Development and translational validation of AVB-406: an intravenous AAV-miRNA targeting MAPT for the treatment of Alzheimer's disease

Romain Joubert[1], Madeline Louise Reilly[1], Deirdre O'Connor[1], Gurdeep Kooner[1], Leonie Sophie Brebner[1], Deborah Ojutalayo[1], Martina Esposito Soccoio[1], Randa Elsayed[1], Catia Andreassi[1], Emily Dellow[1], Bibiana C Mota[2], Neda Ali Mohammadi[2], Andrea Mortorana[1], Michael MacDonald[1], Peter Boyce[1], Agnieszka M Ule[1], Carlos J Miranda[1], Christopher E Shaw[1,2], John Isaac[1], Alex Bloom[1]

[1]AviadoBio Ltd, 20 Water Street, London E14 5GX, UK; [2]UK Dementia Research Institute, Maurice Wohl Clinical Neuroscience Institute, 5 Cutcombe Road, King's College London, SE5 9RT, UK

AVIADOBIO

Poster #9005

Tuesday-0045

OBJECTIVE

- **To develop a potent, durable and well-tolerated intravenous gene therapy targeting MAPT for the treatment of Alzheimer's disease and other tauopathies, using the vMiX™ platform.**
- **Translational validation spans from *in vitro* miRNA screening through in vivo rodent studies.**

INTRODUCTION

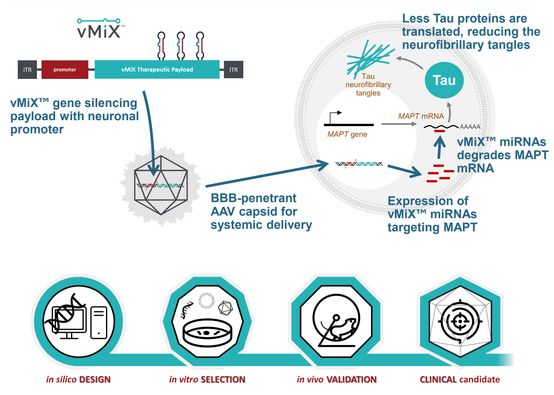
- Tauopathies, including Alzheimer's disease, drive significant global burden with very limited disease-modifying therapies
- Tau pathology correlates more strongly with cognitive decline than amyloid, making MAPT a compelling therapeutic target[1]
- Preclinical MAPT gene silencing shows therapeutic potential across tauopathies, with clinical validation from MAPT ASO trials[2,3]
- Established biomarkers, diagnostic processes and clinical endpoints support a tractable development pathway

AVB-406: An investigational gene therapy

A one-time RNAi gene silencing

- vMiX™ decouples miRNA and mRNA processing at polyadenylation, preventing pathway competition and enhancing silencing potency
- Pol II-based design enables tissue/cell-specific promoter usage for precise expression control
- Multiple miRNA hairpins within a single payload allow enhanced, dose-dependent target knockdown
- AVB-406 combines the vMiX™ payload with a BBB-crossing TfR1-targeting capsid (CapX) for intravenous CNS delivery

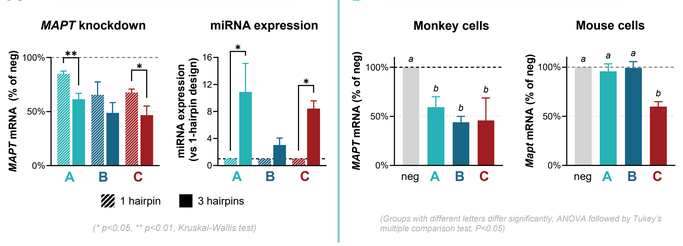
Figure 1: AVB-406: payload design and development pipeline



Identification of a lead miRNA candidate

- 1,039 potential miRNA target sites identified across all tau isoforms via *in silico* analysis
- 30 candidates selected for comprehensive in vitro evaluation, assessing knockdown potency, hairpin processing fidelity and strand loading
- Three lead miRNA candidates advanced to cross-species activity testing and multi-hairpin configuration optimisation

Figure 2: Three-hairpin configuration enhances knockdown and confirms miR-C as lead candidate with cross-species activity



(A) *Plasmid transfection in Kelly cells.* ***(B)*** *Plasmid transfection in COS-7 (monkey) and N2a (mouse) cells. MAPT expression level and miRNA expression analysed by RT-dPCR. Data shown represent mean ± SD.*

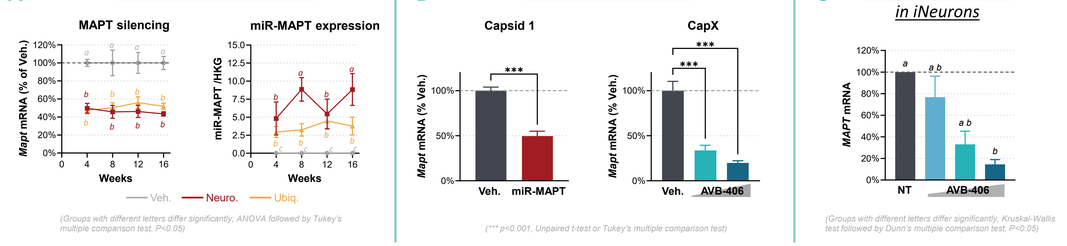
A. 3-hairpin configuration significantly enhances *MAPT* knockdown and miRNA expression versus single-hairpin design

B. miR-C demonstrates cross-species activity in mouse cells, supporting its selection as lead candidate

From components to candidate: promoter and capsid validation

- *In vitro*, neuron-specific and ubiquitous promoters show equivalent silencing potency across MOIs in iPSC-derived neurons
- CapX binds exclusively to the human form of TfR1, enabling receptor-mediated transcytosis across the BBB[4] with AAV9-like manufacturability
- TfR1 is the most extensively characterised BBB receptor[4] and has been clinically validated[5]
- Extensive CNS biodistribution with up to 80% transduction across the cortex, including neurons and astrocytes.

Figure 3: AVB-406 optimisation: neuron-specific promoter and CapX selected for clinical development based on safety and superior *in vivo* performance



(A) *Wild-type mice (C57Bl/6) administered IV with vehicle or AAV, surrogate BBB-penetrating capsid (Capsid 1), single dose; samples collected at 4, 8, 12 and 16 weeks.* ***(B)*** *Wild-type (Capsid 1) or hTfR1 (CapX) mice administered IV with vehicle or AAV; samples collected 4 weeks post-dose. (C) iPSC-derived neurons transduced with AVB-406. Data shown represent mean ± SD.*

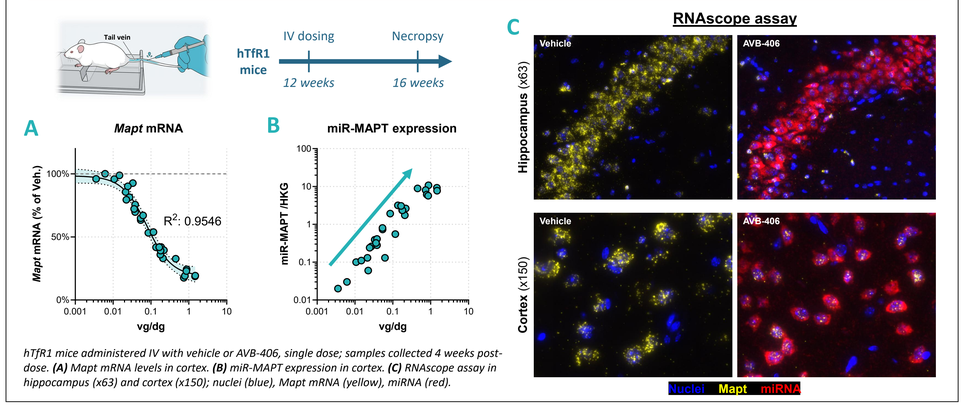
A. Neuron-specific and ubiquitous promoters show equivalent silencing potency in vivo, supporting selection of the neuron-specific promoter for its better IV safety profile

B. CapX delivers better *Mapt* knockdown in vivo than Capsid 1 (-80% vs -50%), driven by a higher proportion of transduced neurons

C. CapX combined with the neuron-specific promoter achieves robust *MAPT* silencing in iPSC-derived human neurons

AVB-406 in action: one IV dose, potent brain-wide MAPT reduction

Figure 4: AVB-406 in vivo, dose-response and target engagement



hTfR1 mice administered IV with vehicle or AVB-406, single dose; samples collected 4 weeks post-dose. ***(A)*** *Mapt mRNA levels in cortex.* ***(B)*** *miR-MAPT expression in cortex.* ***(C)*** *RNAscope assay in hippocampus (x63) and cortex (x150); nuclei (blue), Mapt mRNA (yellow), miRNA (red).*

A. AVB-406 achieves robust, dose-dependent cortical *Mapt* mRNA knockdown after a single IV dose, with an IC_{50} lower than 1 vg/dg

B. miR-MAPT expression increases linearly with dose, confirming predictable and dose-proportional transgene expression

C. Silencing and miRNA expression are confined to neurons, confirming neuron-selective target engagement in vivo

CONCLUSIONS

- miR-C selected as lead candidate, demonstrating potent and cross-species MAPT knockdown in human and mouse cells
- Neuron-specific promoter selected to restrict transgene expression to neurons, reducing off-target tissue exposure following IV administration
- CapX selected as the BBB-crossing capsid, delivering superior in vivo *Mapt* knockdown compared to Capsid 1
- AVB-406 demonstrates robust, durable and dose-dependent MAPT knockdown after a single IV injection, achieving up to 80% cortical knockdown (see **Poster #8707**)
- Manufacturing scalability confirmed, with CapX achieving consistent target knockdown at bioreactor scale

➢ **AVB-406 is positioned for clinical study initiation in 2026**

REFERENCES: [1]Congdon EE & Sigurdsson EM. Nat Rev Neurol. 2018;14(7):399–415. [2]Mummery CJ, et al. Nat Med. 2023;29(6):1437–1447. [3]Shulman M, et al. Nat Aging. 2026;6(2):445–453. [4]Pardridge WM & Chou T. Pharmaceuticals. 2021;14(6):535. [5]AVLAYAH. FDA summary of prescribing information. 2026.

ABBREVIATIONS: AAV – adeno-associated virus, BBB – Blood-brain barrier, CapX – hTfR1-targeting AAV capsid, CNS – central nervous system, dg – diploid genome, FDA – Food and Drug Administration, hTfR1 – human Transferrin receptor 1, IC50 – half-maximum inhibitory concentration, IND – Investigation New Drug, iPSC – induced pluripotent stem cell, IV – intravenous, MAPT – microtubule-associated protein tau, miR/miRNA – microRNA, MOI – Multiplicity of infection, RNAi – RNA interference, RT-dPCR – Reverse transcription digital PCR, vg – vector genomes

ACKNOWLEDGMENTS & DISCLOSURES: This study was funded by AviadoBio Ltd. RJ, MLR, DOC, GK, LSB, DO, MES, RE, CA, ED, AM, MM, PB, AU, CM, CS, JI, and AB are employees and shareholders of AviadoBio Ltd. BM, NAM, and CS are employees of King's College London. RJ, MLR, CS, JI, AB are named in patents related to vMiX™ or AVB-406. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE).