Preclinical Development Of AVB-406: An Intravenous AAV-miRNA Achieving Sustained *MAPT Kn*ockdown To Treat Alzheimer's Disease

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INTRODUCTION

- Tau has emerged as a key biomarker and therapeutic target in AD and other tauopathies as it plays a central role in disease pathophysiology, progression, and clinical manifestations[1]
- Extensive preclinical data support therapeutic potential of MAPT gene silencing across tauopathies, including AD and FTD
- Dysfunctional tau more strongly correlated with functional decline than Ab plaques[2]
- MAPT ASO Ph1/2 clinical trial shows generally well-tolerated safety and reduction in pathological tau[3,4]
- AVB-406 is being developed as a one-time *MAPT* gene therapy approach for the treatment of AD and other tauopathies

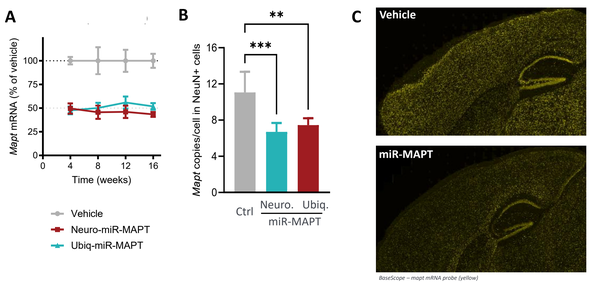
METHODS

- Animal studies conducted in wild-type and P301S mice used a surrogate AAV blood-brain-barrier (BBB) crossing capsid expressing miR-MAPT (identical genome to AVB-406)
- Studies were conducted in B-hTFR1 mice using the CapX BBB crossing capsid expressing miR-MAPT (AVB-406)
- CapX is a human TFR1 targeting capsid which has broad CNS transduction after iv delivery[5,6]
- Mice were monitored in life for any adverse symptoms and were weighed weekly.
- CNS tissue was analysed for vector genomes (Vg) and levels of mRNA expression
- *In situ* hybridisation (ISH) was conducted to determine cell-specific miR guide expression, level of *Mapt* expression and co-localisation with NeuN staining
- Immunohistochemistry for AT8 staining was performed in the P301S mice to identify the level of p-Tau post-vector administration
- The level of total tau in the P301S mice after vector administration was determined using the Jess Automated Western Blot system.

RESULTS

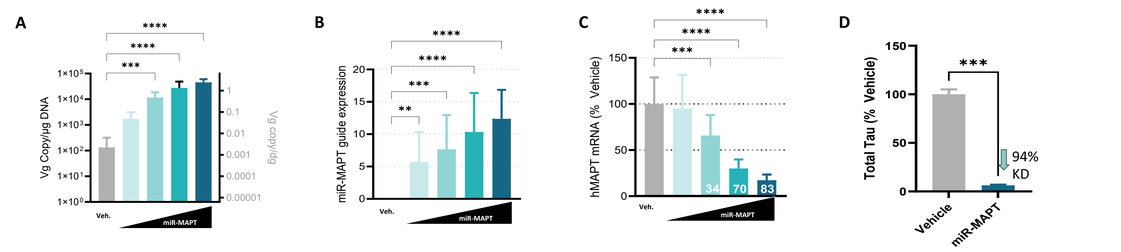
- AAV-miR-MAPT demonstrated robust (~50%) and sustained (out to 16 weeks, study endpoint) knockdown of *Mapt* with both a ubiquitous and CNS-specific promoter in mice (**Figure 1**). Neuronal promoter was selected for further development.
- In the P301S mouse model of tauopathy, AAV-miR-MAPT showed a dose-response in Vg, miR guide expression and knockdown of *MAPT* (>80%.at the highest dose). Strong reduction in total tau was shown at the highest dose (>90%) (**Figure 2**).
- IHC for p-tau (AT8 staining) showed a robust reduction in p-tau at all four doses of AAV-miR-MAPT tested (>90%) (**Figure 3**)
- In the hTFR1 mouse model AVB-406 showed broad distribution across the brain and strong knockdown of *Mapt* in the cortex and hippocampus (~75%) (**Figure 4**)
- AVB-406 showed a strong dose-response in both Vg and knockdown of *Mapt* (**Figure 5**)
- Analysis of biodistribution showed the highest Vg in the CNS with lower levels detected in peripheral tissues including the liver (**Figure 5**)

Figure 1: AAV-miR-MAPT drives sustained *Mapt* knockdown.



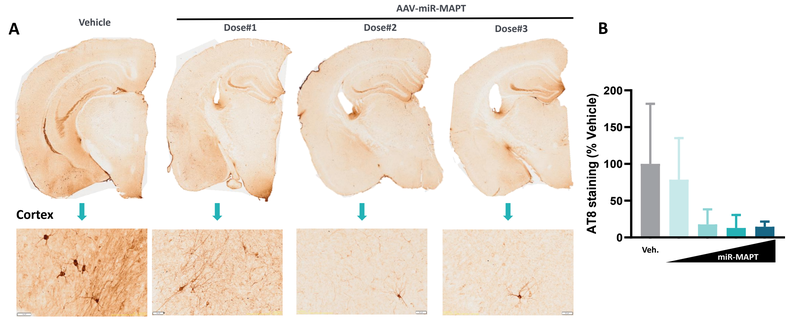
*Wild type mice (C57Bl/6, adult); N= 6 males per dose group; Surrogate BBB-penetrating capsid single IV dose; data shows as mean ± SD; **p<0.01; *** p<0.001. Neuro – Neuronal promoter; Ubiq. – Ubiquitous promoter.* **A.** *Mapt* levels in cortex; **B.** *Mapt* copies in NeuN+ cells; **C.** ISH for *Mapt* in cortex

Figure 2: AAV-miR-MAPT results in a dose-dependent knockdown of MAPT/Tau in P301S mouse model.



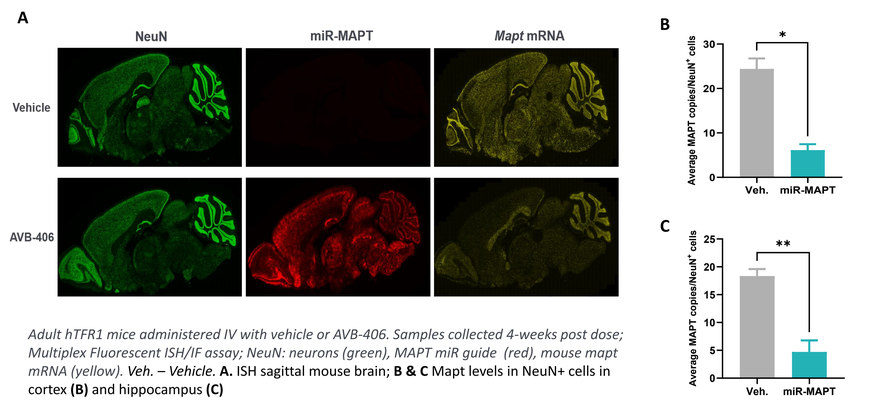
*3-month old B6;C3-Tg(Prnp-MAPT*P301S)PS19Vle/J mice administered IV with vehicle or AAV-miR-MAPT (surrogate capsid). Samples collected 8-weeks post dose; N= 16 (8 males and 8 females) per dose group; Data shown represent mean ± SD; *p<0.05; **p<0.01, ***p<0.001; ****p<0.0001; IHC male cohort only. Veh. – Vehicle.*
A Vector genomes; **B** Guide expression; **C** MAPT levels and **D** Total Tau in the cortex

Figure 3: AAV-miR-MAPT reduces phospho-Tau in P301S mouse model of tauopathy



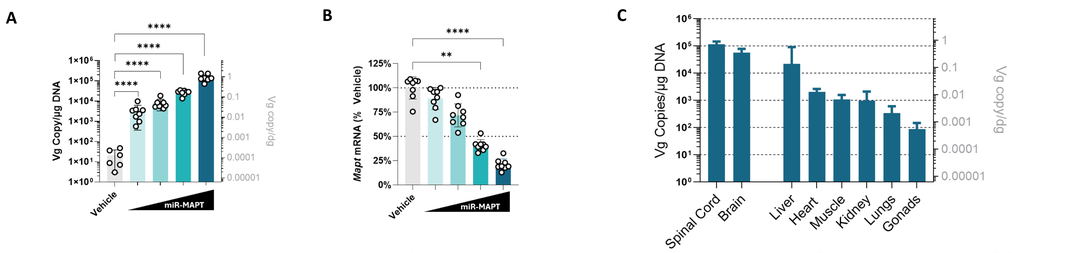
*3-month old B6;C3-Tg(Prnp-MAPT*P301S)PS19Vle/J mice administered IV with vehicle or AAV-miR-MAPT (surrogate capsid). Samples collected 8-weeks post dose; N= 16 (equal number males and females) per dose group; Data shown represent mean ± SD; *p<0.05; **p<0.01, ***p<0.001; ****p<0.0001; IHC male cohort only. WT – Wild type mice* ***A*** *AT8 IHC for p-Tau* ***B*** *Quantification of level of p-tau in treated mice as a percentage of vehicle.*

Figure 4: AVB-406 administration results in widespread reduction of *mapt* mRNA in the 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. **A.** ISH sagittal mouse brain; **B & C** Mapt levels in NeuN+ cells in cortex **(B)** and hippocampus **(C)**

Figure 5: AVB-406 shows a clear dose-response in *Mapt* knockdown with reduced peripheral tissue exposure



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. **A** Vg in the cortex. **B** *Mapt* levels in the cortex. **C** Vg in CNS and peripheral tissues .

CONCLUSIONS

- **AVB-406 is a potential one-time AAV gene therapy for tauopathies including Alzheimer's disease**
- **AVB-406 results in robust and sustained MAPT knockdown in mice**
- **Strong reduction in p-tau pathology in P301S tauopathy model is achieved with AVB-406 administration**
- **AVB-406 has a CNS selective biodistribution with 10--100 higher levels in CNS compared to peripheral tissues**
- **AVB-406 has been well-tolerated in all animal studies conducted to date**
- **A GLP toxicology study of AVB-406 is ongoing**

REFERENCES: 1. Frost et al, Alzheimer's & Dementia 2025, 2. Pluta and Ulamek-Kozol Alzheimer's Disease: Drug Discovery, 2020, 3. Mummery et al., Nature Med (2023), 4. Shulman et al., Nature Aging (2025), 5. Huang *et al., Science 2024, 5. Apertura Gene Therapy*

ABBREVIATIONS: AAV – adeno-associated virus, CNS – central nervous system, IHC – immunohistochemistry, ISH – in situ hybridisation, i.v. – intravenous, MAPT – microtubule-associated protein tau, miR – microRNA, Vg – vector genomes

ACKNOWLEDGMENTS & DISCLOSURES: This study was funded by AviadoBio Ltd. DOC, ED, AE, ZW, AA, GK, MD, AM, MS, JKS, GL, DD, DC, PB, RJ, AB, JI and CM are employees and shareholders of AviadoBio Ltd. BM, NM, JY, QA, CS are employees of KCL.. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE).