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 and other tauopathies

Deirdre O'Connor | Director, *In vivo* Pharmacology, AviadoBio | 29th October, 2026

Disclosures

- Deirdre O'Connor 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

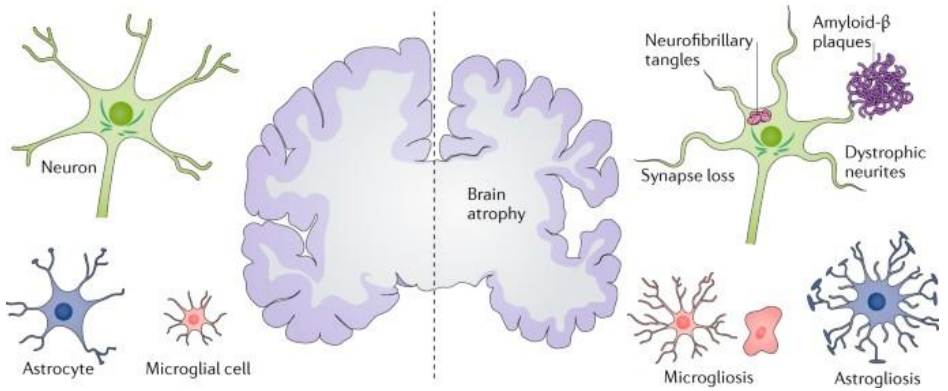
Established disease biology

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**[3]

Extensive preclinical data support **therapeutic potential of MAPT gene silencing** across tauopathies, including AD[4]

The defining pathological hallmarks of Alzheimer disease[1]



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

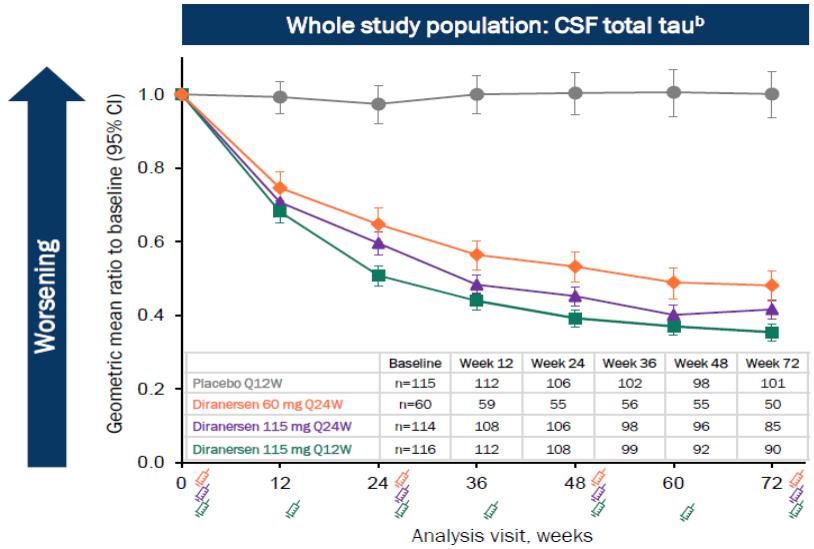
De-risked tractable clinical development

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 Ph2 clinical trial shows a dose dependent reduction in CSF t-tau and slowing of cognitive decline[5,6]

Ability to move into other tauopathies with established natural history



Mummery *et al., 2026*

[1]Congdon & Sigurdsson, Nat Rev Neurol (2018); [2]Congdon et al., Nat Rev Neurol (2023); [3]Pluta and Ulamek-Koziol, 2020, [4]DeVos et al., 2017 [5]Mummery et al., (2026); [6]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

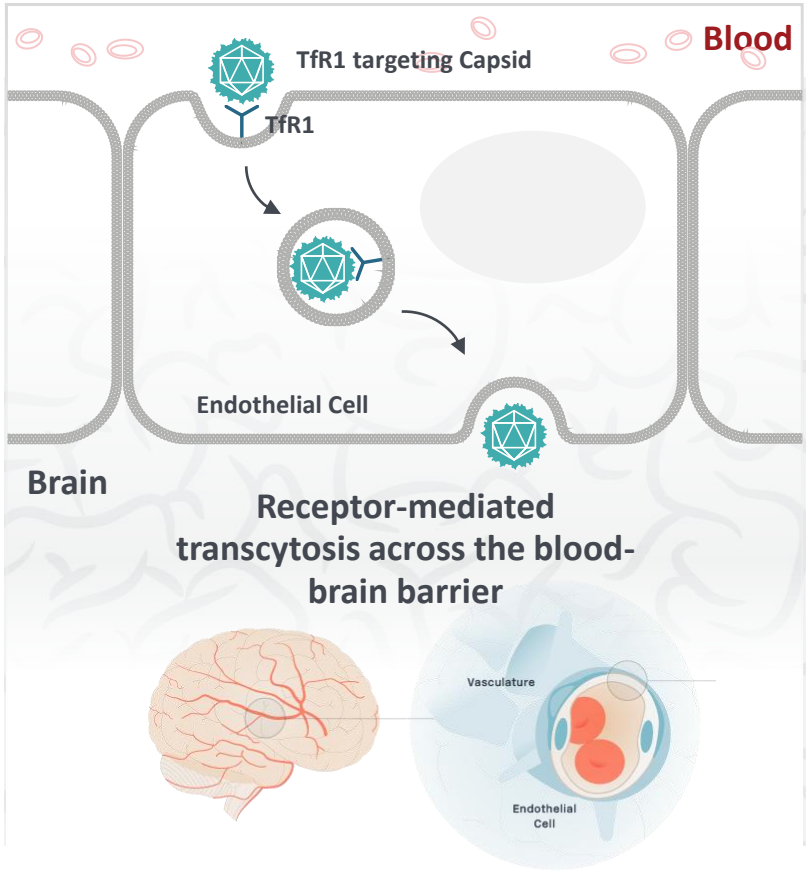


vMiX™ a one-time RNA silencing platform engineered for best-in-class specificity, potency, and neuron-selective regulation.

DELIVERY

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

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

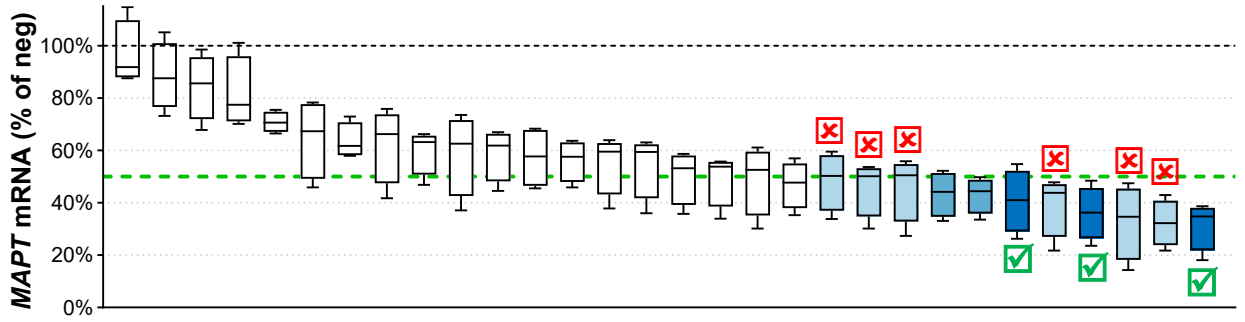
[1]Huang et al., Science 2024; [2]Apertura Gene Therapy.

vMiX™ platform identified miR sequences through systematic screening

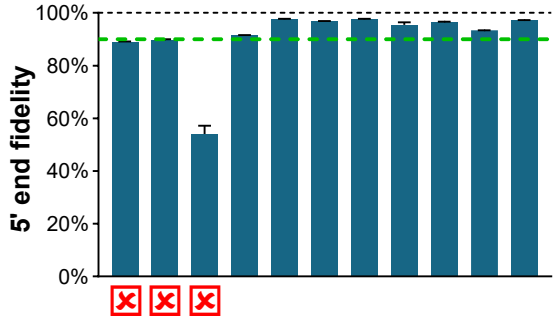
MAPT miRNA screening

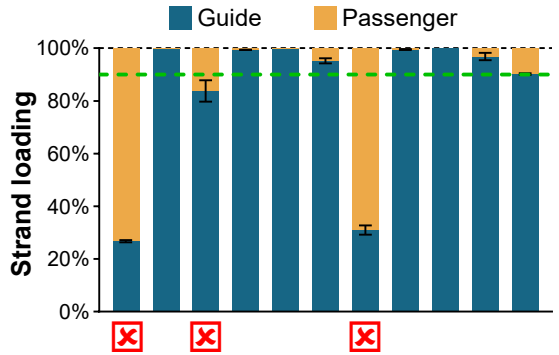
Goal: identify the best miRNAs from 30 candidates

- *in vitro*: miRNA plasmid transfection

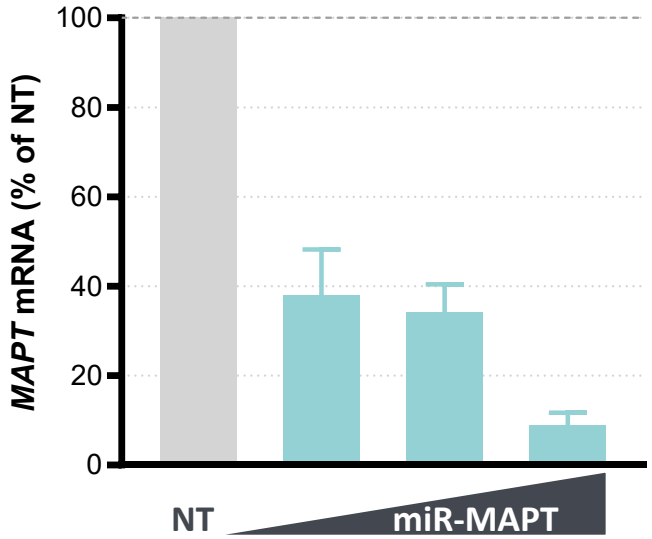


- miRNA hairpin processing





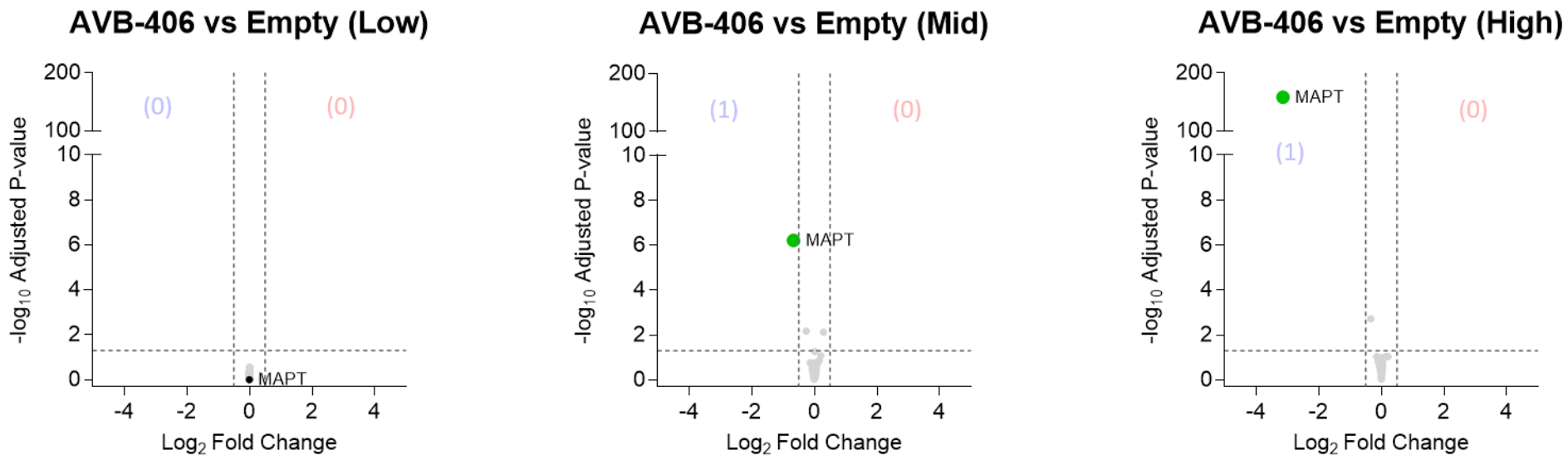
Human glutamatergic neurons



Dose-dependent knockdown in iPSC-derived glutamatergic neurons. 96 well plate; 7 days post transduction. NT– Non-transduced.

miR-MAPT-TA35 target specificity in human iPSC-derived neurons: low off-target risk confirmed *in vitro*

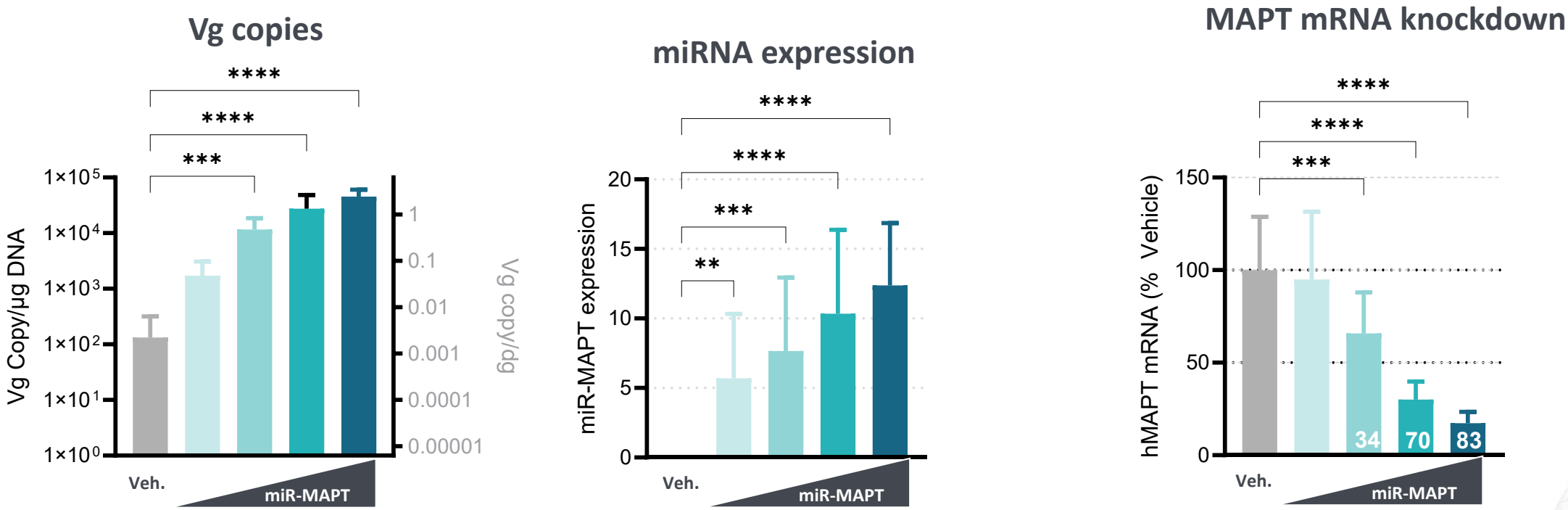
iPSC-derived Glutamatergic neurons, N=3/group; AVB-406 vs dose-matched vMiX-empty at three MOIs; polyA-RNA-seq. Thresholds: adj. p<0.05, $|log_2FC|>0.5$.



- 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.

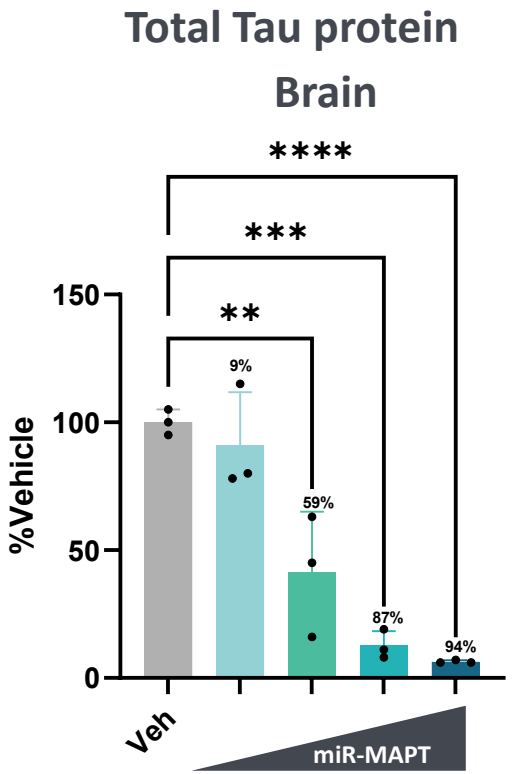
Poster #0070 ***Silencing of MAPT via AVB-406 in human iPSC-derived neurons: a translational framework for neurodegenerative diseases*** **— Martina Esposito Soccoio**

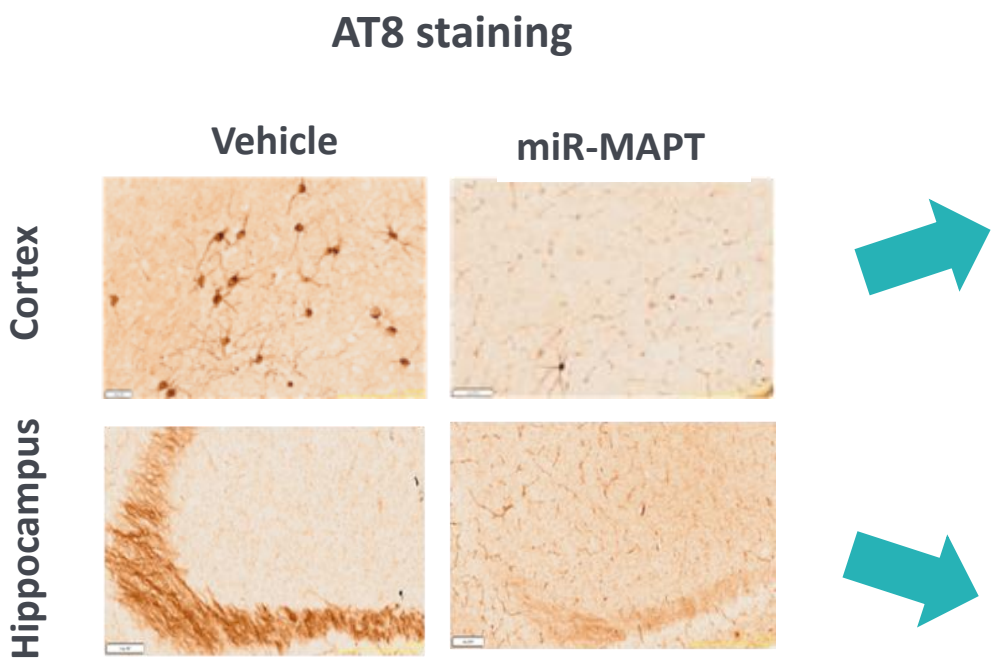
AAV-miRNA-MAPT results in a dose dependent MAPT knockdown in P301S mice

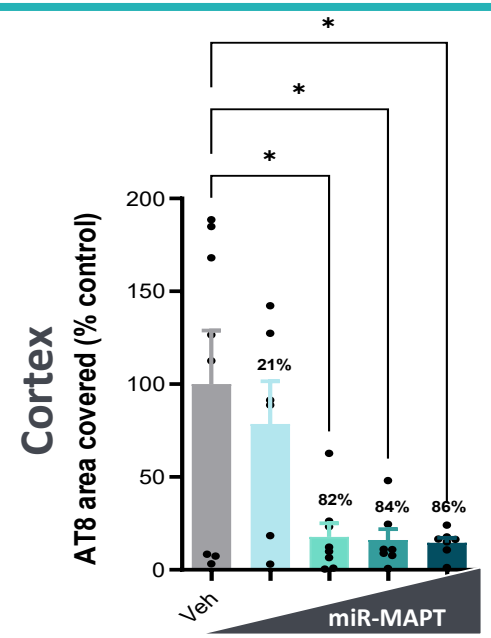


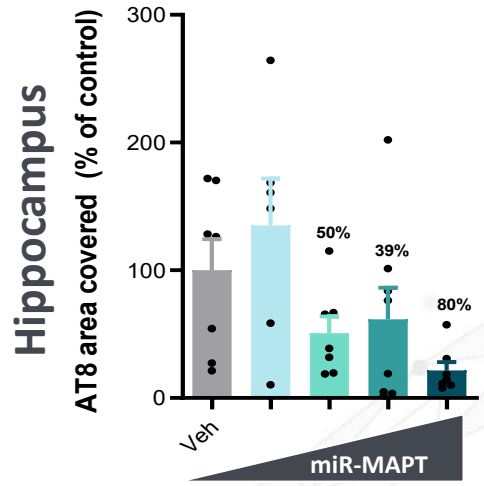
*3-month old B6;C3-Tg(Prnp-MAPT*P301S)PS19Vle/J mice administered IV with vehicle or AAV-miR-MAPT (surrogate capsid). Samples collected 8-weeks post dose; N= 16 (8 males and 8 females) per dose group; Data shown represent mean ± SD; *p<0.05; **p<0.01, ***p<0.001; ****p<0.0001; IHC male cohort only. Veh.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

AAV-miR-MAPT results in a dose-dependent reduction of total tau in the brain and AT8 tau pathology in cortex and hippocampus of P301S mice



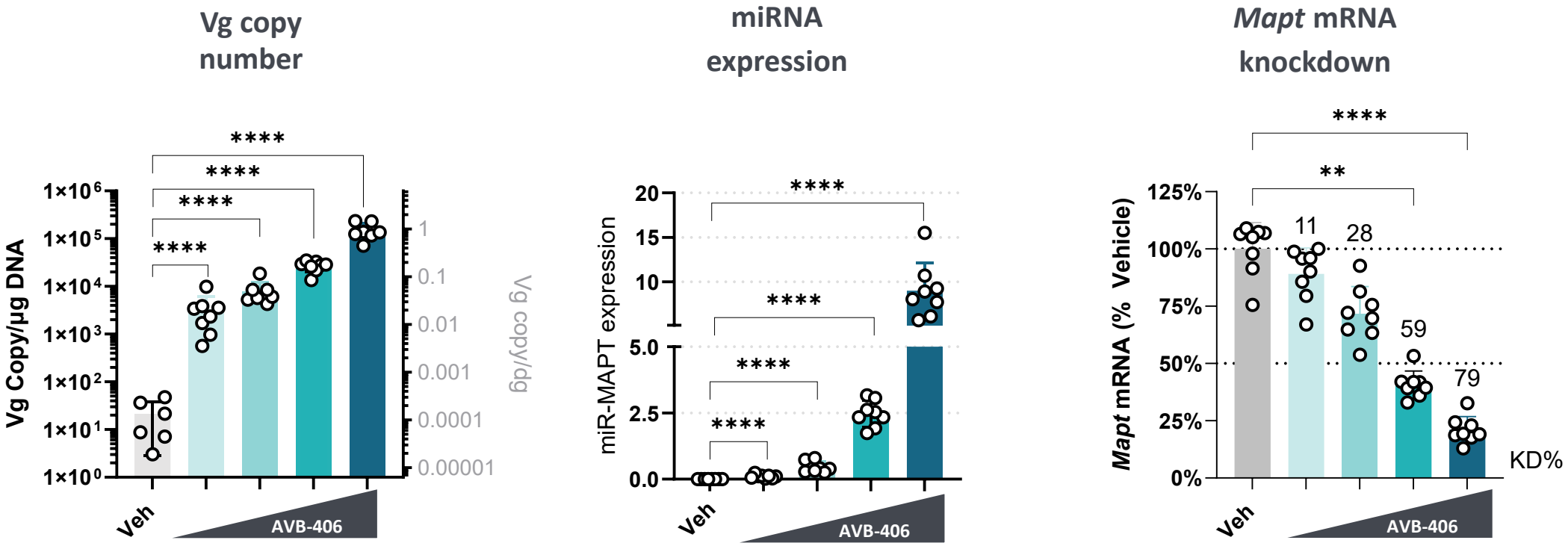






*3-month old B6;C3-Tg(Prnp-MAPT*P301S)PS19Vle/J mice administered IV with vehicle or AAV-miR-MAPT (surrogate capsid). Samples collected 8-weeks post dose;AT8 counts were performed in Lower cortex (cortex) and CA2-CA3 hippocampus (hippocampus), N= 6-8 data shown represent mean ± SD; *p<0.05; **p<0.01, ***p<0.001; ****p<0.0001; IHC male cohort only*

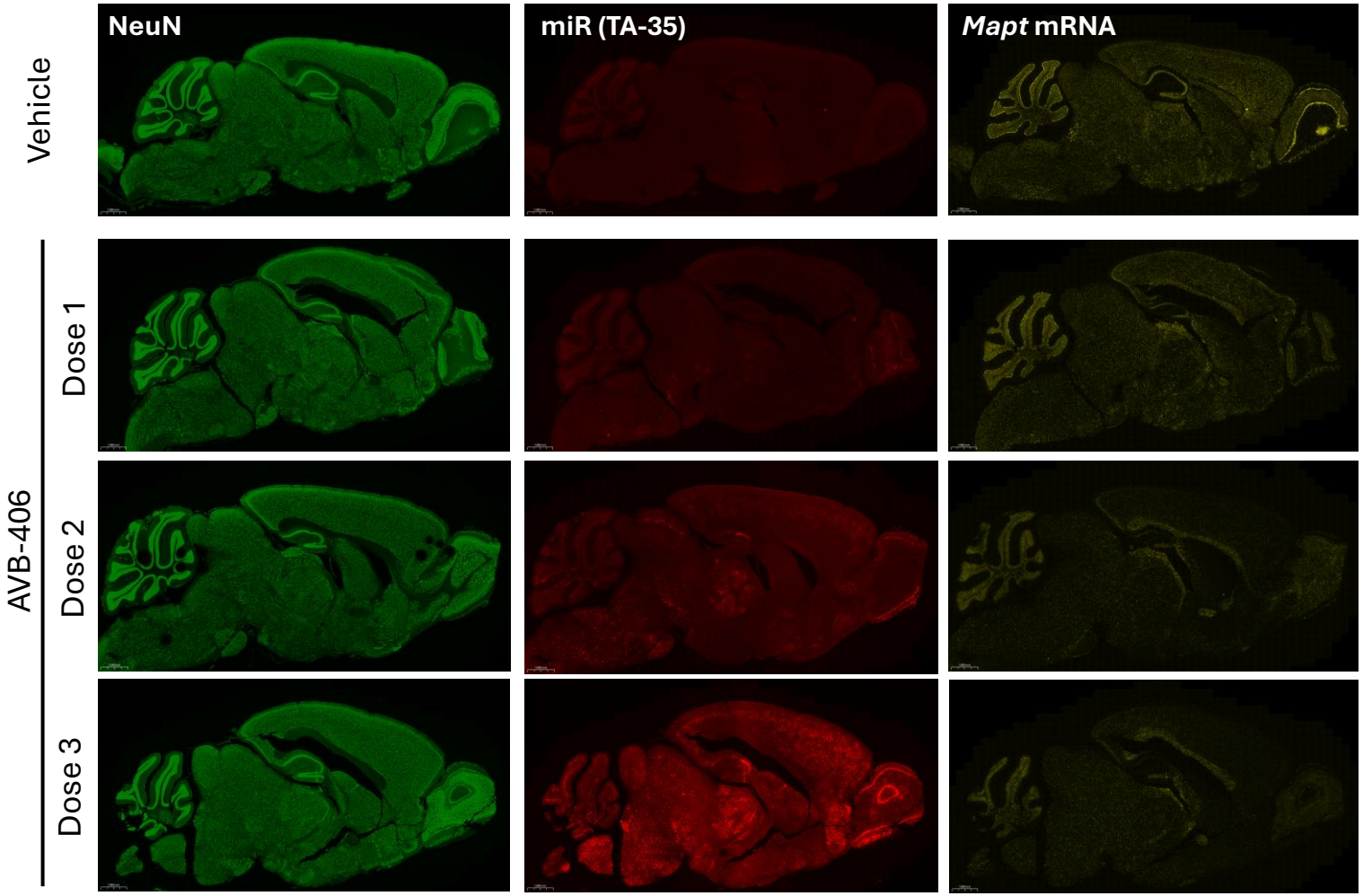
In a dose-range finding study in B-hTFR1 mice, a single IV dose of AVB-406 drives dose-dependent transduction, miRNA expression, and MAPT knockdown in the brain



miR-MAPT expression was not detected in peripheral tissues – expression restricted to the CNS

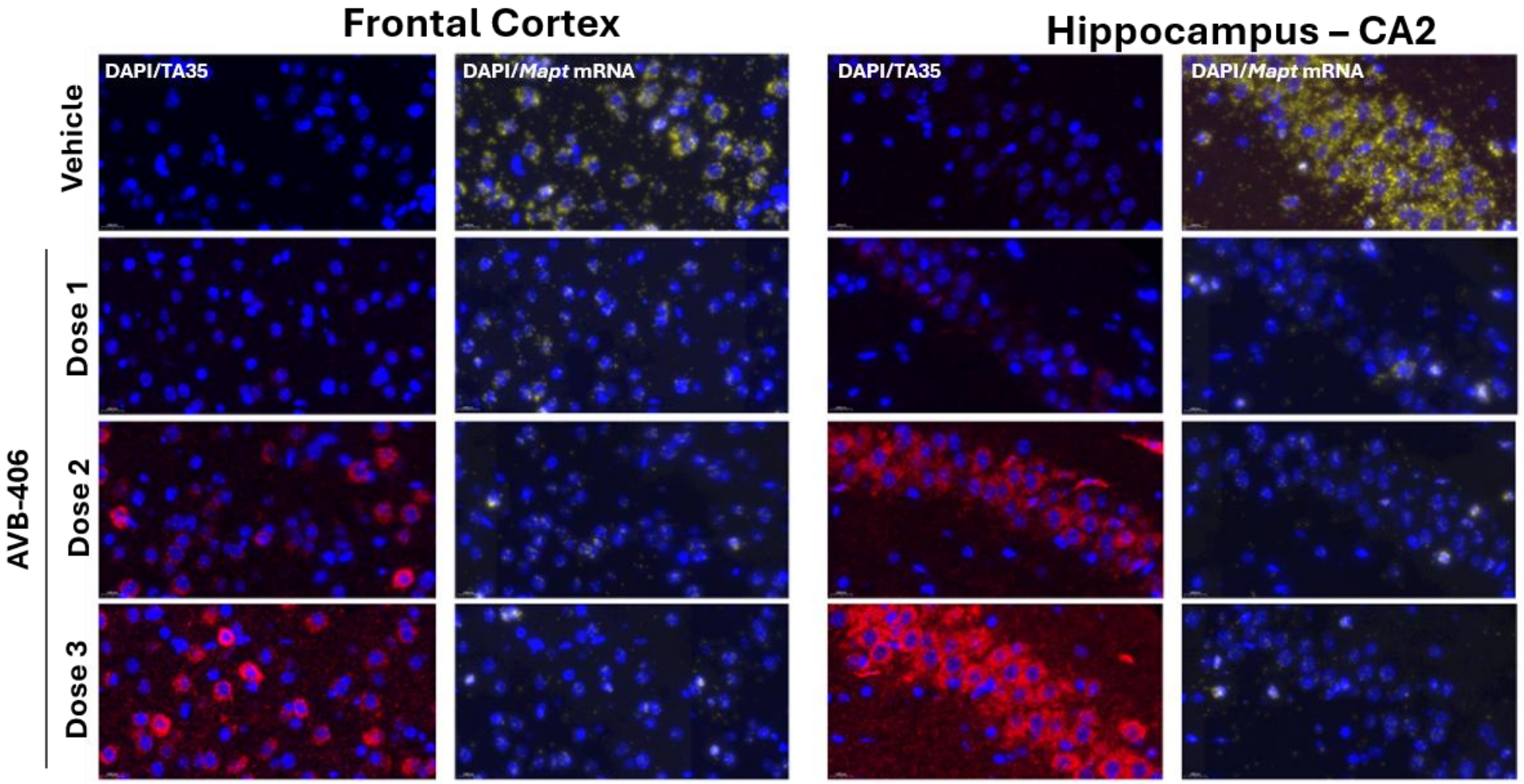
*Adult B-hTFR1 mice administered IV with vehicle (P120) or AVB-406; N = 8 (4 males, 4 females) per group. Data shown as mean ± SD. No data points were excluded from analysis. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.*

Dose-dependent miR-MAPT-TA35 expression and *Mapt* mRNA knockdown across the 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 (yellow); Images at 1.2x magnification, scale bar 1.0 mm.

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



Representative fields from frontal cortex and hippocampal CA2

HALO analysis is ongoing

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

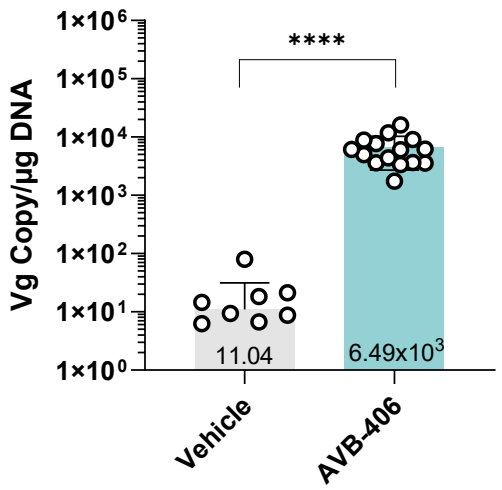
Long-term tolerability study

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

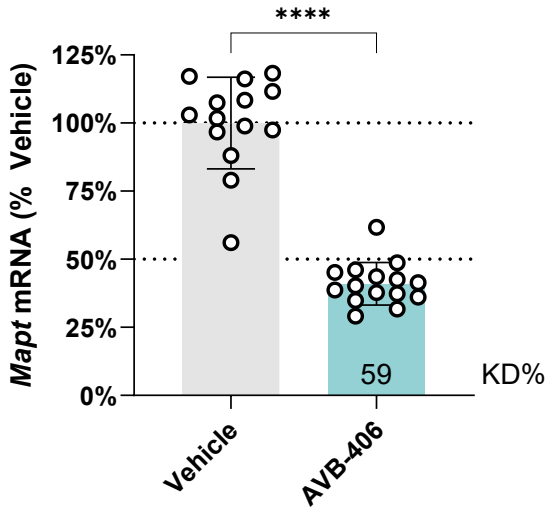
- No adverse clinical signs; body weight gain unaffected
- Functional observational battery unchanged from controls
- *Mapt* mRNA silencing and tau reduction confirmed in tissues post-sacrifice at 6 months

Durable knockdown with no in-life tolerability signal

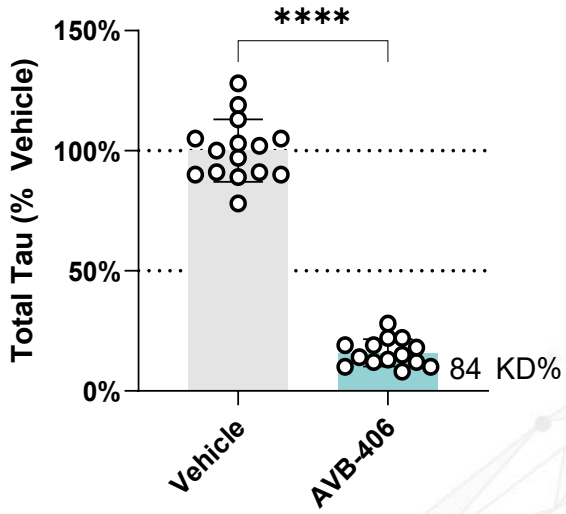
Vg copy number



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

Acknowledgments

AVIADOBIO

Discovery
Romain Joubert
Leonie Brebner
Louise Reilly
Randa Elsayed
Martina Esposito Soccoio
Deborah Ojutalayo
Catia Andreassi

Vector Sciences
Gurdeep Kooner
Amrita Abhilash
Dan Cox

Preclinical
Carlos Miranda
Deirdre O'Connor
Douglass Dey
Emily Dellow
Guillaume Lo
Anna Ettorre
Zoe Walker
Phil Coan

CMC
Andrea Martorana
Peter Boyce
Lily Li
Hawaa Cumar
Magda Sztyler
Michael MacDonald
Rebecca Lyth
Jaya Kenth-Shah
Megan Donnelly
Alex Foster
Alex Bloom

AVB-406 program team
Agnieszka Ule
Alinda Fernandes
Ana Perez
Ann Gorman
Anne-Laure Moreau
Chris Powell
Yige Huang

King's College London

Chris Shaw
Neda Ali Mohammadi
Bibiana Mota
Joshua Hei Yeung
Quwam Akinlawon

Advent Life Sciences
astellas
Dementia Discovery Fund
EQT Life Sciences
F-PRIME
Johnson&Johnson
LIFEARC VENTURES
NEA
MGC