AVIADOBIO

Chasing **Cures.** Delivering **Hope.**™

Preclinical development of AVB-406: An intravenous AAV-miRNA achieving sustained MAPT knockdown for the treatment of Alzheimer's disease

Carlos Miranda | VP, Preclinical | May 13th, 2026

Disclosures

- Carlos Miranda is an employee of AviadoBio Ltd and holds equity in the company. No other relevant financial relationships to disclose.

- AVB-406 is an investigational product and has not been approved by any regulatory authority.

Tauopathies: Established disease biology with a tractable clinical development pathway

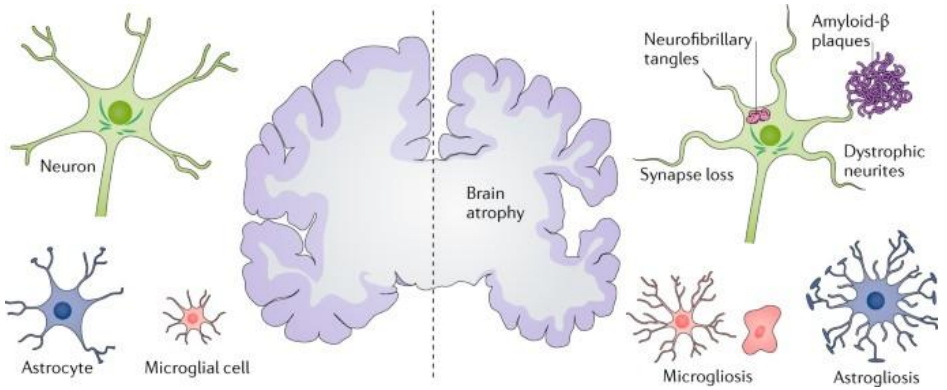
Established disease biology

Tauopathies share **pathological tau aggregation and neurodegeneration** as a common mechanism across affected brain regions[1,2]

In AD, tau pathology originates in medial temporal regions and spreads through limbic and cortical areas, **correlating with cognitive decline more strongly than amyloid pathology**

Extensive preclinical data support **therapeutic potential of MAPT gene silencing** across tauopathies, including AD and FTD

The defining pathological hallmarks of Alzheimer disease1



Congdon et al 2018 Nature Reviews Neurology 19: 715-736

De-risked tractable clinical development

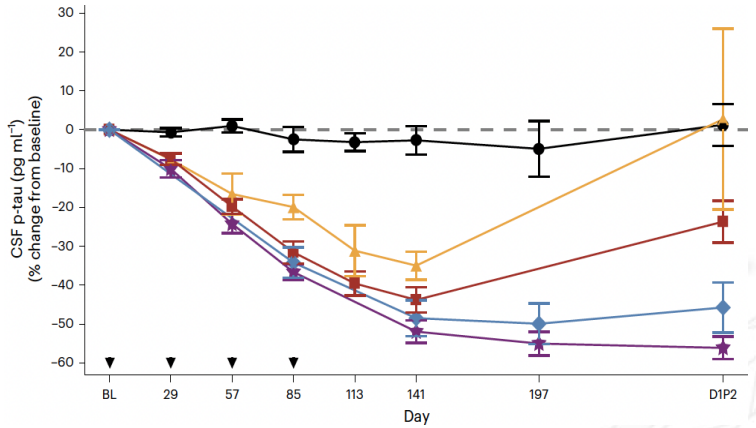
Established diagnostic and patient ID processes for AD and FTD.

Established clinical endpoints with a robust toolkit of **clinically validated biomarkers in AD**

MAPT ASO Ph1/2 clinical trial shows generally **well-tolerated safety** and reduction in pathological tau[3,4]

Ability to move into other rarer tauopathies with established natural history

Reduction in pathological tau (p-tau181) with MAPT ASO in early AD patients



Mummery et al 2023 Nature Medicine Vol 29, 1437–1447

[1]Congdon & Sigurdsson, Nat Rev Neurol (2018); [2]Congdon et al., Nat Rev Neurol (2023); [3]Mummery et al., Nature Med (2023); [4]Shulman et al., Nature Aging (2025)

POWERED BY PRECISION™

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.

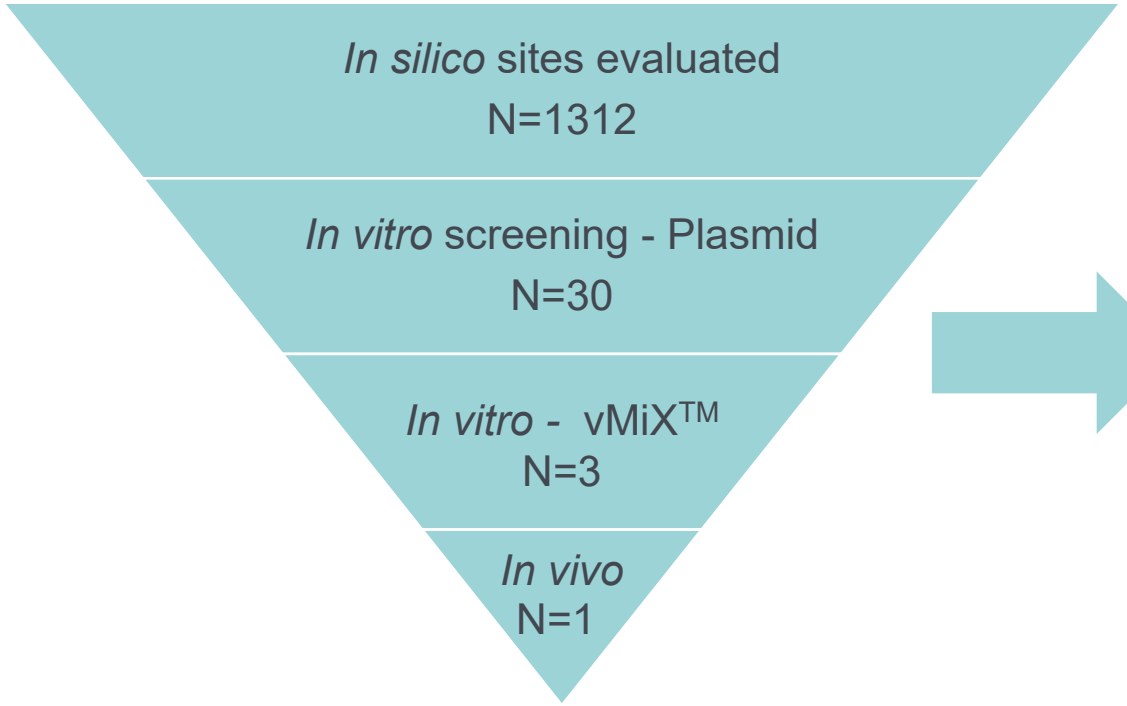
PAYLOAD

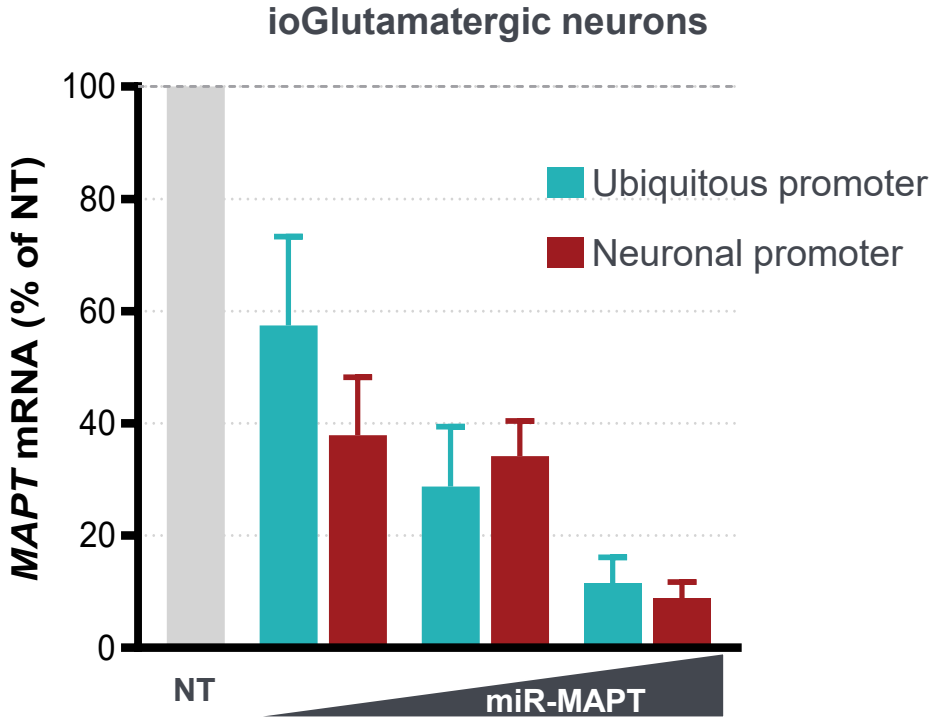
vMiX™ a one-time RNA silencing platform engineered for best-in-class specificity, potency, and neuron-selective regulation.

DELIVERY

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

vMiX™ platform identified miR sequences through systematic screening

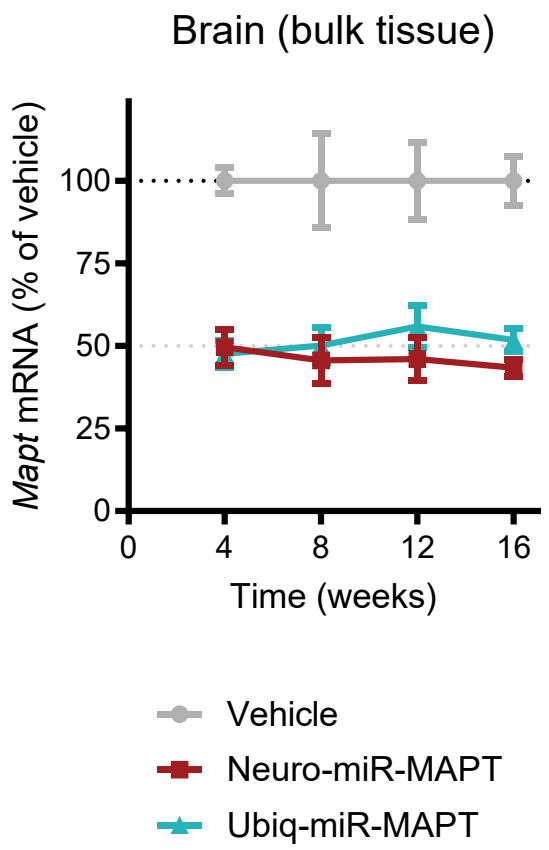


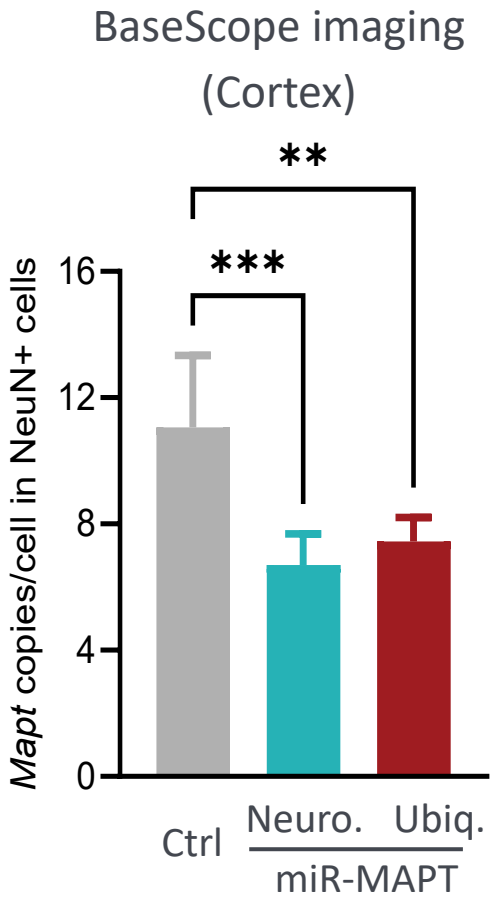


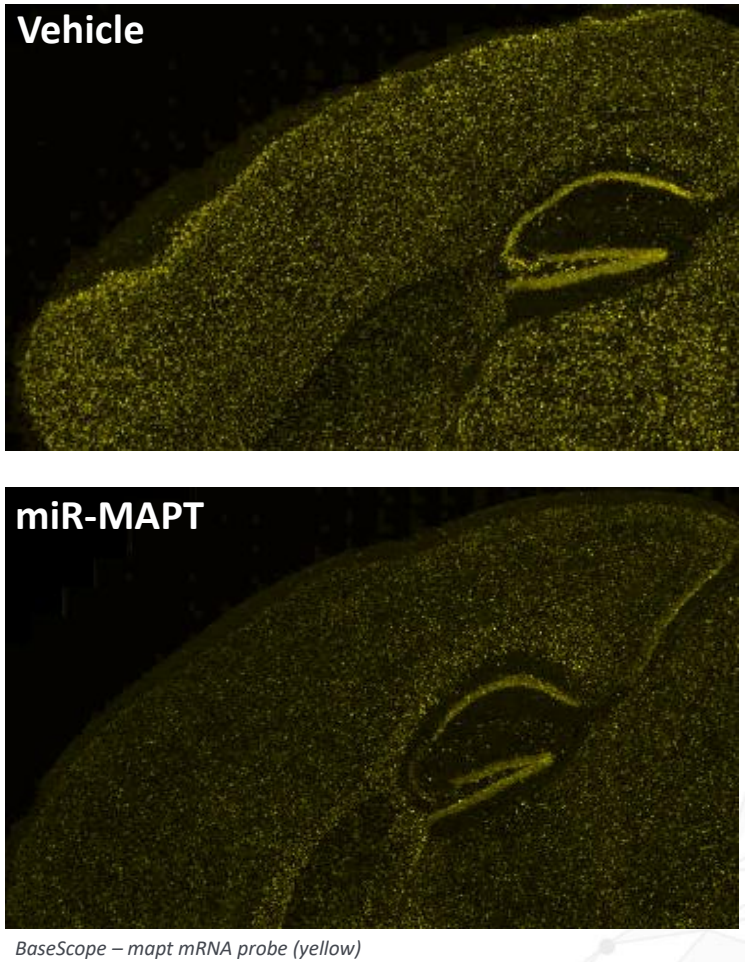
Dose-dependent knockdown; ubiquitous and neuronal promoters equivalent in iPSC-derived glutamatergic neuron. 96 well plate; 7 days post transduction. NT– Non-transduced.

For further details on development and translational validation of AVB-406 and vMiX™ platform please attend the presentation by Romain Joubert – Neurologic diseases V, Thursday, May 14th 10:45 - 11:00 AM, Presentation ID 354

Neuron-selective promoter drives sustained MAPT knockdown



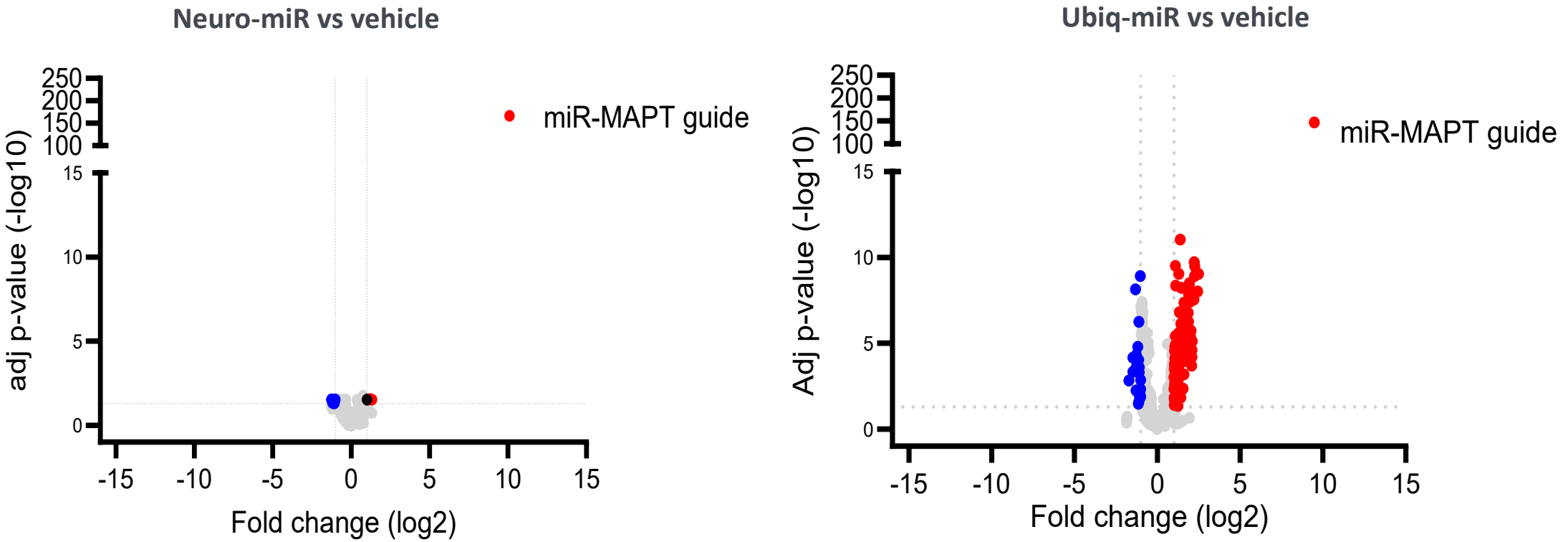




BaseScope – mapt mRNA probe (yellow)

*Wild type mice (C57Bl/6, adult); N= 6 males per dose group; Surrogate BBB-penetrating capsid single IV dose; data shows as mean ± SD; **p<0.01; *** p<0.001. Neuro – Neuronal promoter; Ubiq. – Ubiquitous promoter.*

Neuronal promoter-driven AAV-miR-MAPT in mouse CNS preserves endogenous miRNA homeostasis compared with a ubiquitous promoter

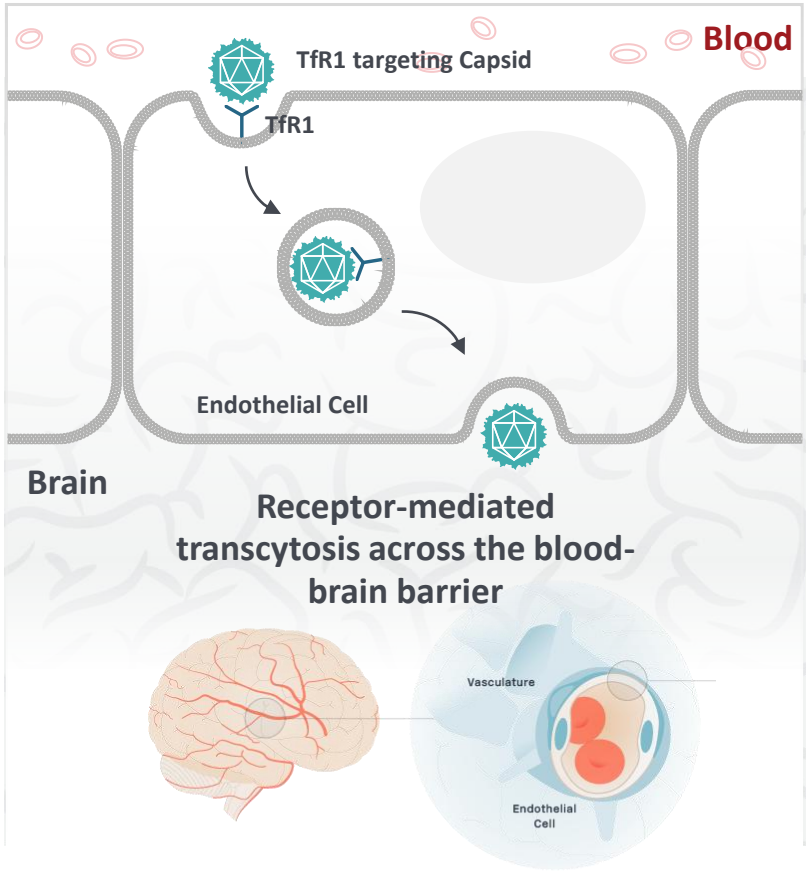


- No mir-MAPT expression or *mapt* knockdown observed with Neuro-miR-MAPT constructs outside of the CNS

Neuronal promoter chosen for clinical construct — equivalent activity to ubiquitous, with neuron-restricted expression minimising expression outside of the CNS.

*Wild type mice (C57Bl/6, adult); N= 6 males per dose group; Surrogate BBB-penetrating capsid single IV dose; data shows as mean ± SD; **p<0.01; *** p<0.001. Neuro – Neuronal promoter; Ubiq. – Ubiquitous promoter.*

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
- Opportunity for lower effective dose

Translational pathway[2]

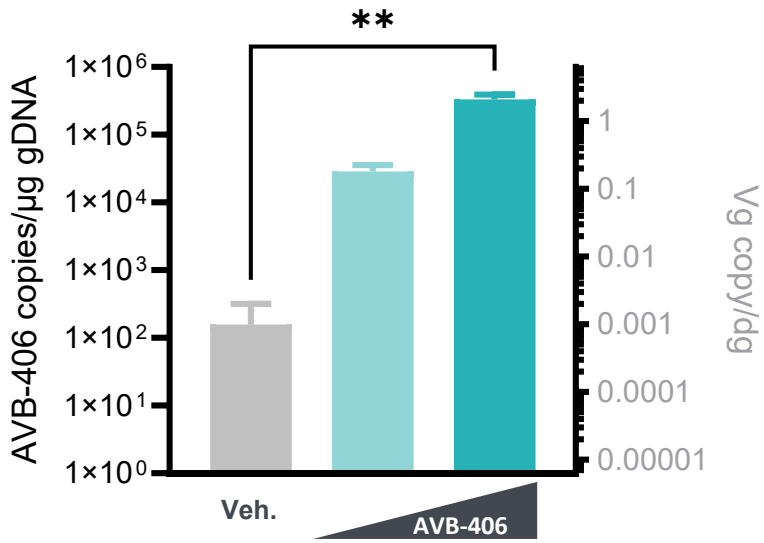
- B-hTfR1 mouse is the pharmacologically relevant model for biodistribution & toxicology
- NHPs are pharmacologically irrelevant (no hTfR1 binding)
- Surrogate capsids enables dose-range finding in disease models

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

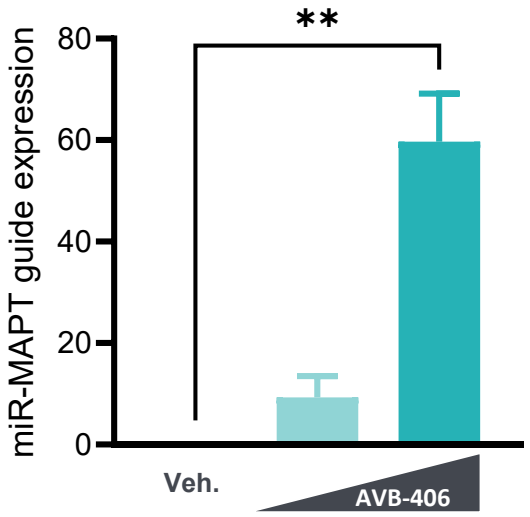
For further details on Development of a scalable platform production process for AVB-406 please attend the presentation by Andrea Martorana - AAV downstream manufacturing II, Thursday, May 14th 04:00 – 04:15 PM, Presentation ID 366.

AVB-406 produces dose-dependent Vg uptake, miR guide expression, and MAPT knockdown in CNS tissues

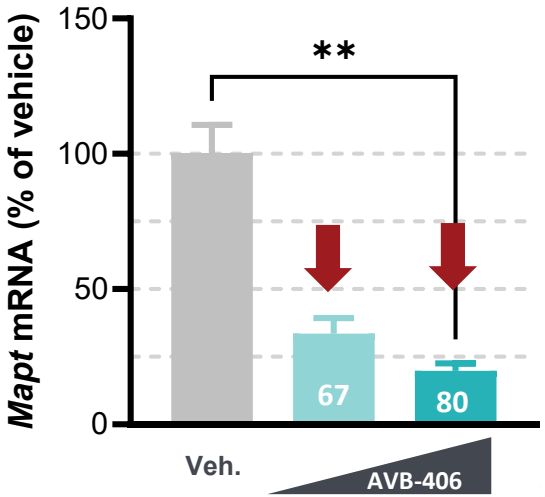
Vg copies



Guide expression

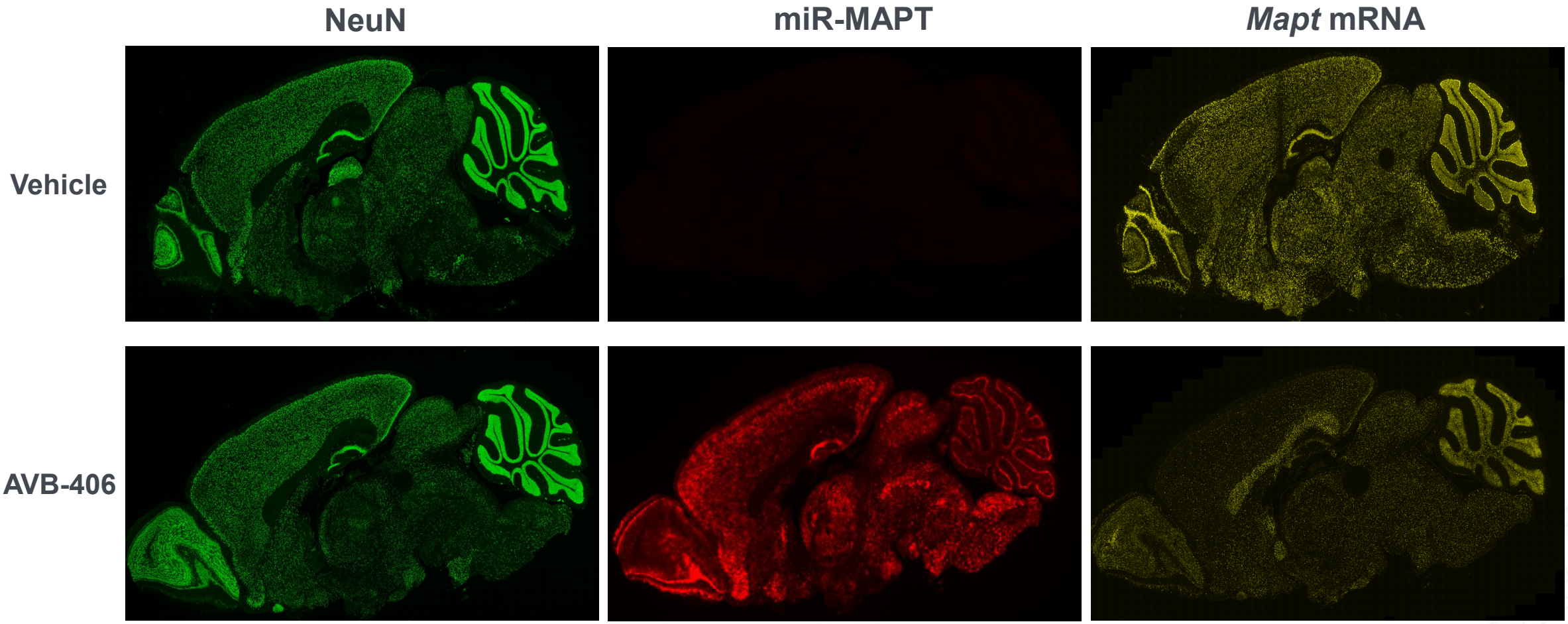


Mapt knockdown



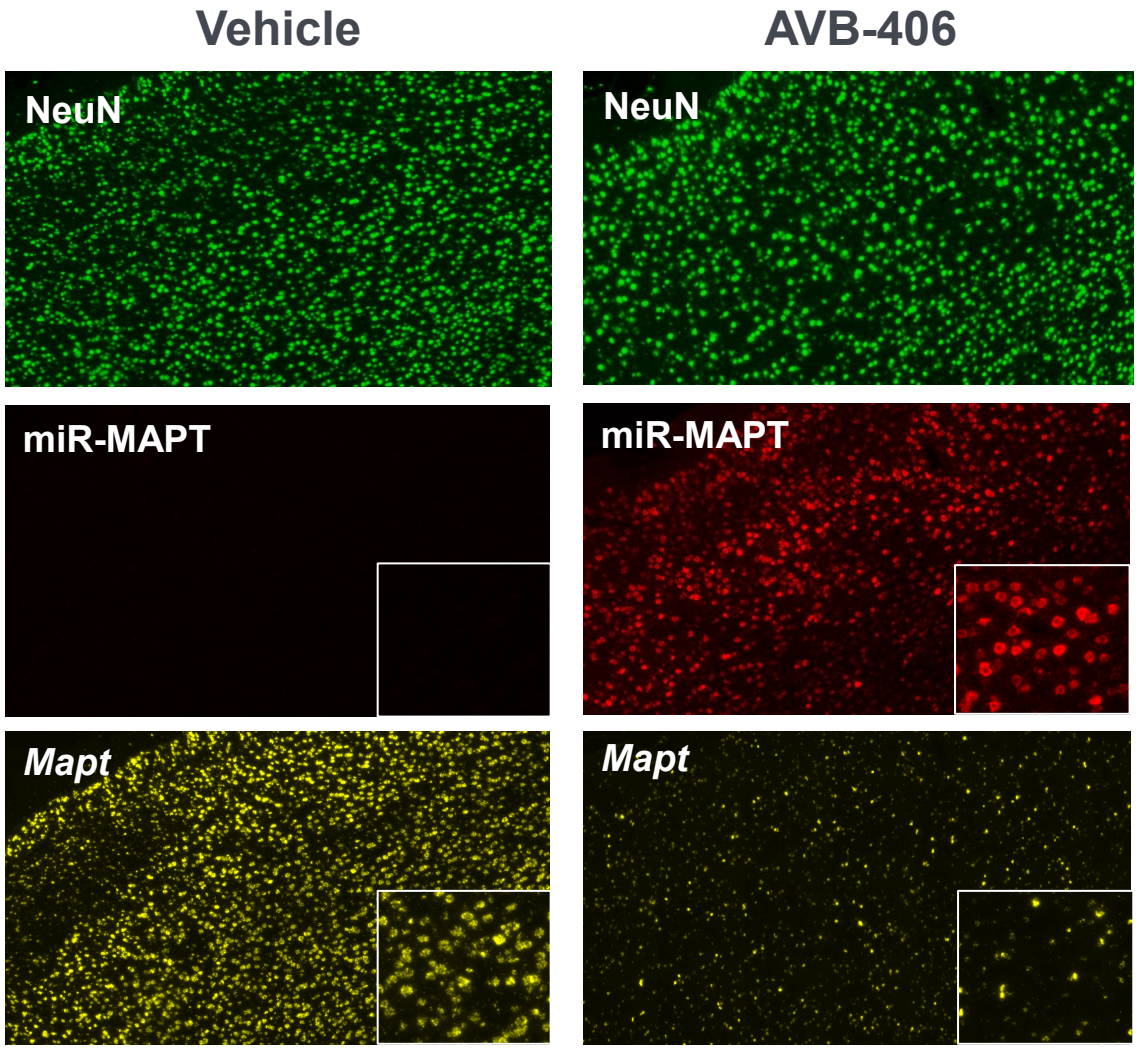
*Adult hTFR1 mice administered IV with vehicle or AVB-406. Samples collected 4-weeks post dose; N= 4 (2 males and 2 females) per dose group; Data shown represent mean ± SD; *p<0.05; **p<0.01.*

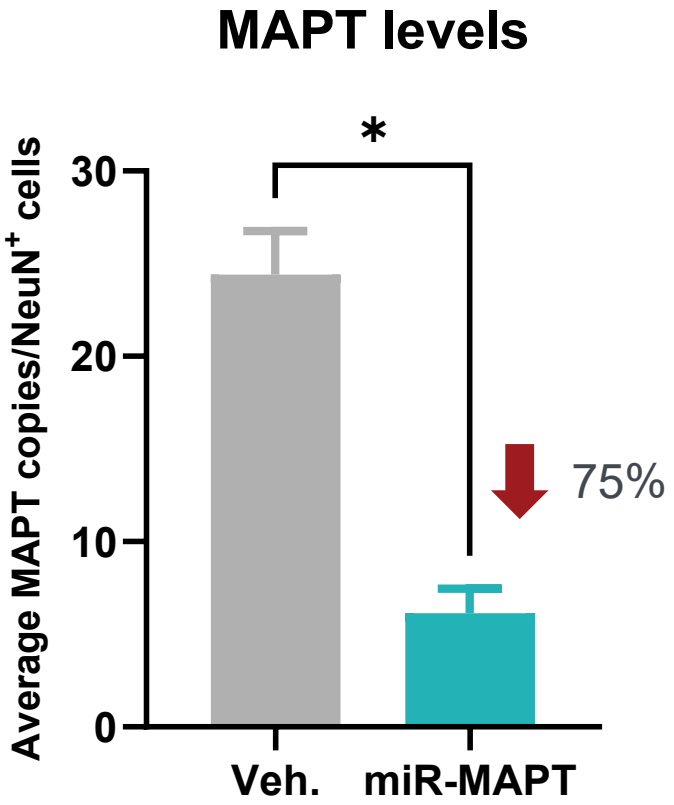
AVB-406 results in widespread reduction of *mapt* mRNA in mouse brain



Adult hTFR1 mice administered IV with vehicle or AVB-406. Samples collected 4-weeks post dose; Multiplex Fluorescent ISH/IF assay; NeuN: neurons (green), MAPT miR guide (red), mouse mapt mRNA (yellow). Veh. – Vehicle.

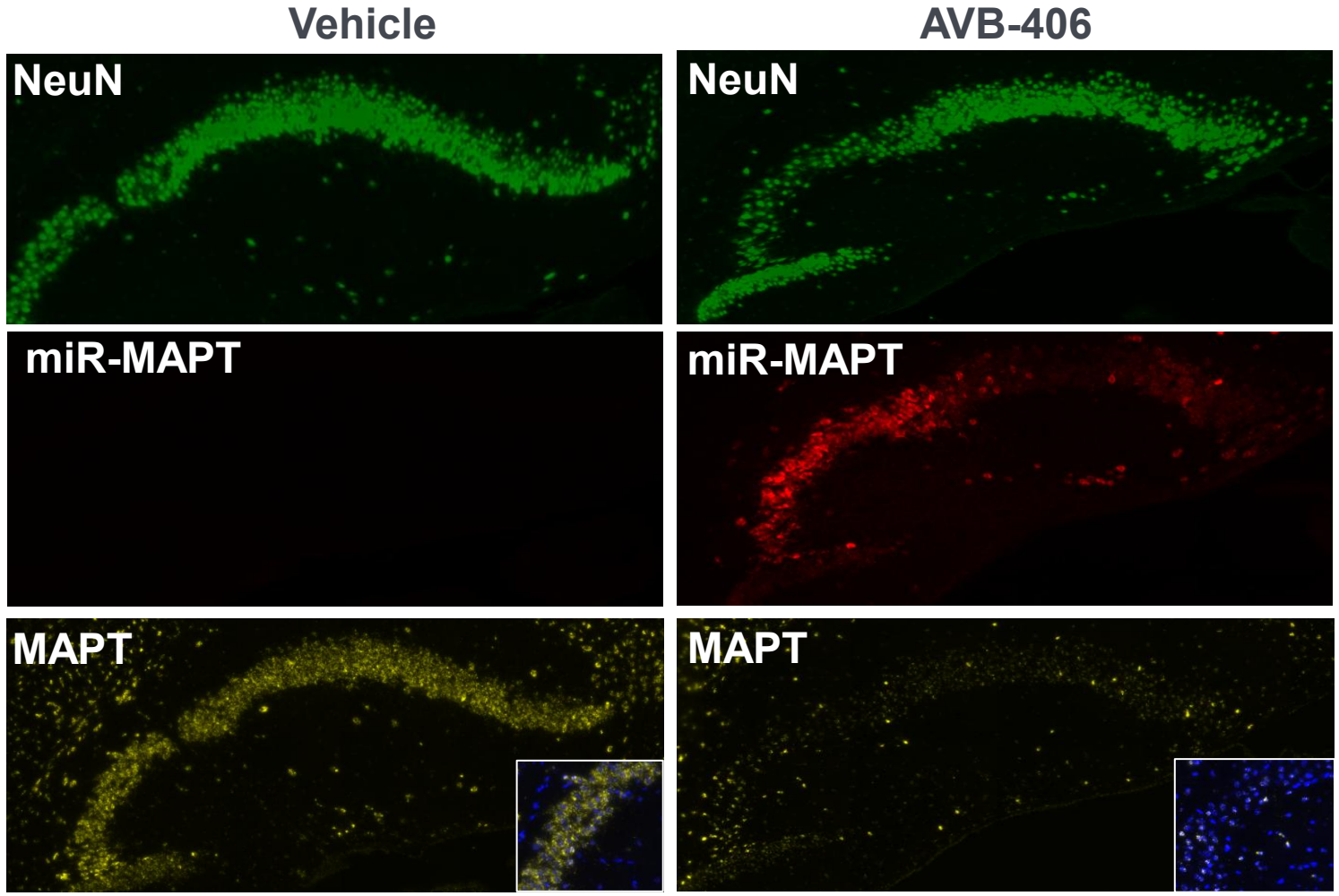
AVB-406 leads to marked reduction of *mapt mRNA* in the cortex

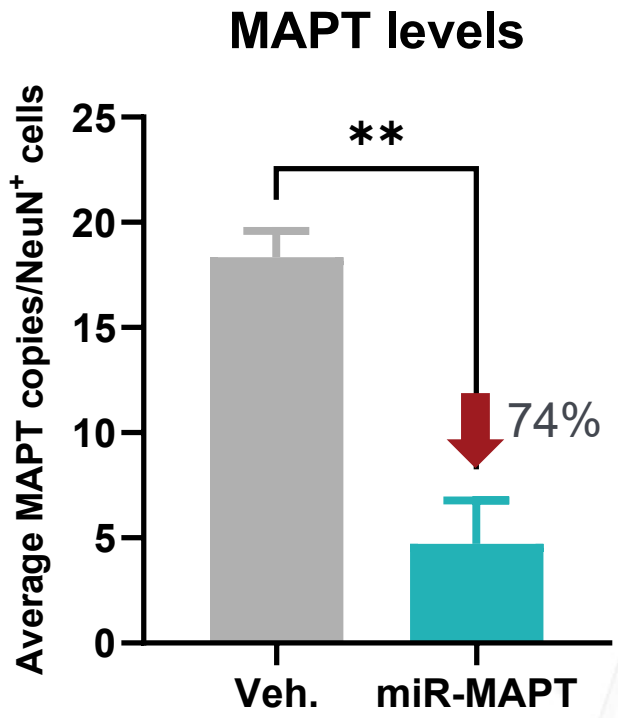




*Adult hTFR1 mice administered IV with vehicle or AVB-406. Samples collected 4-weeks post dose; Multiplex Fluorescent ISH/IF assay; NeuN: neurons (green), MAPT miR guide (red), mouse MAPT (yellow); Magnification 10x with inset 20x. Data shown as mean± SD; * p≤0.05. Veh. – Vehicle.*

AVB-406 leads to marked reduction of *mapt mRNA* in the hippocampus

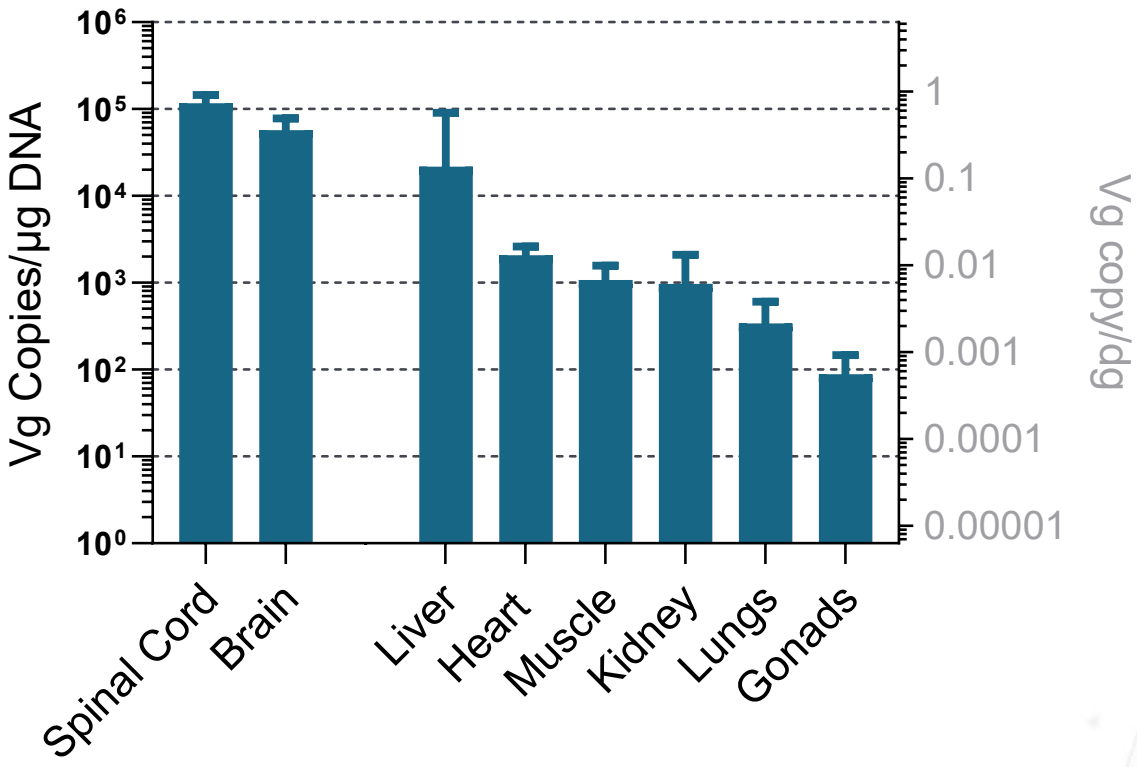




*Adult hTFR1 mice administered IV with vehicle or AVB-406. Samples collected 4-weeks post dose; Multiplex Fluorescent ISH/IF assay; NeuN: neurons (green), MAPT miR guide (red), mouse MAPT (yellow); DAPI, blue. Data shown as mean± SD. ** p≤0.01. Veh. – Vehicle.*

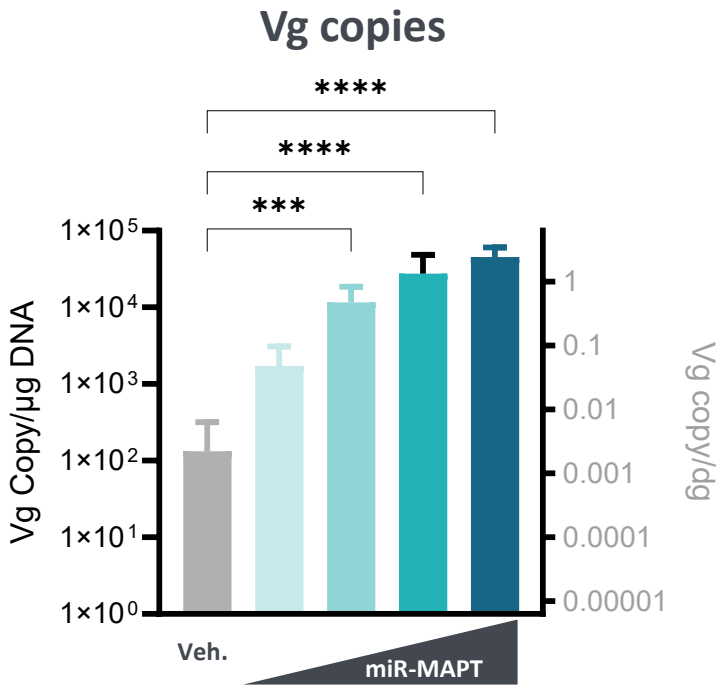
AVB-406 achieves CNS-wide biodistribution with reduced peripheral exposure

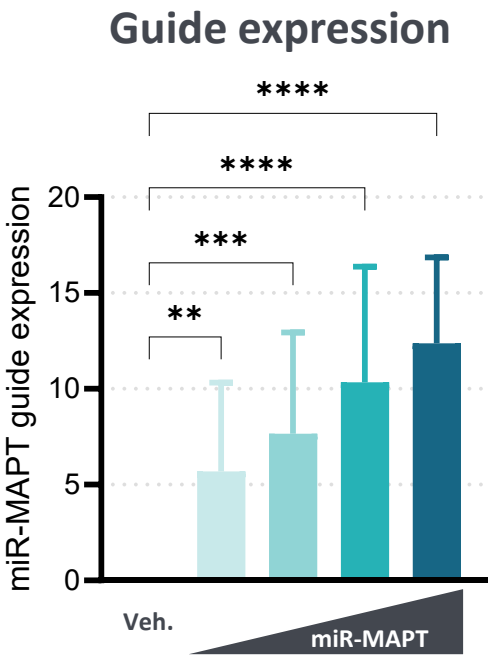
- Brain and spinal cord: ~10^5 Vg/µg DNA (bulk tissue) — highest of all tissues assessed
- Peripheral tissues, including the Liver, show lower Vg, 10 – 100× below CNS
- No miR-MAPT guide expression detected outside the CNS — on-target silencing restricted to target tissue



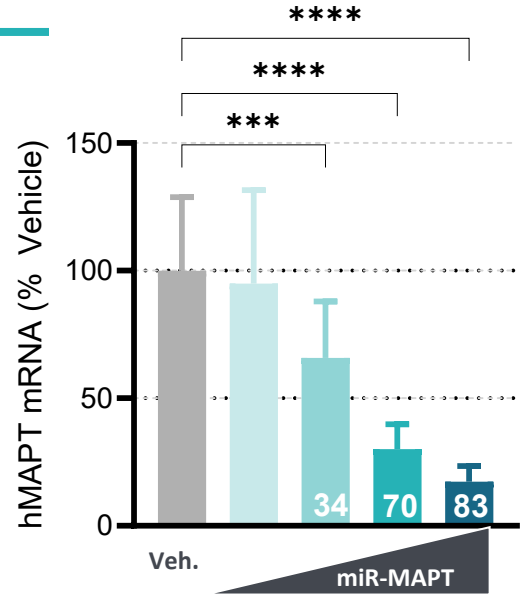
Adult hTFR1 mice administered IV with vehicle or AVB-406. Samples collected 4-weeks post dose; N= 4 to 6 (equal numbers of males and females) per dose group; Data shown represent mean ± SD..

AAV-miRNA-MAPT results in a dose dependent MAPT/Tau knockdown in P301S mice

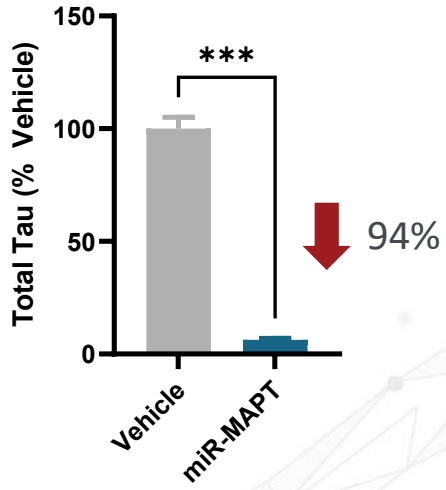




MAPT

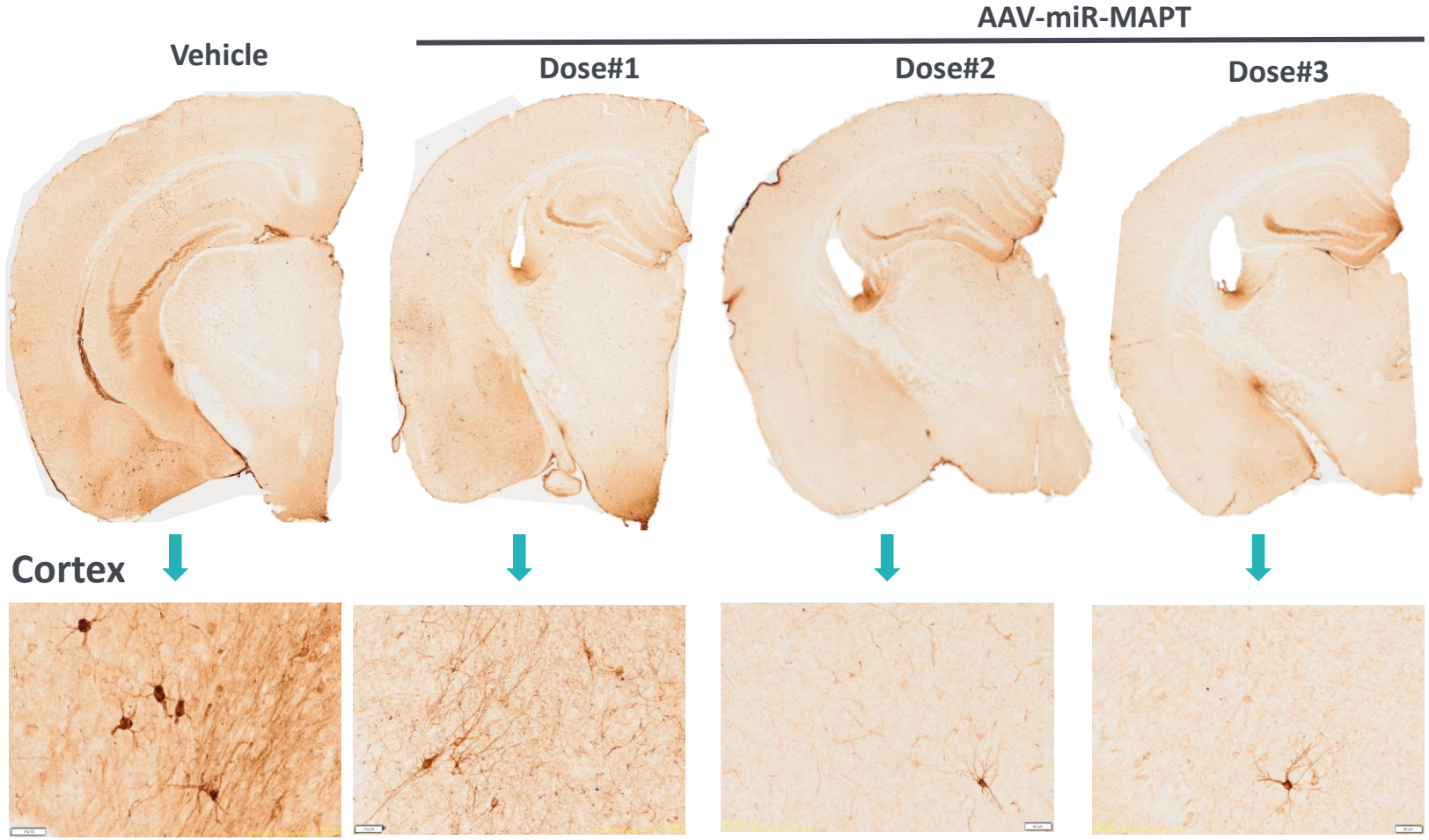


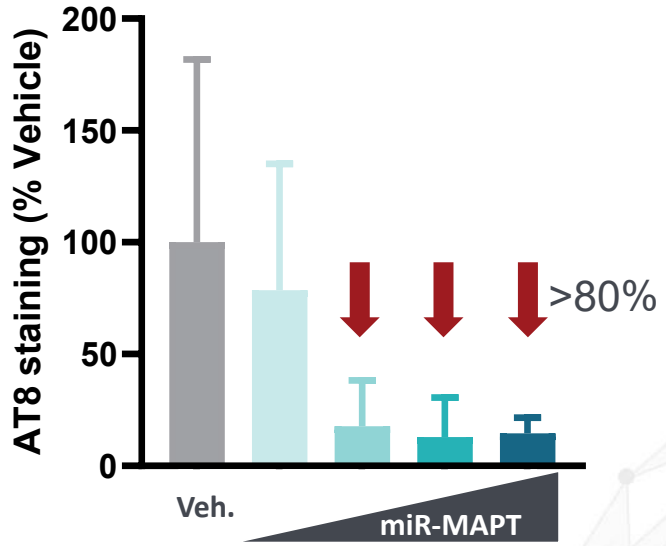
Tau



*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; IHC male cohort only. Veh. – Vehicle.*

AAV-miRNA-MAPT reduces phospho-Tau in P301S mouse tauopathy model





*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 (equal number males and females) per dose group; Data shown represent mean ± SD; *p<0.05; **p<0.01, ***p<0.001; ****p<0.0001; IHC male cohort only. WT – Wild type mice*

Summary & Roadmap to the Clinic

WHAT HAVE WE SHOWN

1. **AVB-406 is a potential one-time IV gene therapy** combining a BBB-penetrant hTfR1 (CapX) capsid, the vMiX™ miRNA platform, and a neuron-selective promoter.
2. **Robust, durable MAPT knockdown** in mouse CNS: up to 80% in cortex, sustained through 16 weeks; neuronal specificity confirmed by ISH.
3. **CNS-selective biodistribution and expression**: >10 - 100× higher Vg in CNS than peripheral tissues; no miR-MAPT guide expression outside the CNS.
4. **Pathology amelioration** in P301S tauopathy model with >80% reduction in phospho-tau (AT8).
5. **Well tolerated across all animal studies conducted to date**, with no treatment-related adverse findings at doses achieving maximal knockdown.

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 secured
- ✓ IND-enabling GLP toxicology underway
- ➢ Scalable bioreactor manufacturing ongoing (for details please attend Andrea Martorana talk, Oral presentation ID 366, AAV downstream manufacturing II, Thursday 14th, 4:00 PM)
- ➢ First-in-human initiation planned in Q4 2026

Acknowledgments

AVIADOBIO

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F-PRIME
Johnson&Johnson
LIFEARC VENTURES
NEA
MOC

Additional oral presentation from AVB:

- *Thursday, May 14th 10:45 - 11:00 AM, Presentation ID 354 – Development and translational validation of AVB-406: An intravenous AAV-delivered miRNA targeting MAPT for the treatment of Alzheimer's disease (by Romain Joubert)*
- *Thursday, May 14th 04:00 – 04:15 PM, Presentation ID 366 - Manufacture of AVB-406, a BBB–crossing AAV vector for MAPT knockdown in Alzheimer's disease (by Andrea Martorana)*

DELIVERING CURATIVE GENETIC MEDICINES
FOR NEURODEGENERATIVE DISORDERS

THANK YOU FOR YOUR TIME

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