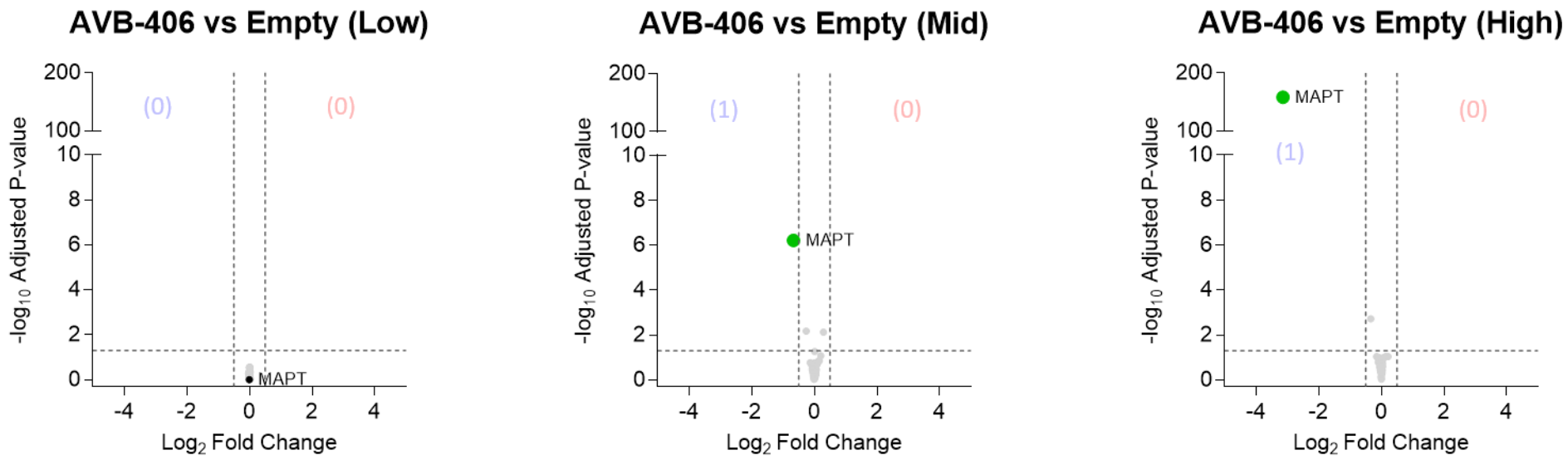
Translational pathway[2]

- B-hTfR1 mouse is the pharmacologically relevant model for biodistribution & toxicology
- NHPs are pharmacologically irrelevant (no hTfR1 binding)
- Surrogate capsids enables testing mechanistic proof of concept of the payload in disease models

[1]Huang et al., Science 2024; [2]Apertura Gene Therapy.

miR-MAPT-TA35 target specificity in human iPSC-derived neurons: no off-target risk detected *in vitro*

iPSC-derived Glutamatergic neurons, N=3/group; AVB-406 vs dose-matched vMiX-empty at three MOIs; polyA-RNA-seq. Thresholds: adj. p<0.05, $|log_2FC|>0.5$.

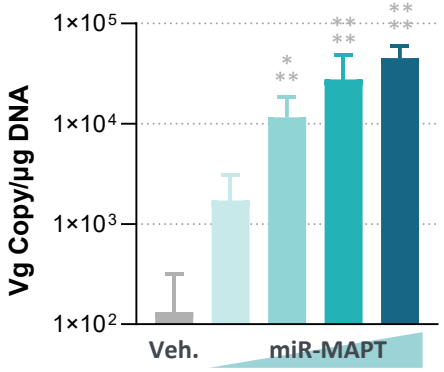


- Dose-matched vMiX-empty controls isolate the effect of miR-MAPT-TA35 itself, separating miRNA activity from vector and transduction effects.
- ***MAPT* is the only transcript significantly changed at any MOI** — downregulated dose-dependently, as intended. No off-target transcriptomic changes detected above threshold.

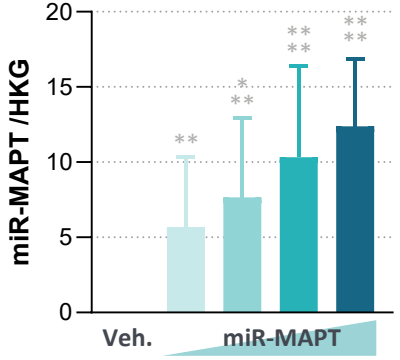
AAV-miRNA-MAPT results in a dose dependent MAPT knockdown and AT8 tau pathology in cortex and hippocampus in P301S mice

Bulk tissue

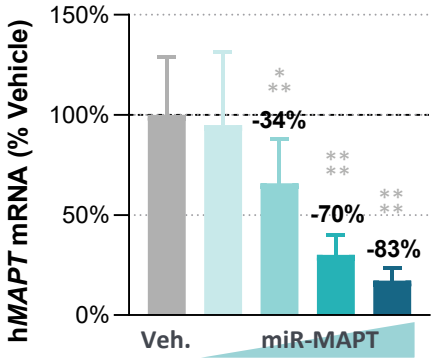
Vg copies



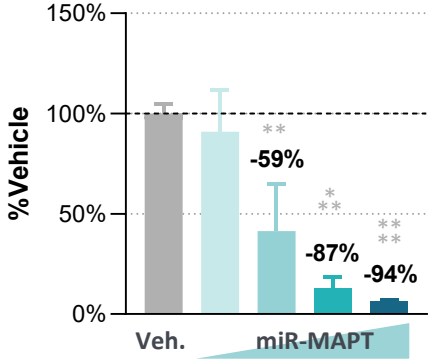
miRNA expression



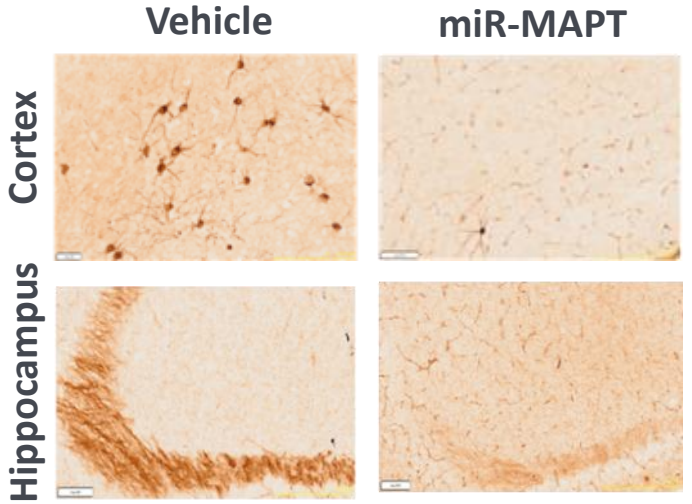
MAPT mRNA



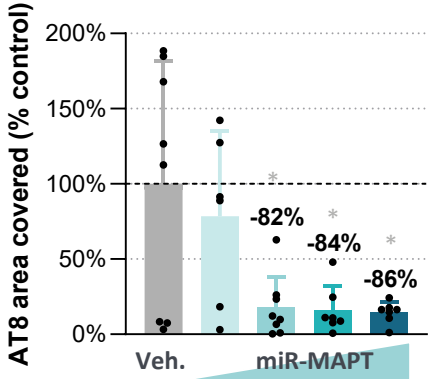
Total Tau protein



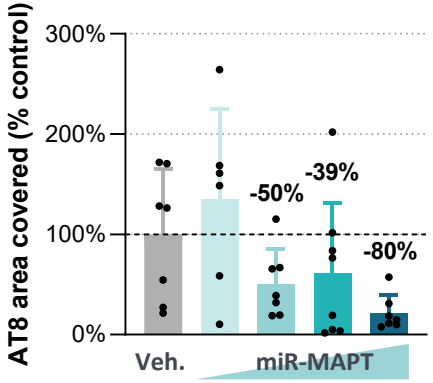
AT8 staining



Cortex

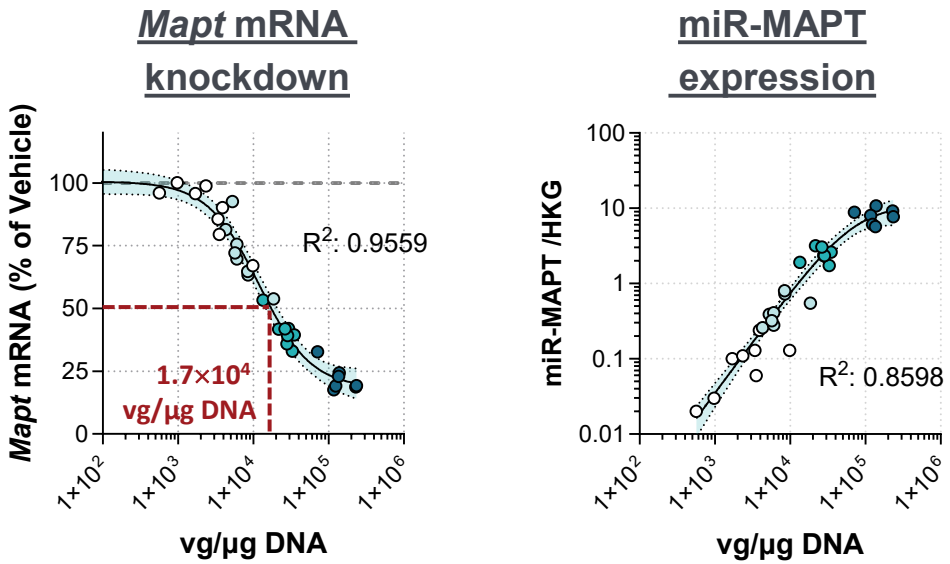


Hippocampus

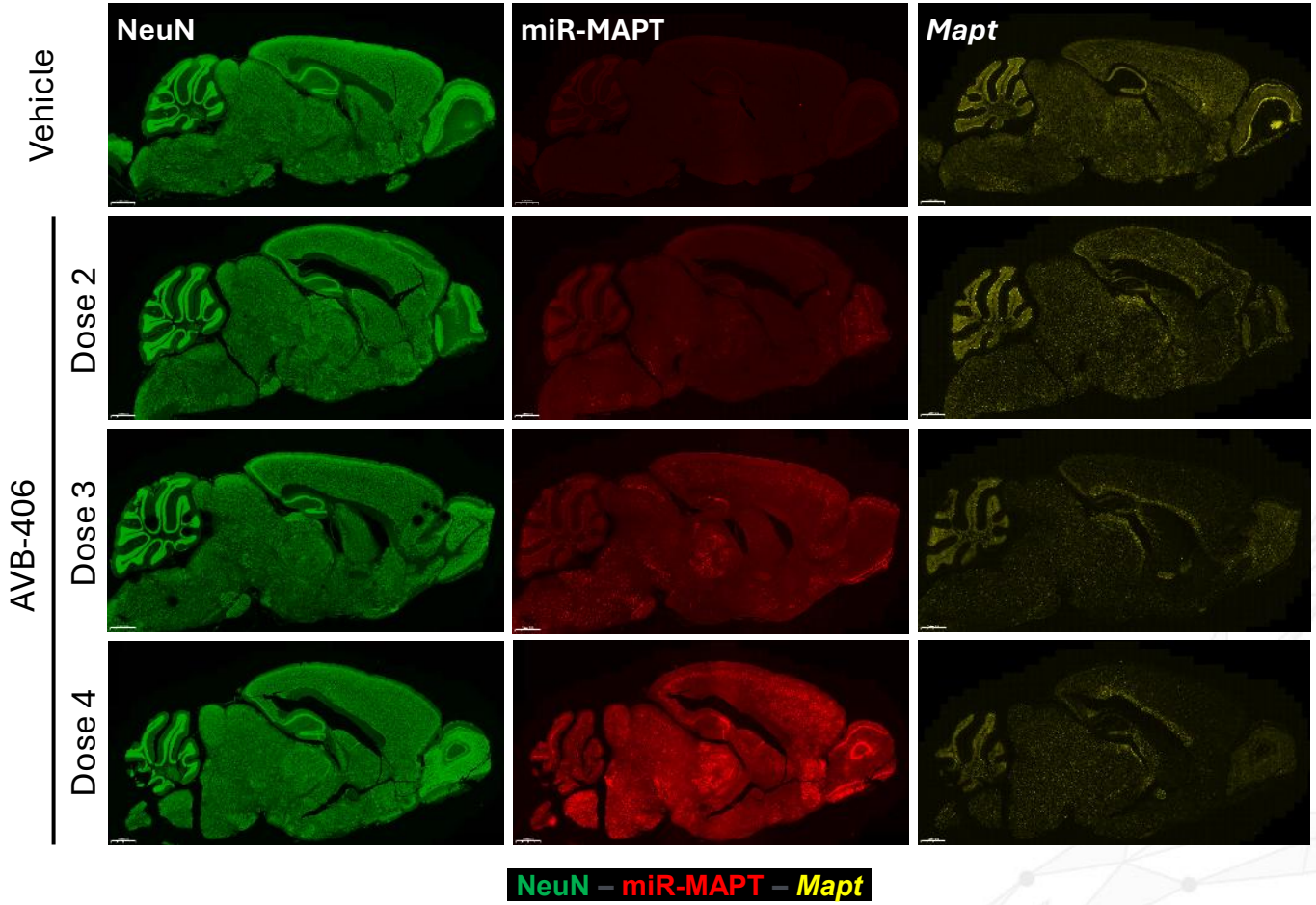


*3-month old B6;C3-Tg(Prnp-MAPT*P301S)PS19Vle/J mice administered IV with vehicle or AAV-miR-MAPT (surrogate capsid). Samples collected 8-weeks post dose; N= 16 (8 males and 8 females) per dose group; Data shown represent mean ± SD; *p<0.05; **p<0.01, ***p<0.001; ****p<0.0001 compared to Vehicle; IHC male cohort only. Veh. – Vehicle.*

In a dose-range finding study in B-hTFR1 mice, a single IV dose of AVB-406 drives dose-dependent transduction, miRNA expression, and *Mapt* knockdown in the brain

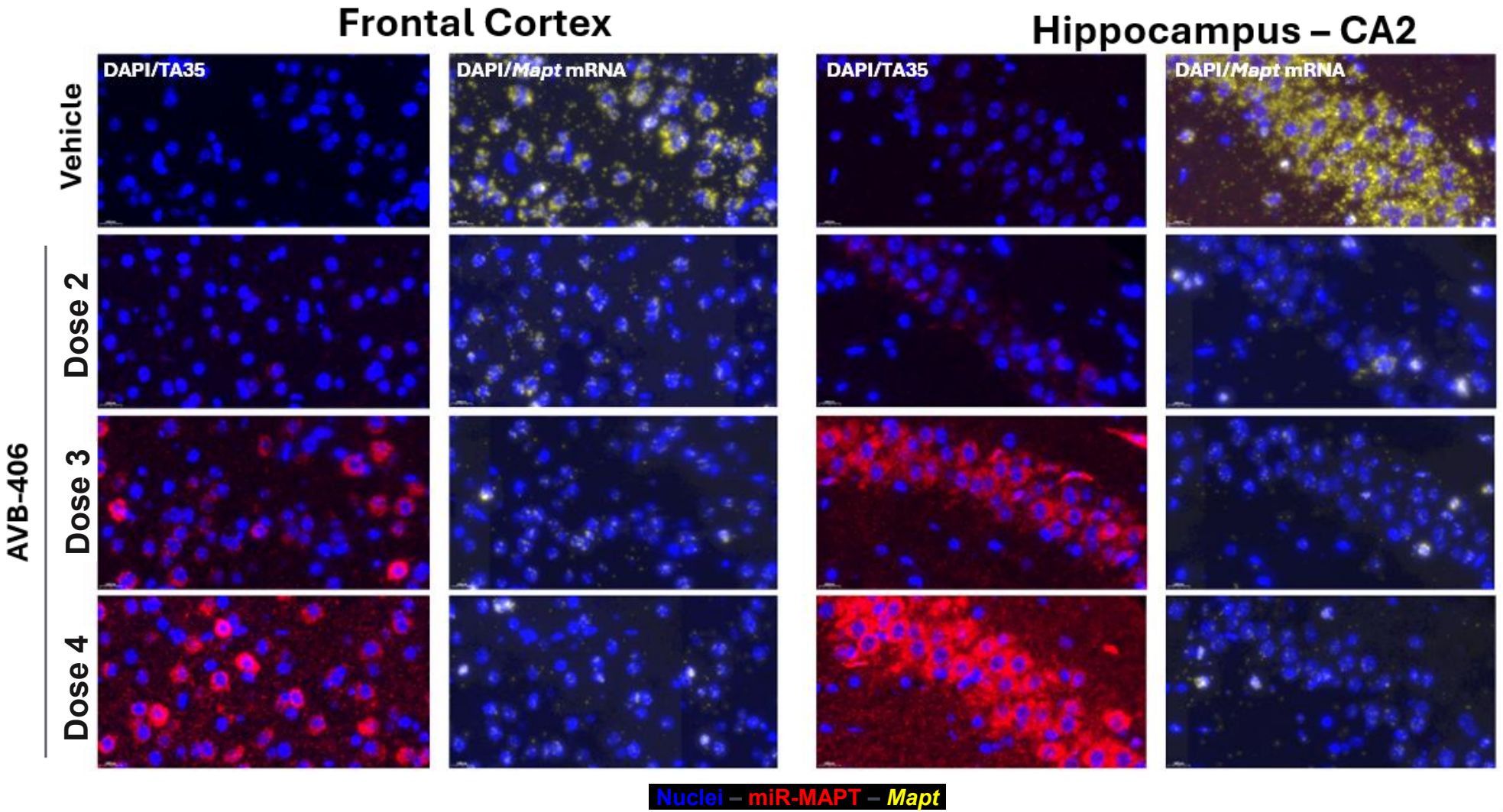


- Robust, dose-dependent MAPT knockdown in bulk tissue
- Linear dose-dependent miR-MAPT expression
- Silencing and expression limited to neurons/CNS
- miR-MAPT expression was not detected in peripheral tissues



Adult hTFR1 mice administered IV with vehicle or AVB-406 (4 doses). Samples collected 4-weeks post dose. RNAscope assay: NeuN/neurons (green), miR-MAPT (red), mouse Mapt (yellow)

Frontal cortex and hippocampal CA2: dose-dependent miR-MAPT-TA35 expression with reciprocal silencing of *Mapt* mRNA



HALO analysis is ongoing

Representative fields from frontal cortex and hippocampal CA2

AVB-406 shows sustained reduction of *Mapt* mRNA after single IV injection

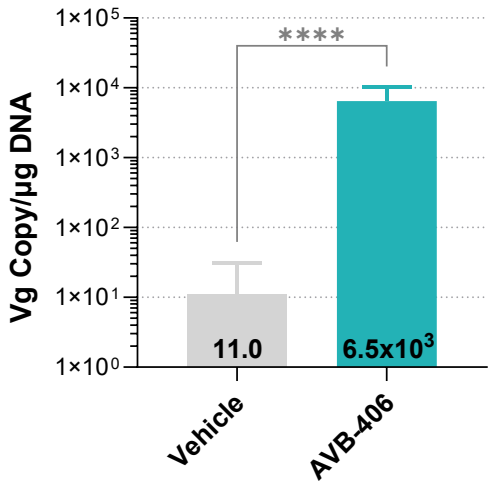
Long-term tolerability study

Single dose · B-hTFR1 mice · 6 months in life

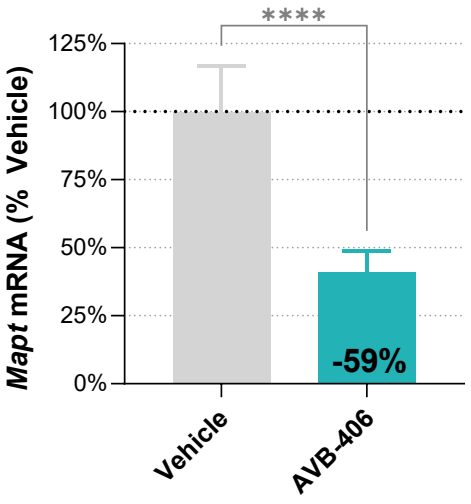
- No adverse clinical signs; body weight gain unaffected
- Functional observational battery unchanged from controls
- *Mapt* mRNA silencing and tau reduction confirmed in tissues post-sacrifice at 6 months

Durable knockdown with no in-life tolerability signal

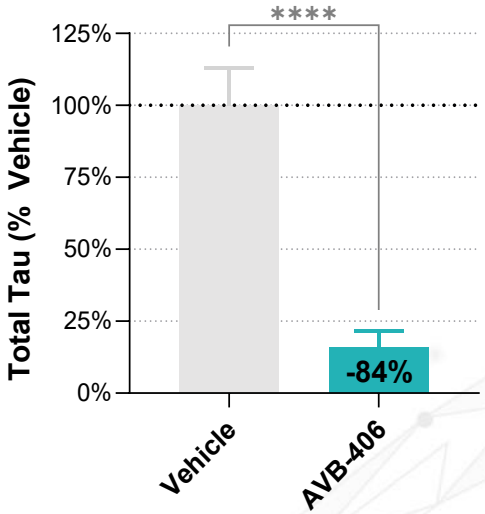
Vg copy number



Mapt mRNA knockdown



Total Tau protein



Summary & Roadmap to the Clinic

WHAT HAVE WE SHOWN

1. **AVB-406 combines a BBB-penetrant hTfR1 binding capsid (CapX), the vMiX™ miRNA platform, and a neuron-selective promoter.**
2. **Target specificity of miRNA-MAPT confirmed in human neurons**
3. **Robust, dose-dependent MAPT knockdown**
4. **Pathology amelioration** in P301S tauopathy model demonstrated in cortex and hippocampus
5. **Well tolerated across all animal studies and durability of silencing demonstrated** out to 6 months

WHY IT MATTERS

- AVB-406 is positioned as a one-time IV treatment for Alzheimer's disease and other tauopathies, addressing durability, CNS distribution, and access limitations of current tau-lowering approaches.

NEXT STEPS

- ✓ pIND complete — FDA alignment on non-clinical strategy secured
- ✓ GLP toxicology ongoing
- ➢ Anticipated clinical dose range significantly below approved systemic AAV gene therapies
- ➢ Regulatory submissions planned; first-in-human study to follow

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AVB-SNCA

AAV gene silencing
SNCA to treat Parkinson's disease and other synucleinopathies

TARGET

Toxic **accumulation and aggregation of α-synuclein** drives neuronal dysfunction and death in Parkinson's disease and other synucleinopathies.

RNA-level silencing of the *SNCA* gene reduces α-synuclein at source, lowering both monomeric and aggregated species regardless of where pathology has spread.

PAYLOAD



vMiX™ a one-time RNA silencing platform engineered for best-in-class specificity, potency, and neuron-selective regulation.

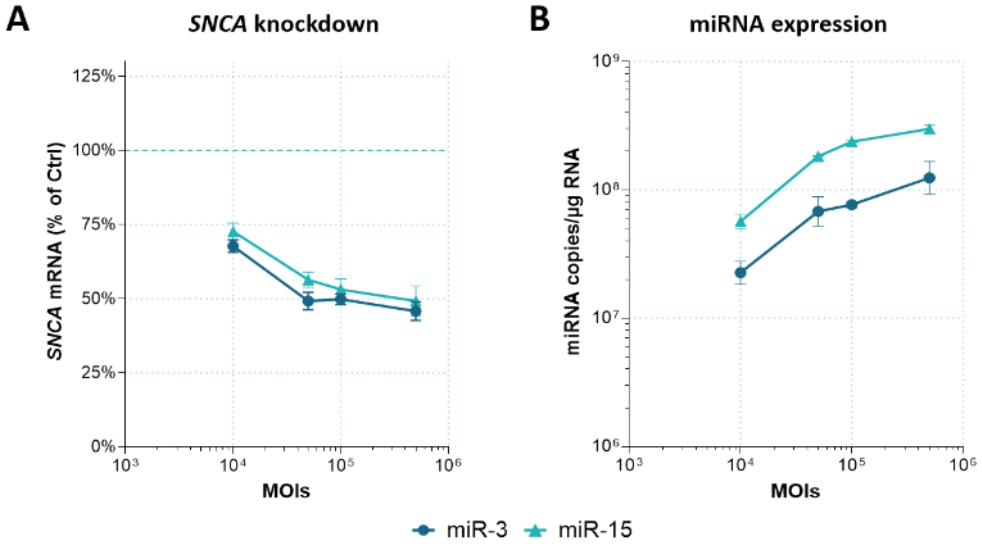
DELIVERY

One-time IV dosing of a **novel capsid targeting human TfR1 (CapX™)**, supporting broad CNS biodistribution with reduced peripheral exposure.

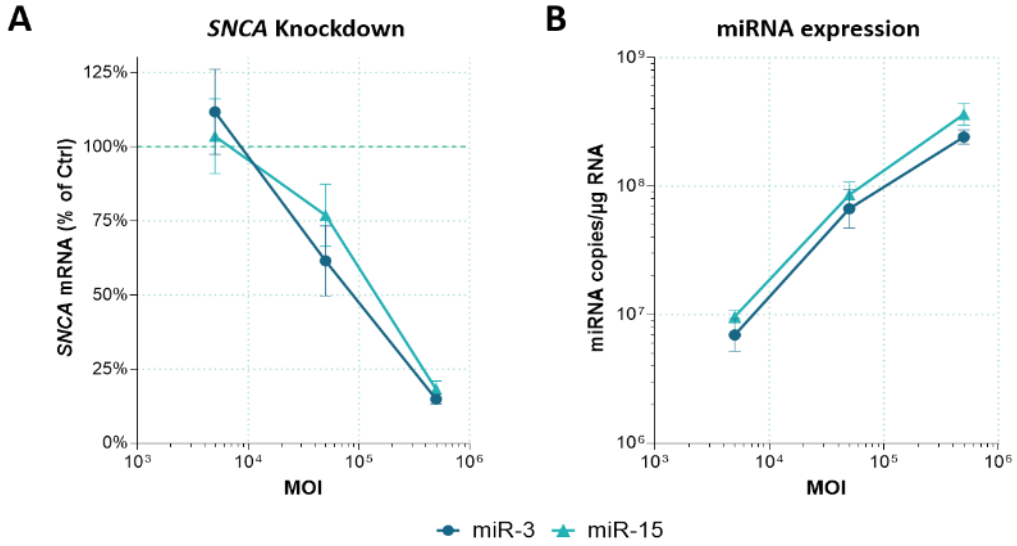
The top two AAV vMiX-*SNCA* miRNA constructs show *in vitro* activity in HeLa cells and human iPSC-derived neurons

The miR-3 and miR-15 vMiX triple hairpin payloads were vectorised into a BBB-crossing AAV capsid under the control of a ubiquitous promoter.

HeLa cells



Human iPSC-derived neurons

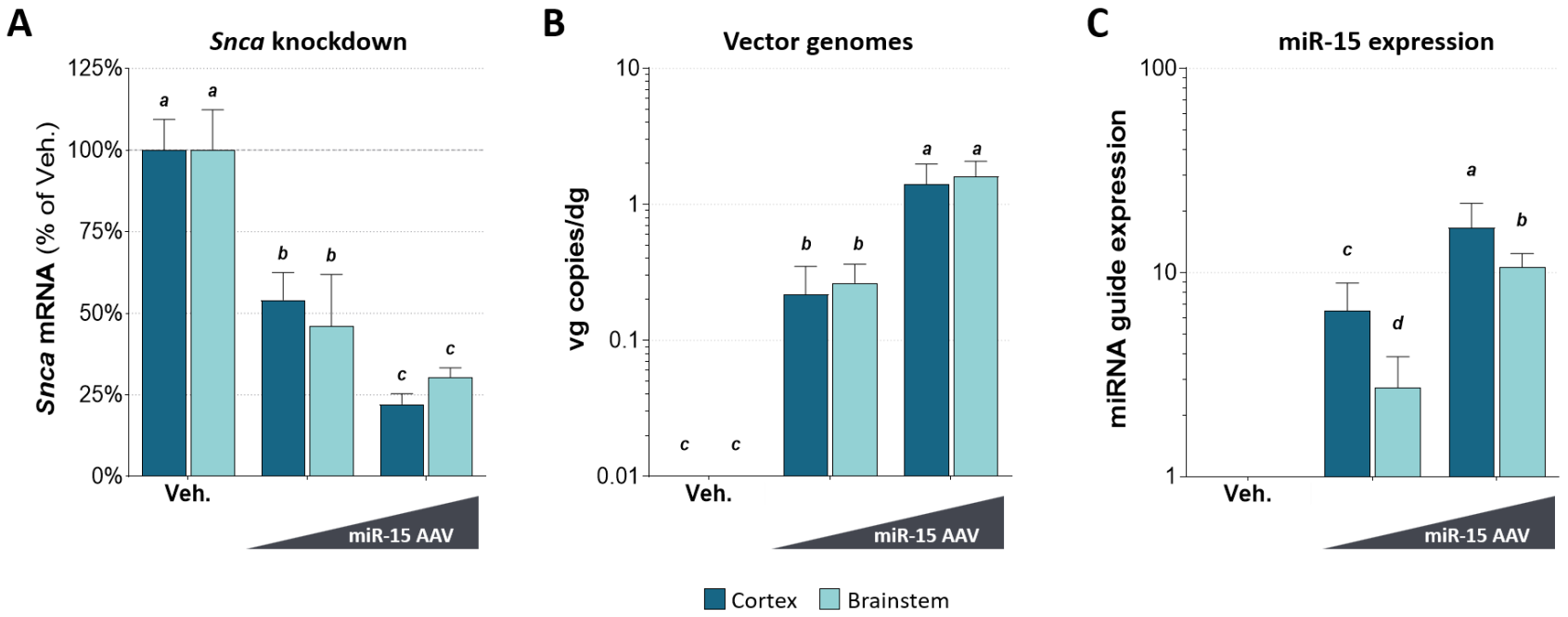


- Both AAV constructs showed dose-dependent *SNCA* mRNA knockdown and miRNA expression, achieving ~ 50% and 80% knockdown at the highest MOIs in HeLa cells and iPSC-derived neurons, respectively.
- While both miR-3 and miR-15 showed similar SNCA mRNA knockdown, miR-15 had a better guide processing profile.

➢ **miR-15 selected as the lead vMiX-*SNCA* miRNA.**

miR-15 AAV demonstrates *in vivo* proof of mechanism, achieving ≥ 50% *SNCA* mRNA knockdown in mouse brain

The CapX-miR-15 AAV was evaluated in proof-of-mechanism study in hTfR1 mice at two doses (4 weeks in life).



(Groups with different letters differ significantly from each other, 2-Way ANOVA with Tukey's multiple comparisons, P<0.05)

- miR-15 demonstrated dose-dependent *Snca* mRNA knockdown in cortical and brainstem tissues, achieving ~ 50% and 75% knockdown in both tissues at the low dose and high dose, respectively.
- Dose-dependent vector biodistribution and miRNA guide expression was also observed in both tissues.

➢ **miR-15 demonstrates potent activity in mouse.**

Conclusions & next steps

- The vMiX platform was successfully applied to silence *SNCA*, with miR-15 selected as the lead vMiX-*SNCA* miRNA.
- When vectorised into a BBB-crossing AAV capsid, miR-15 demonstrated dose-dependent *Snca* mRNA knockdown (up to 75%) *in vivo* in CNS regions relevant to synucleinopathies.
- The transcriptional response to miR-15 AAV in mouse cortex was dominated by on-target downregulation of *Snca.*
- **These data support continued development of vMiX-*SNCA* as a single-dose *SNCA*-lowering gene therapy for Parkinson's disease and other synucleinopathies.**

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AVB-203

AAV gene silencing
SOD1 to treat SOD1-mediated amyotrophic lateral sclerosis

TARGET

Toxic **accumulation of misfolded SOD1 protein** drives motor neuron degeneration in SOD1-mediated amyotrophic lateral sclerosis (**SOD1-ALS**).

RNA-level silencing of the *SOD1* gene reduces total SOD1 at source, addressing toxic gain of function independently of the causative mutation.

PAYLOAD



vMiX™ a one-time RNA silencing platform engineered for best-in-class specificity, potency, and neuron-selective regulation.

DELIVERY

One-time IV dosing of a **novel capsid targeting human TfR1 (CapX™)**, supporting broad CNS biodistribution with reduced peripheral exposure.

Genome copy number and KD in Cortex and Spinal Cord of shortlisted miRNAs

DESIGN

Model - WT C57BL/mice

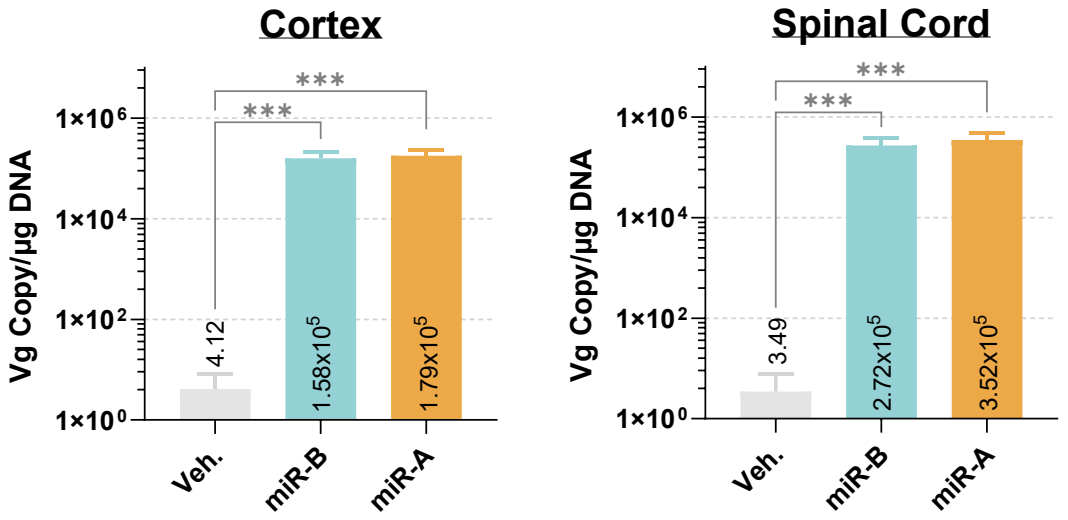
Age/RoA - Approx 7-8 weeks, tail vein injection (100µL)

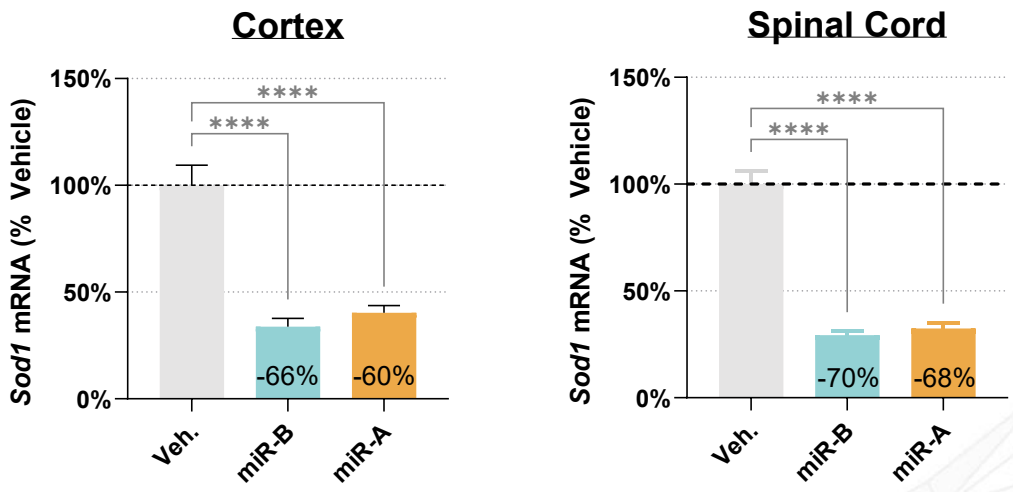
Test articles - PHP.eB hSYN1-miR-SOD1-A, PHP.eB hSYN1-miR-SOD1-B, Vehicle (Veh.)

Treatment groups – 4e13 vg/kg, Formulation buffer

In-life - 4 weeks

- The **PHP.eB-miR-SOD1-B** and **PHP.eB-miR-SOD1-A** vector brought about comparable viral genome copies in both the cortex and spinal cord
- **PHP.eB-miR-SOD1-B** brought about similar levels of *Sod1* knockdown, compared to **PHP.eB-miR-SOD1-A** in both cortex and spinal cord.





One-way ANOVA with Tukey's HSD post-hoc test

One-way ANOVA

*p<0.05

**p<0.01

***p<0.001

****p<0.0001

Survival and body weight in B6.SOD1-G93A mice

Study Design

Model: SOD1 G93A

Age/RoA: Approx 7-8 weeks, tail vein injection (100µL)

Test articles: PHP.eB.hSyn.miR-A

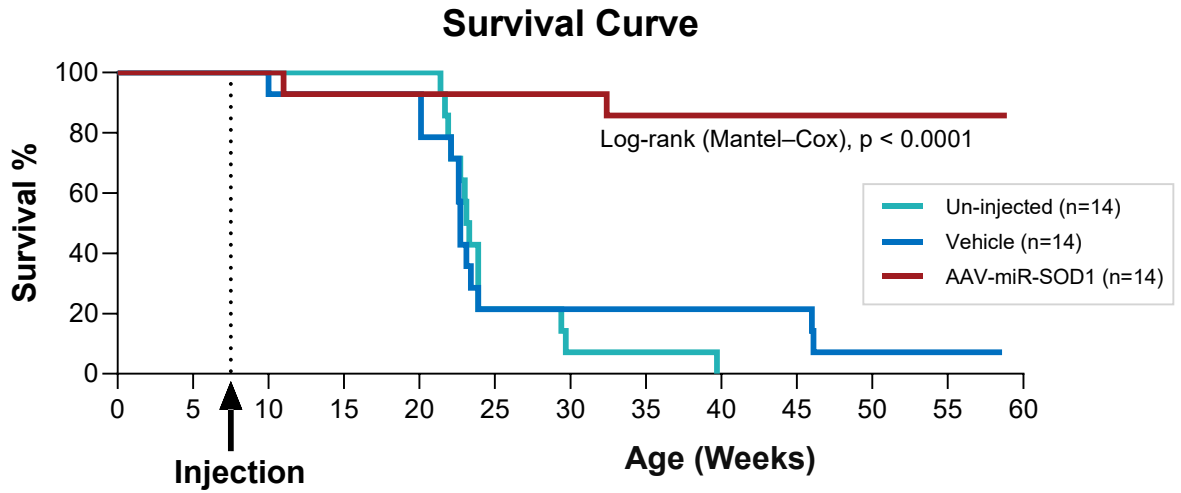
Treatment groups: 1 vector dose at 4e13 vg/kg, vehicle control and un-injected

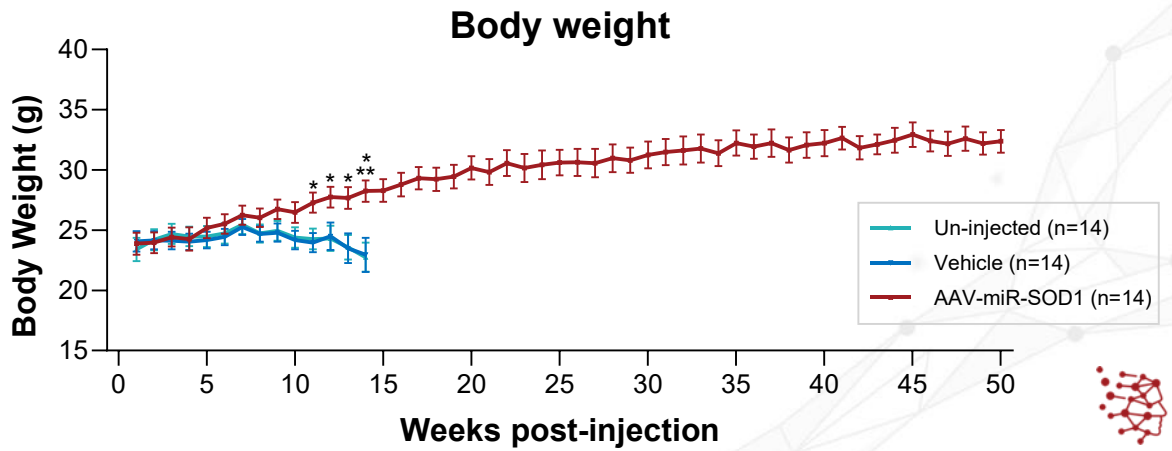
- At 58-weeks post-injection
  - AAV-miR-SOD1 - 12 out of 14 mice
  - Vehicle (F120) – 1 out of 14 mice
  - Untreated – 0 out of 14 mice

- SOD1-G93A animals treated with AAV-miR-SOD1 show significantly increased body weight at 13, 15, and 16-weeks post-injection.

- Loss of *SOD1* copy number could be a reason for survival of mice in the vehicle group. This will be confirmed at the end of the study.

Survival will continue to be monitored





Rotarod and multiple behavioural score in B6.SOD1-G93A mice







Advancing a pipeline of vMiX™ RNA silencing medicines

PROGRAM	TARGET	INDICATION	DISCOVERY		PRECLINICAL	CLINICAL	PARTNER
			Screening	Lead miRNAs			
AVB-406	MAPT	AD & Other Tauopathies				**FIH 2027**	**WHOLLY OWNED**
AVB-203	SOD1	ALS					**WHOLLY OWNED**
AVB-SNCA	SNCA	PD, LBD, MSA					**WHOLLY OWNED**
Undisclosed (multiple additional programs)	Undisclosed	Neurodegenerative diseases					**WHOLLY OWNED / PARTNERED**

From screening to preclinical, every programme follows the same vMiX™ design and workflow. Only the miRNA changes.

AD, Alzheimer's disease. ALS, amyotrophic lateral sclerosis. FIH, first-in-human. LBD, Lewy body disease. MAPT, microtubule-associated protein tau. MSA, multiple system atrophy. PD, Parkinson's disease. SNCA, synuclein alpha. SOD1, superoxide dismutase 1.

One platform, multiple targets: what vMiX™ brings to a new programme

- Across MAPT, SNCA and SOD1, the same design and validation workflow has delivered potent, dose-dependent knockdown in vivo and specificity confirmed by transcriptome-wide analysis, with durability out to six months and functional benefit demonstrated in tauopathy and ALS models.

Inherited from the platform	Built for each target
vMiX™ cassette architecture and pathway decoupling	miRNA screening and lead selection
Multiplexing and silence-and-replace capability	Target-specific potency and specificity package
Design and screening workflow	Disease model and endpoint selection
Off-target assessment (in silico and RNAseq)	Promoter and capsid choice for the target tissue

vMiX™ is target-agnostic by design: applicable wherever durable lowering of a gene product is therapeutic.



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Agnieszka Ule
Alinda Fernandes
Ana Perez
Ann Gorman
Chris Powell
Yige Huang
Anne-Laure Moreau

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Chris Shaw
Neda Ali Mohammadi
Bibiana Mota
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