AVIADOBIO

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

Development and translational validation of AVB-406

An intravenous AAV-delivered miRNA targeting MAPT for the treatment of Alzheimer's disease

Romain Joubert | Senior Director, Discovery | May 14th, 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 and AVB-406.
- AVB-406 is an investigational product and has not been approved by any regulatory authority.

Tauopathies drive significant global burden with very limited disease-modifying therapies

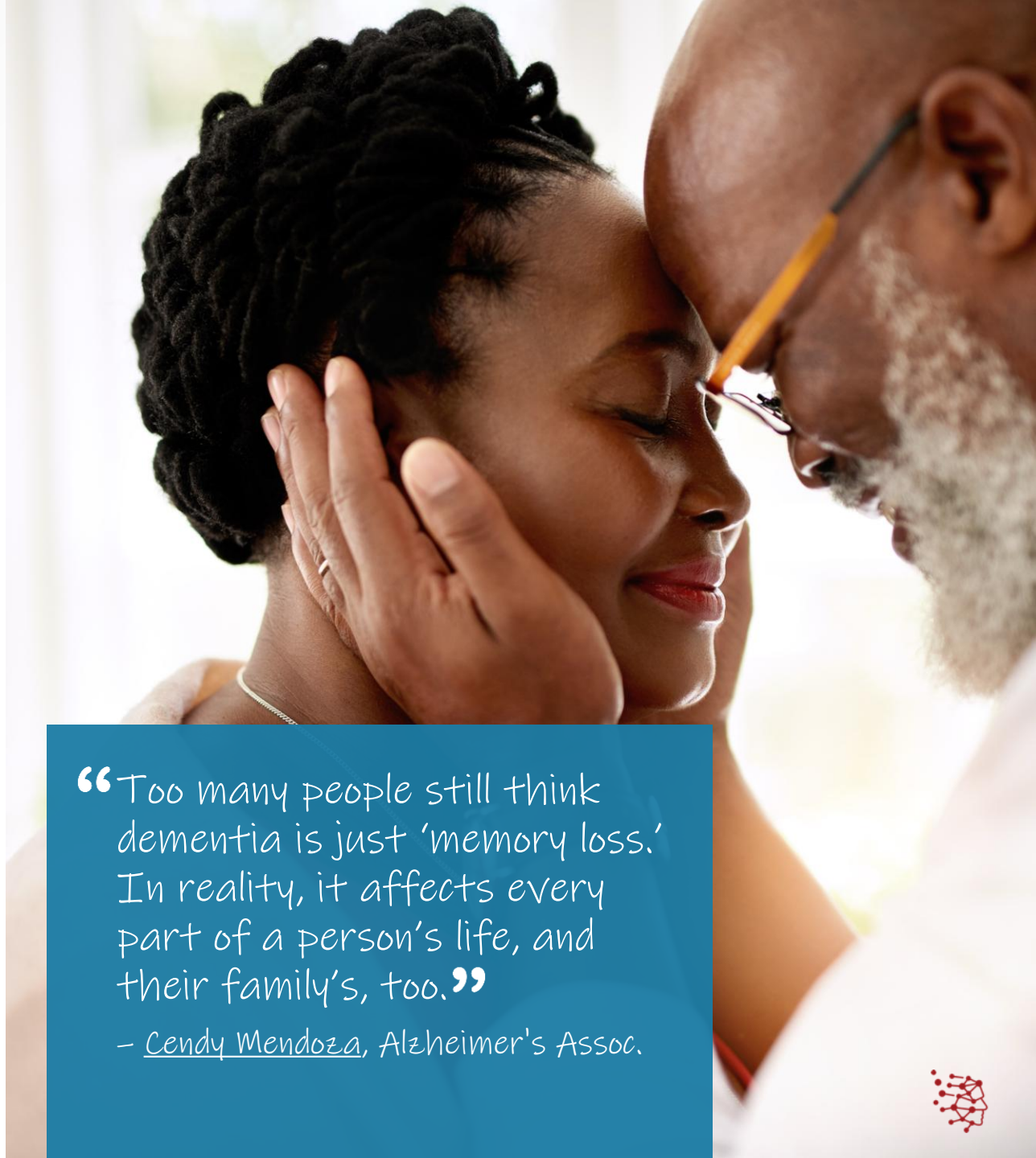
Tauopathies include
Alzheimer's disease (AD), frontal temporal dementia (FTD-MAPT, tau-FTD), PPA, CBD, PSP and CTE

>57 million worldwide have dementia.

Alzheimer's disease is the leading cause contributing to **60-70% of cases**

Progressive memory impairment, cognitive decline, agitation, aggression, and psychosis, **death 4-8 years** post diagnosis

Established **diagnostic processes**, **clinical endpoints** & commercially available and **validated biomarkers** in AD



"Too many people still think dementia is just 'memory loss.' In reality, it affects every part of a person's life, and their family's, too."

– Cendy Mendoza, Alzheimer's Assoc.

Established disease biology with a tractable clinical development pathway

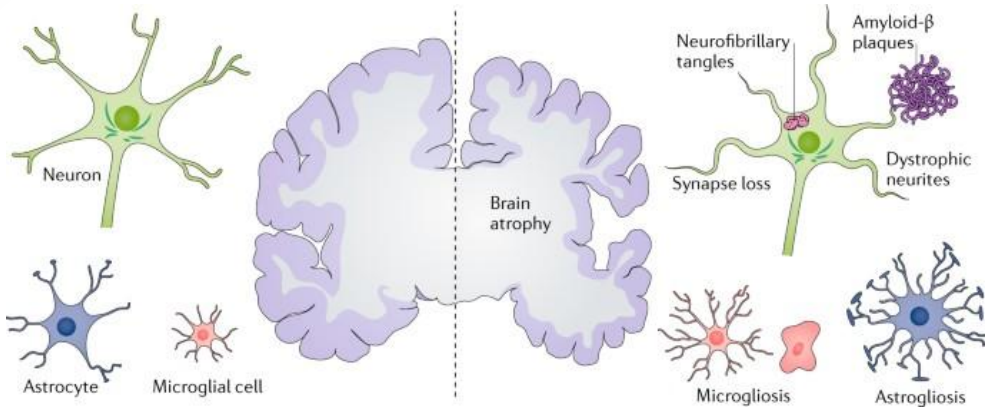
Established disease biology

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 disease.



Congdon & Sigurdsson, Nature Rev Neurol (2018)

De-risked tractable clinical development

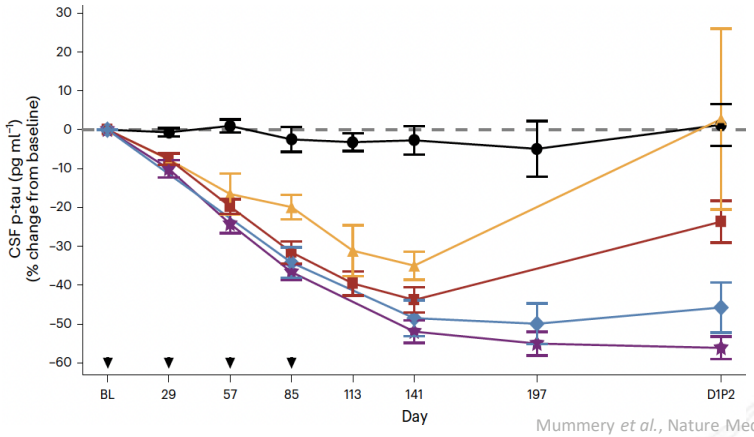
Established diagnostic and patient ID processes for AD and FTD.

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.*, Nature Med (2023)

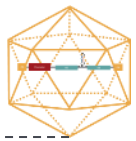
[1]Congdon & Sigurdsson, Nat Rev Neurol (2018); [2]Congdon et al., Nat Rev Neurol (2023); [3]Mummery et al., Nature Med (2023); [4]Shulman et al., Nature Aging (2025)

AVB-406 is being developed as a one-time, IV administered gene therapy to prevent and reverse Tau aggregation in tauopathies

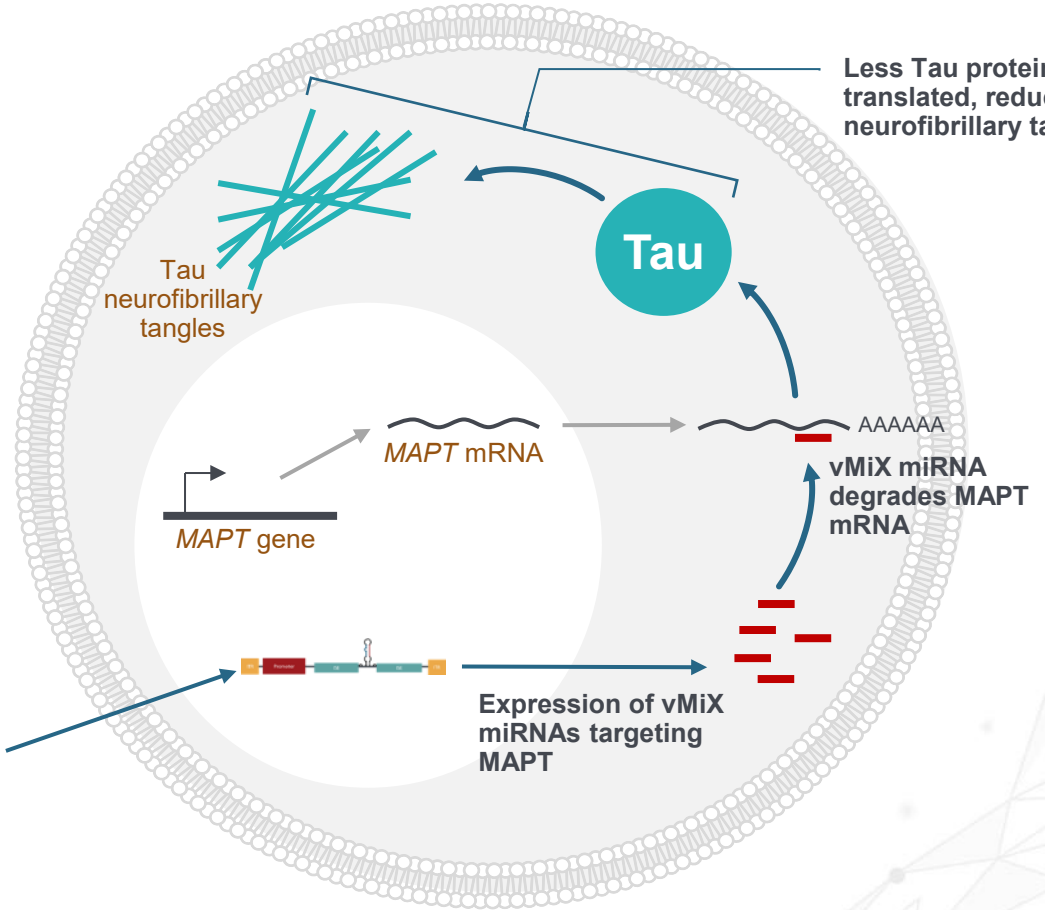
Gene silencing payload with neuronal promoter

BBB-penetrant AAV capsid for systemic delivery

AVB-406



AVB-406 reduces Tau protein production via *Mapt* mRNA silencing, reducing neurofibrillary tangle formation



vMiX™ is a One-Time RNAi Platform Designed for Potent & Safe Gene Silencing

ITR

PROMOTER

Pol II-based design enables tissue/cell specific promoter usage to control expression profile improving targeting and safety.

vMiX THERAPEUTIC PAYLOAD

miRNA delivery using unique hybrid hairpin design, with potential to deliver multiple miRNAs

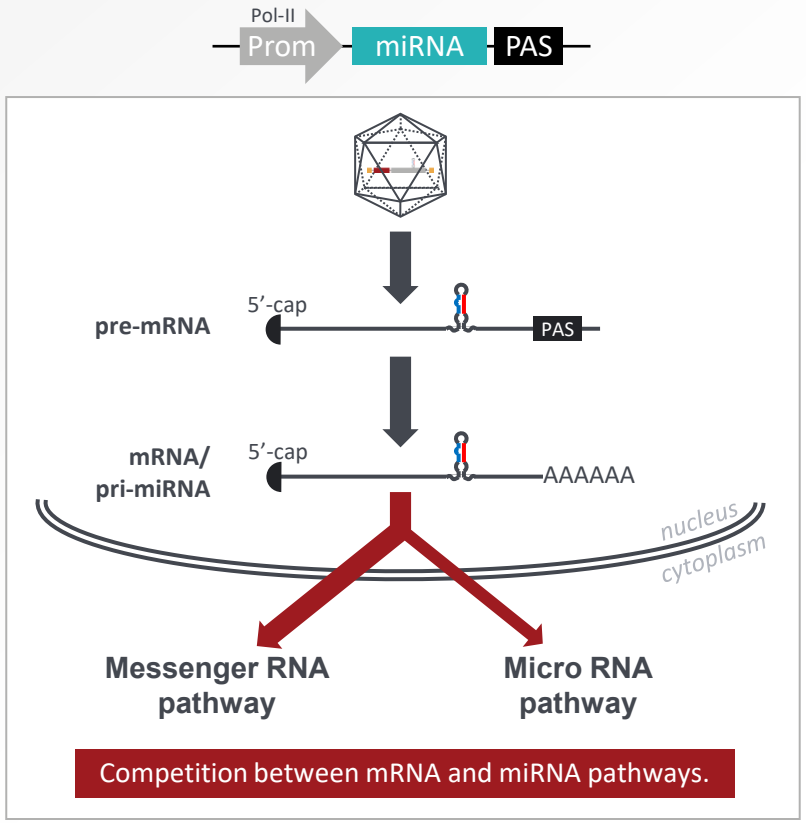
Flexible design allows inclusion of coding cDNA for 'Replace & Silence' strategies

ITR

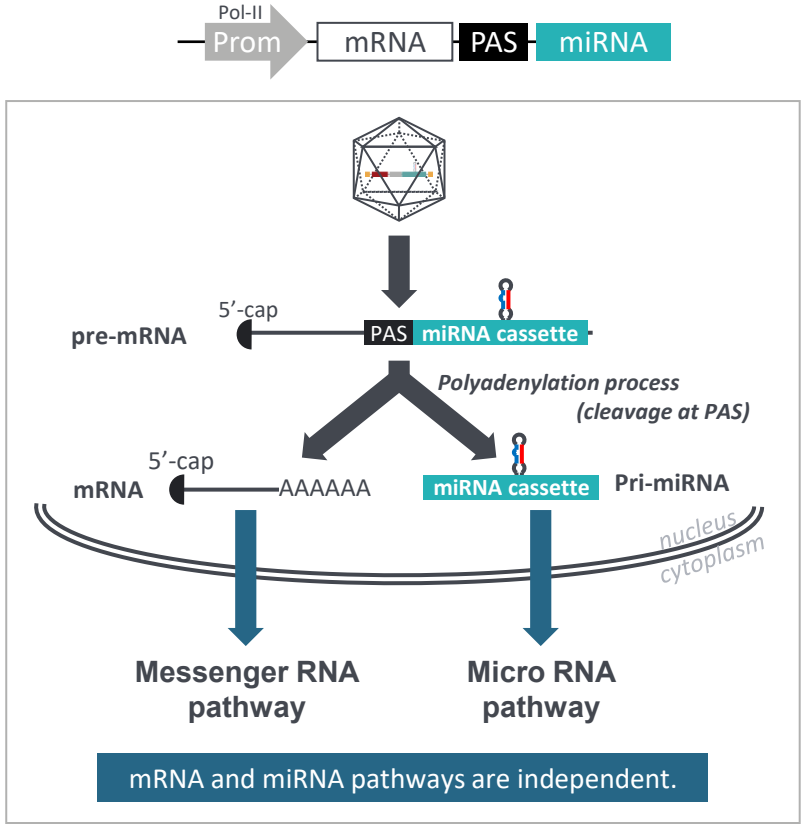
- Efficient silencing of gene targets
- Excellent fidelity miRNA production
- Inert off-target profile
- High translatability from *in vitro* to *in vivo*
- Highly manufacturable in AAV
- Multiple hairpins allow multi-targeting

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

Systematic *in silico* and *in vitro* screening identifies three lead miRNA candidates

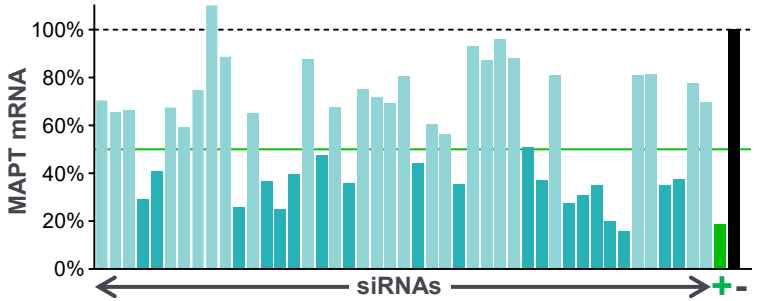
MAPT mRNA characterization

Goal: identify the best sequences to target

- *in silico*: sequence analysis

Human-NHP homology: 81%

- *in vitro*: siRNA transfection



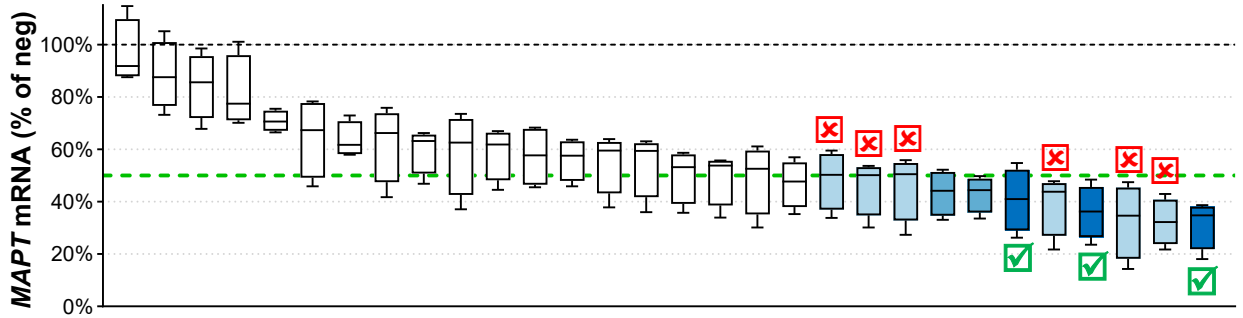
Best targetable regions: 30%

➢ **Potential miRNA guides to screen: 1312 → 210**

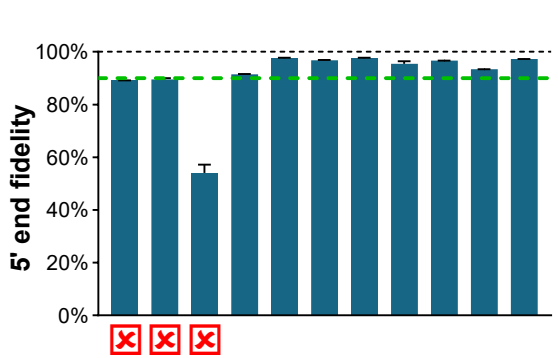
MAPT miRNA screening

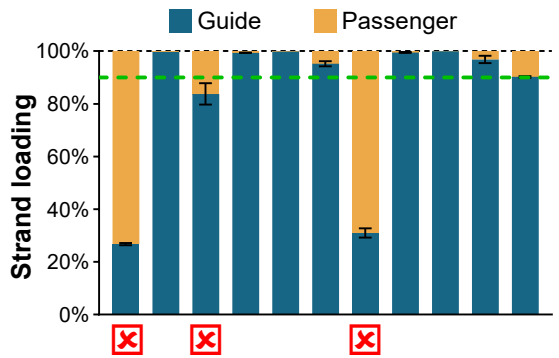
Goal: identify the best miRNAs from 30 candidates

- *in vitro*: miRNA plasmid transfection



- miRNA hairpin processing



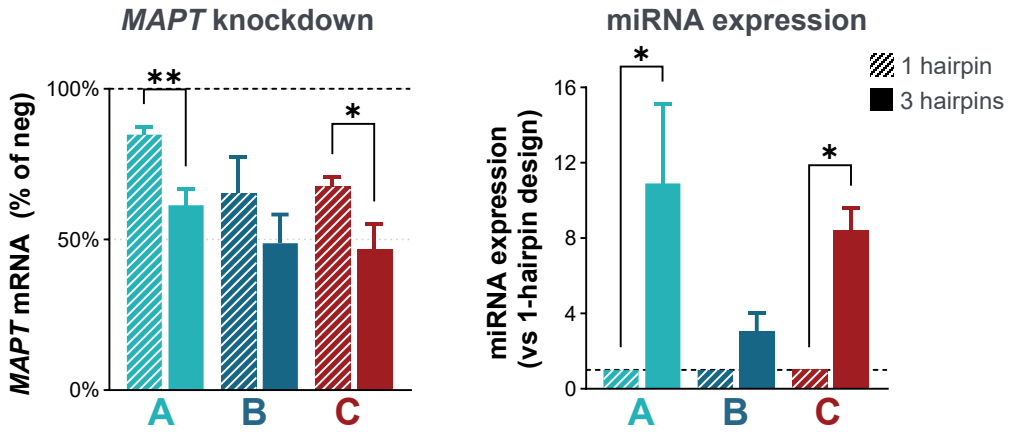


Three-hairpin configuration enhances knockdown and confirms miR-C as the lead candidate with cross-species activity

TOP3 candidates

Goal: compare 1- vs 3-hairpin silencing potency

- *in vitro*: miRNA plasmid transfection



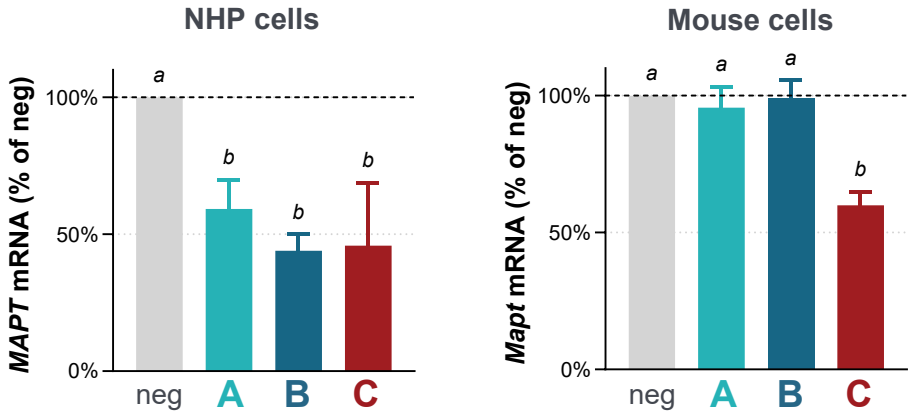
(* p<0.05, ** p<0.01, Kruskal-Wallis test)

➢ **3-hairpin configuration enhances MAPT knockdown and miRNA expression**

Species-specificity target engagement

Goal: identify candidates with NHP and mouse cross-reactivity

- *in vitro*: transfection in NHP (COS-7) and mouse (N2a) cells



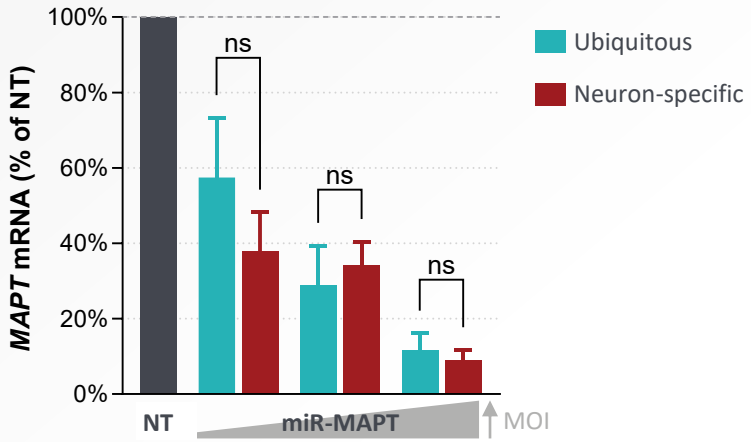
(Groups with different letters differ significantly, Tukey's multiple comparison test)

➢ **miR-C demonstrates cross-species activity in NHP and mouse, supporting its selection as lead candidate**

miR-C selected as lead candidate: superior human potency, cross-species activity in monkey and mouse, and optimal guide processing fidelity in a 3-hairpin configuration.

Promoter comparison confirms neuron-specific selection, with sustained silencing up to 16 weeks in vivo

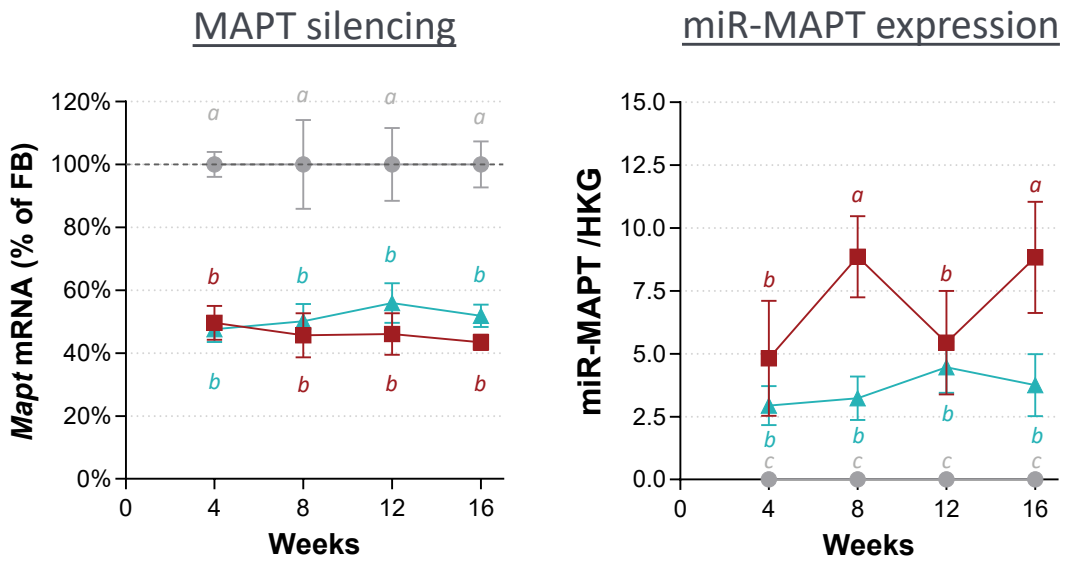
AAV transduction in iNeurons



(ns: non-significant, Kruskal-Wallis test; NT: non-transduced)

➢ No difference between 2 promoters

Mouse study

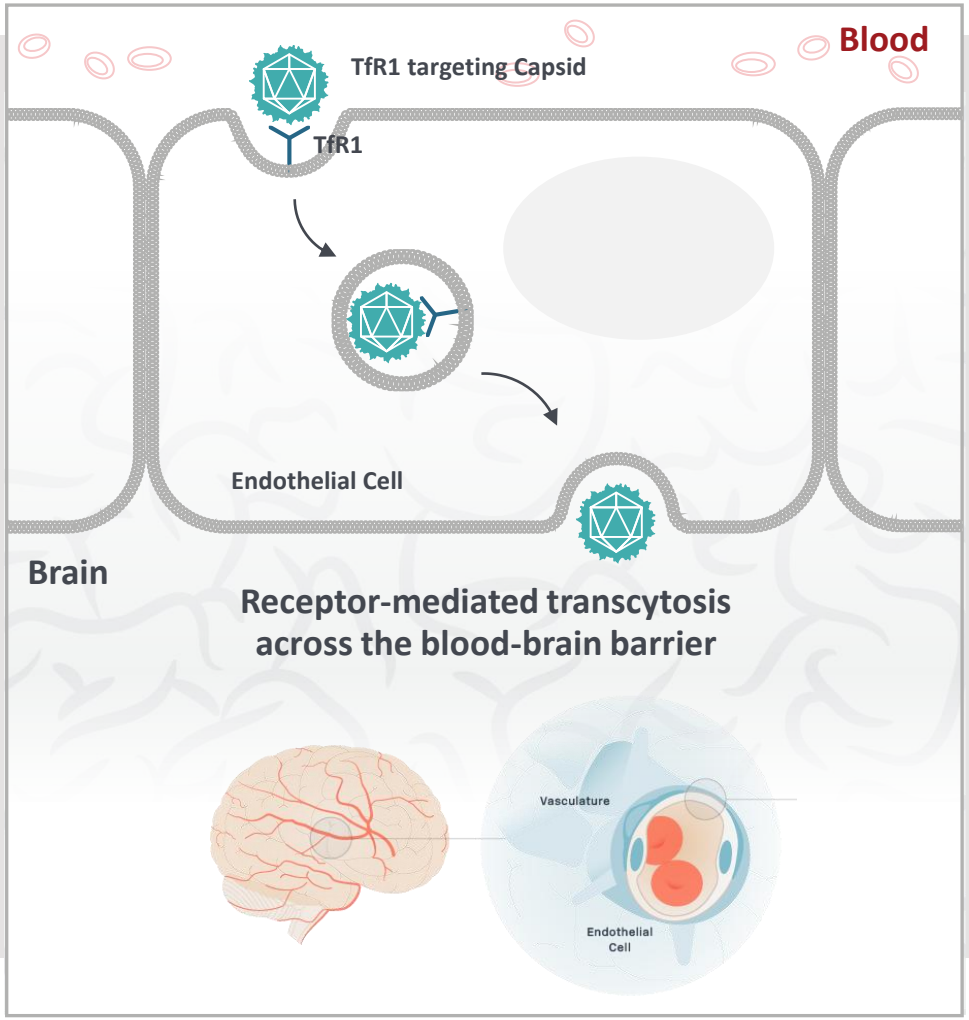


(Groups with different letters differ significantly, Tukey's multiple comparison test)

➢ No major difference between 2 promoters

- Neuron-specific and ubiquitous promoters show equivalent silencing potency in vitro and in vivo
- Neuron-specific promoter selected for IV safety profile, with durable transgene expression and knockdown confirmed at 16 weeks

AVB-406 utilises a TfR1 capsid to enable selective CNS targeting



Benefits of AAV Targeting TfR1

- TfR1 is the **most extensively characterised BBB** [1-3],
- **Clinically validated**[5]**.**
- Rapid kinetics are **ideally suited for AAV gene therapy applications**[4]
- **Capsid binds exclusively to human form of TfR1**.
- Extensive biodistribution across CNS, with **up to 80% transduction across cortex** at low systemic doses and transduction of neurons and astrocytes
- Readily manufacturable. AAV9-like yields provides attractive CoGS

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 (Abstract ID 366)

[1] Bourassa, Mol Pharm. (2019); [2] Pardridge, Front Drug deliv. (2023); [3] Kumabe, Fluids and Barriers of the CNS (2025); [4] Pardridge, Pharmaceuticals (2021); [5] AVLAYAH FDA summary of prescribing information (2026); CoGS: Cost of Goods Sold

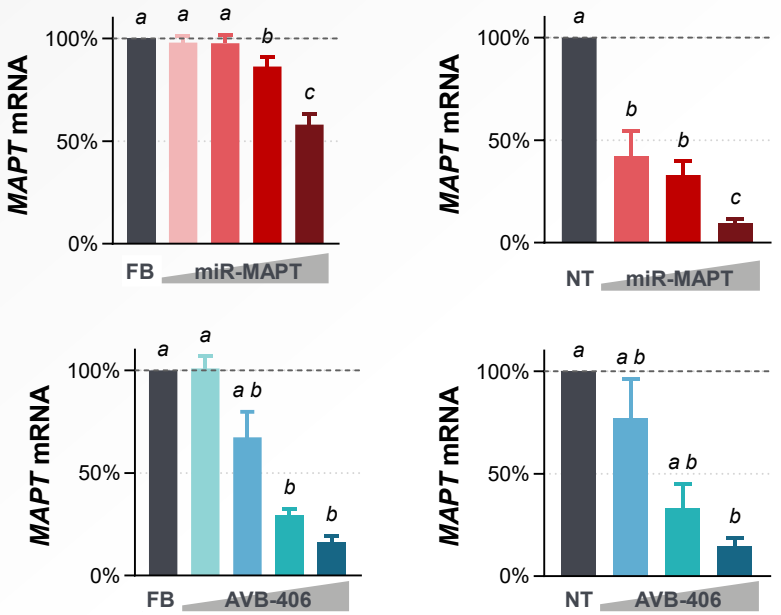
CapX shows superior or equivalent silencing across all models, with clear in vivo advantage over Capsid 1

SH-SY5Y cells

iNeurons

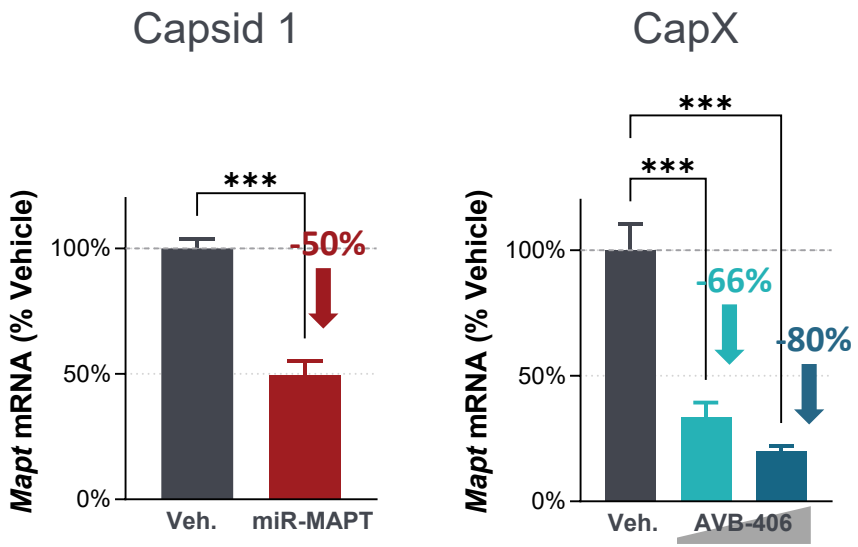
Capsid 1

CapX



(Groups with different letters differ significantly, Tukey's multiple comparison test or Kruskal-Wallis test)

Mouse study



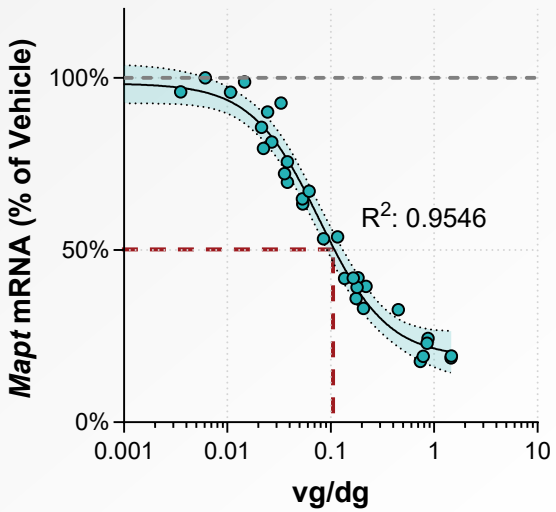
*(*** p<0.001, Unpaired t-test or Tukey's multiple comparison test)*

- CapX achieves superior MAPT silencing in SH-SY5Y cells (potency assay model) and equivalent silencing in iNeurons compared to Capsid 1
- CapX delivers deeper knockdown in vivo, driven by a higher proportion of transduced neurons following IV administration

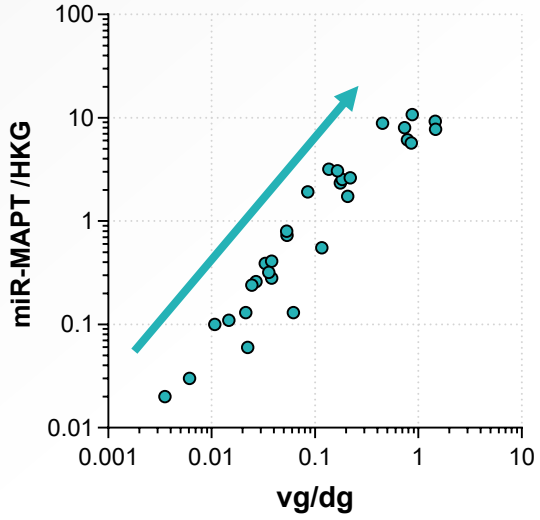
(FB: formulation buffer; NT: non-transduced; Veh: Vehicle)

AVB-406 achieves robust, neuron-selective MAPT knockdown in mice after a single IV dose

Mapt mRNA

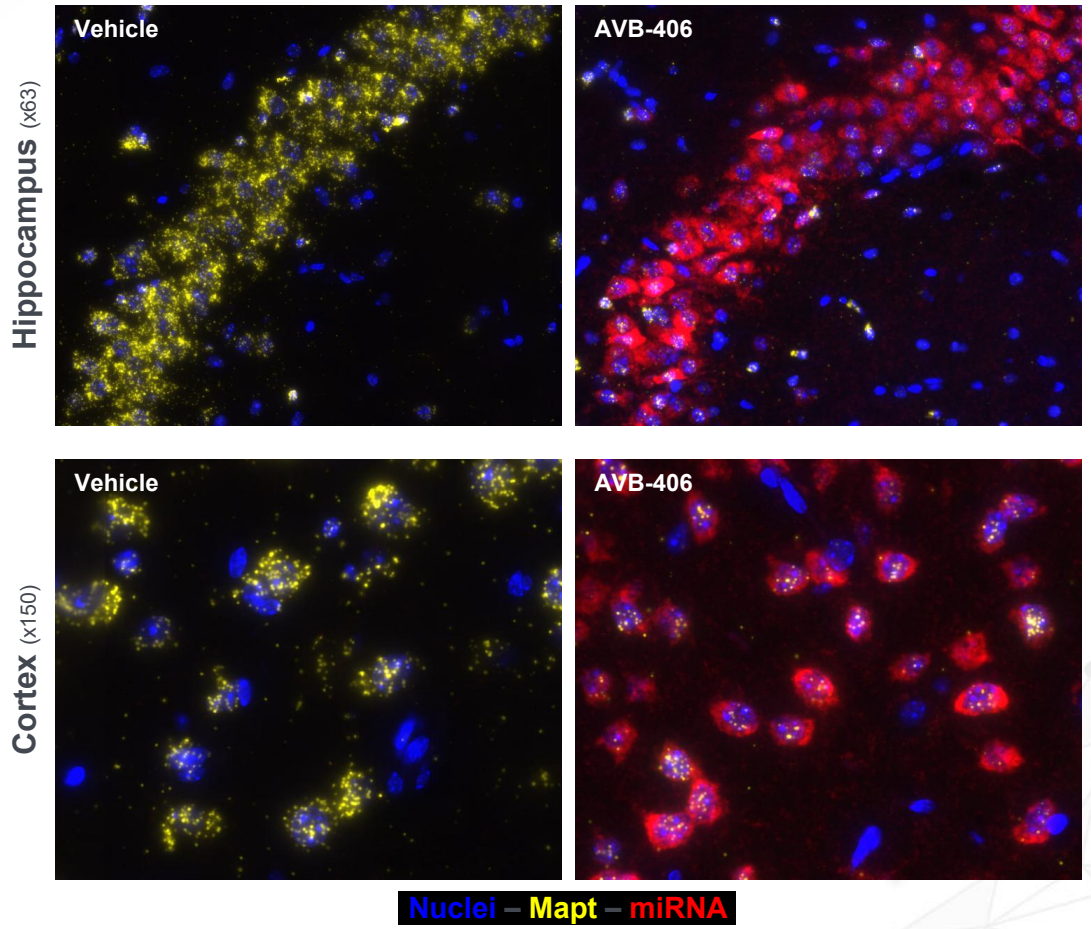


miR-MAPT expression



- Robust, dose-dependent MAPT knockdown in bulk tissue, with an IC_{50} of ≈0.1 vg/dg
- Linear dose-dependent miR-MAPT expression
- Silencing and expression limited to neurons (BaseScope)

RNAscope assay



For further details on Preclinical development of AVB-406, please watch the presentation by Carlos Miranda. Neurologic diseases IV, Wednesday, May 13th 04:00 – 04:15 PM (Abstract ID 234)

AVB • 406

for Alzheimer's Disease and Other Tauopathies

AVB-406 is positioned for clinical study initiation in 2026

SUMMARY

- ✓ miRNA screening: a lead miRNA candidate selected
- ✓ Payload validated: neuron-specific promoter, 3 miRNA hairpins
- ✓ Capsid validated: BBB-crossing capsid for intravenous dosing (CapX, Apertura)
- ✓ pIND meeting: surrogate capsid strategy

NEXT STEPS

- ❑ IND-enabling GLP toxicology study underway
- ❑ First-in-human initiation planned in 2026

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

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