Preclinical Assessment of BBB-Crossing Amyloid-ß Oligomer-Targeting Peptide Using PET, MRI and CSF Biomarkers

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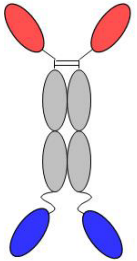
Translational Challenges

- **Animal models – translation across species (mouse, rat, dog)**
- **Design of target engagement and efficacy preclinical study that 'mirrors' typical clinical study design**
- **Use of imaging (PET, MRI) and CSF biomarkers in preclinical study**
- **Translational PK/PD modeling (small brain to large brain)**
- **Analytics that support translation**

Therapeutic Molecule (KAL-ABP-BBB)



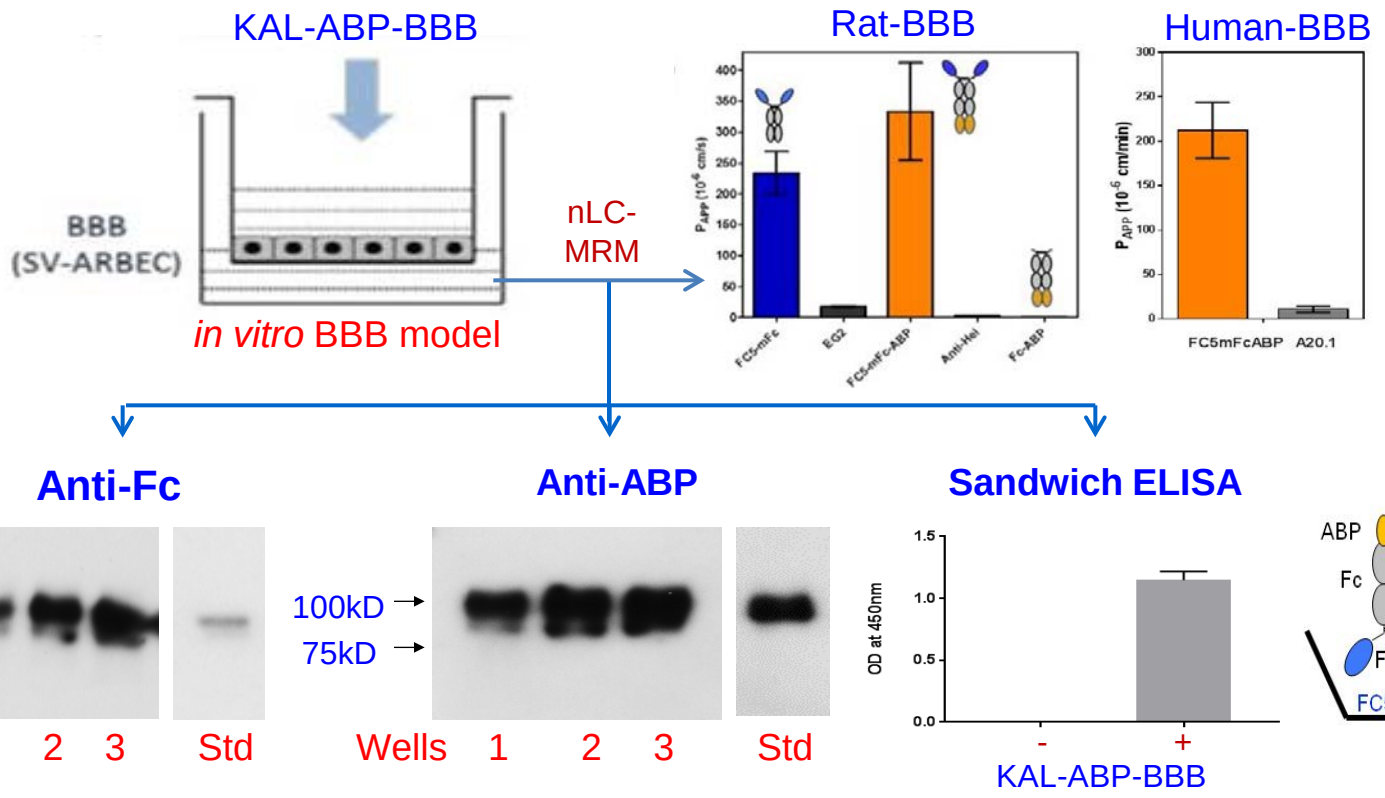
FC5 (camelid V_HH) – [15 kD]
BBB-crossing

IgG Fc fragment [50 kD]
Prolongs serum half-life;

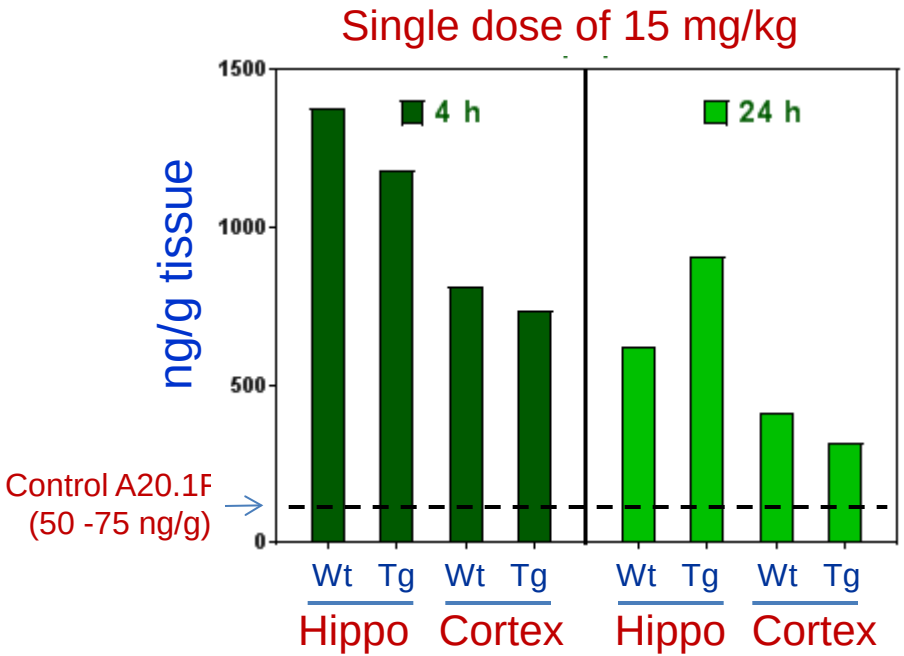
Peptide [4.5 kD]
Amyloid oligomer binding and clearance

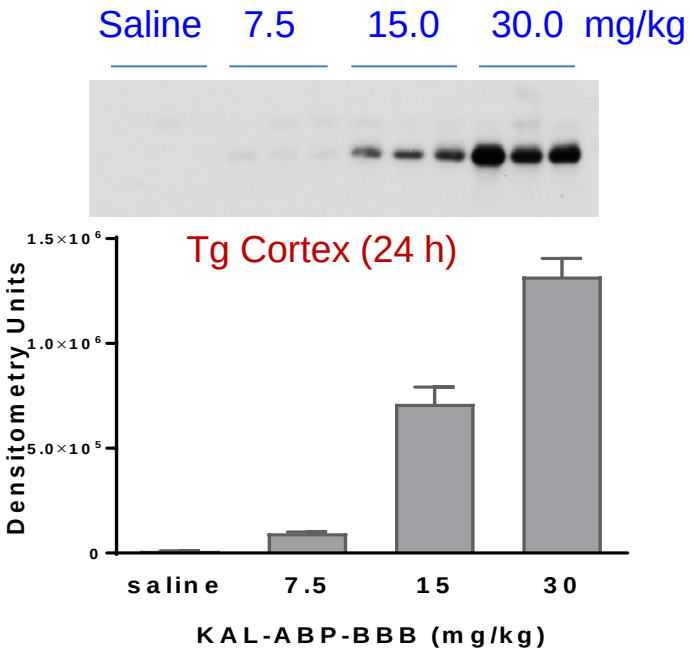
Molecule	Molecule Development	Detection (Analytics)
ABP (4 kD)	Amyloid binding regions from human PCM-1; binds **oligomeric** Aβ with nM affinity	C-terminus-specific monoclonal antibody (ELISA, WB); specific peptides for nanoLC-SRM
FC5 (13 kD)	**BBB-crossing** V_HH; species cross-reactive; humanized	FC5-specific mouse monoclonal antibody (ELISA, WB); specific peptides for nanoLC-SRM
FC5-Fc-ABP-M (90 kD)	**Surrogate molecule for rodent studies**: mouse Fc; camelid FC5	Anti-mouse Fc antibody (ELISA, WB); specific peptides for nanoLC-SRM
FC5-Fc-ABP-H (90 kD)	**Human studies**: humanized FC5, engineered human Fc	Anti-human Fc antibody (ELISA, WB); specific peptides for nanoLC-SRM

KAL-ABP-BBB crosses in vitro BBB intact



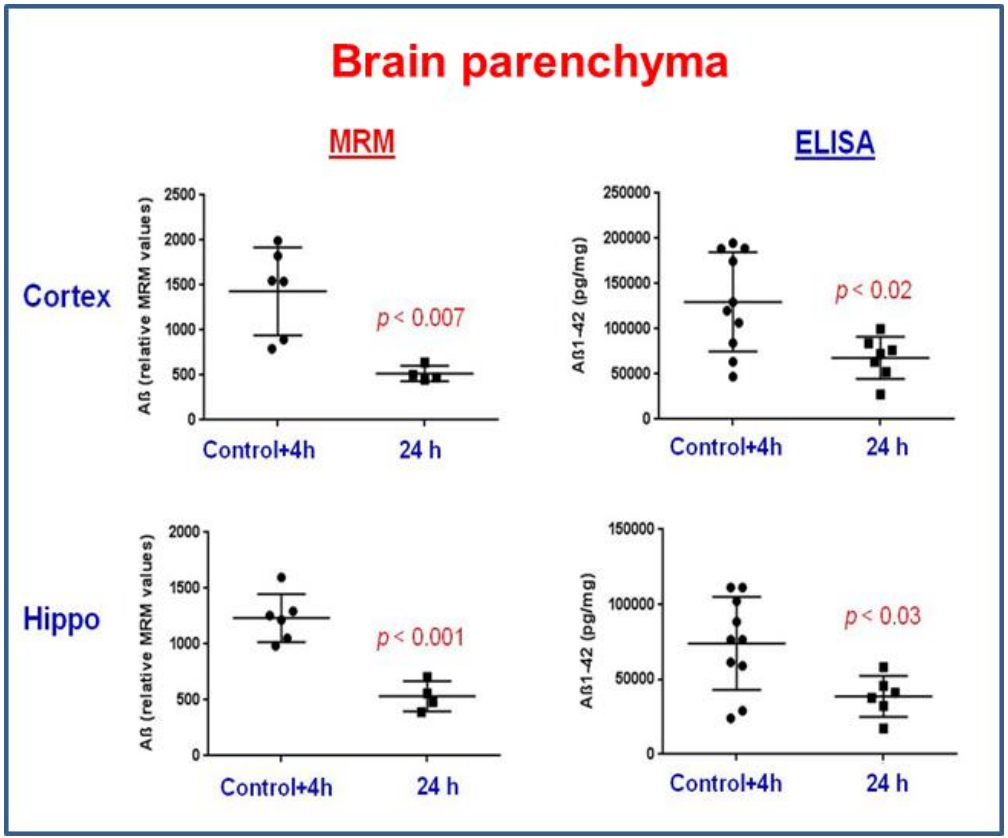
Enhanced Brain Exposure of KAL-ABP-BBB transgenic mice

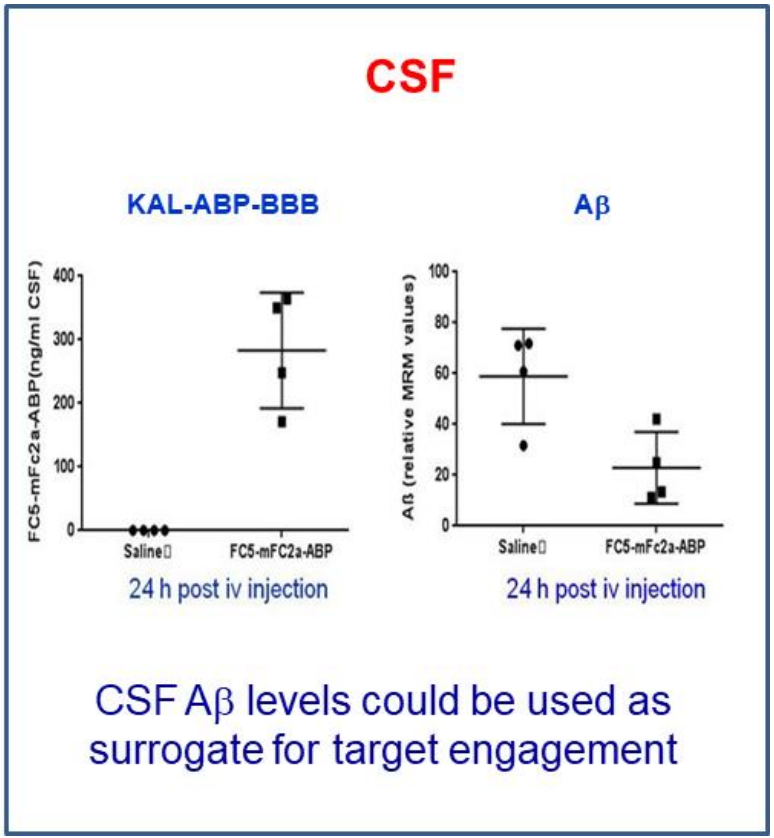




Time- and dose-dependent appearance of KAL-ABP in the tissue indicates delivery of ABP to target regions of the brain by FC5

Reduction of Amyloid-ß levels in KAL-ABP-BBB treated Tg mice

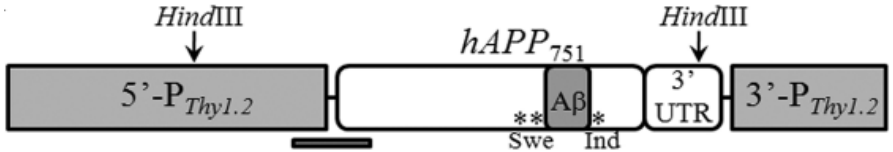


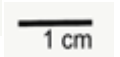


CSF Aβ levels could be used as surrogate for target engagement

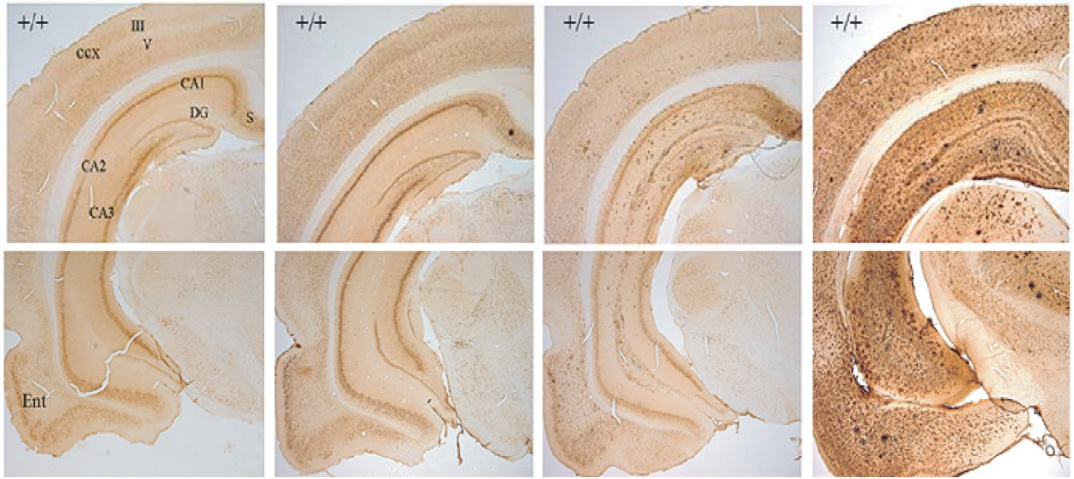
Preclinical Efficacy Study Design: Animal model

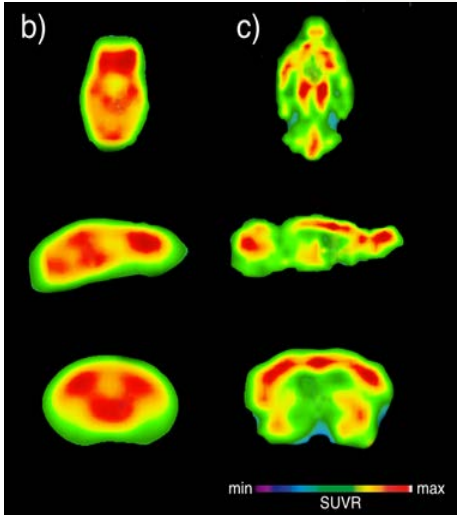
McGill-R-Thy1-APP Tg Model (Claudio Cuello)





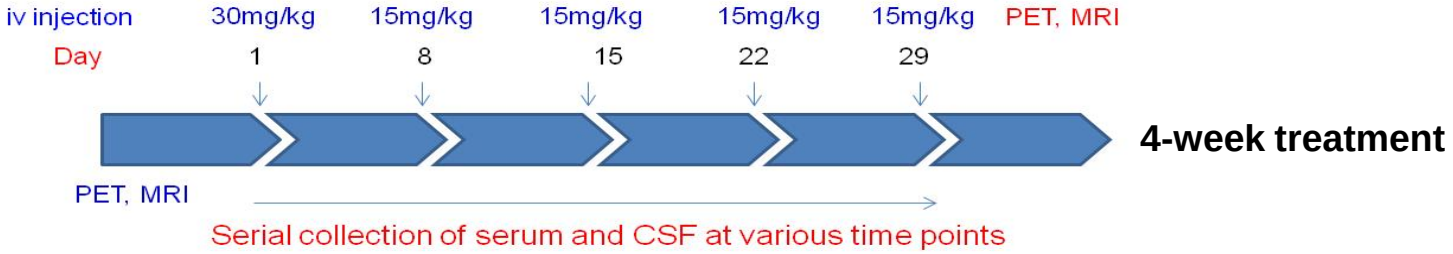
3 months 6 months 13 months 20 months



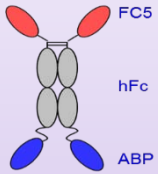


Leon *et al.*, J Alzheimers Dis 2010

Preclinical Efficacy Study Design:
Longitudinal Biomarker Assessment

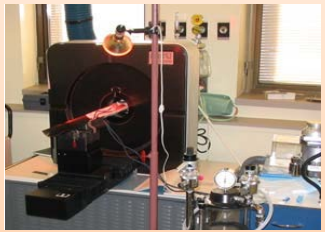


CSF/Plasma

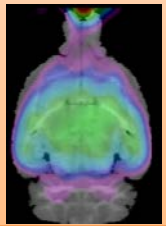


Aβ

PET



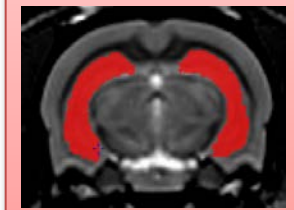
[^{18}F]NAV4694
(Aβ load)

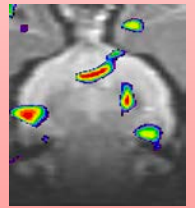


MRI

Hippocampal volume

rsfMRI

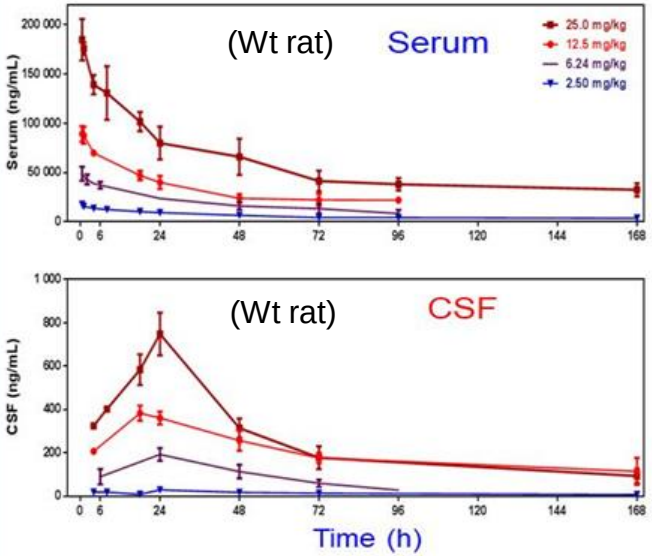




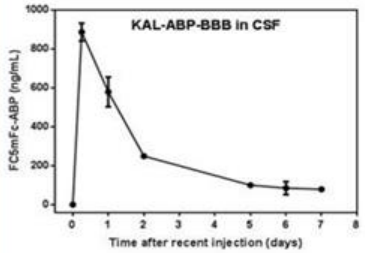
Safety: MR Susceptibility imaging

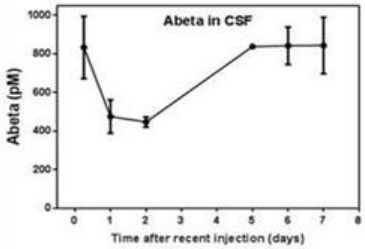
PK and CSF Biomarker (Aβ) Profile

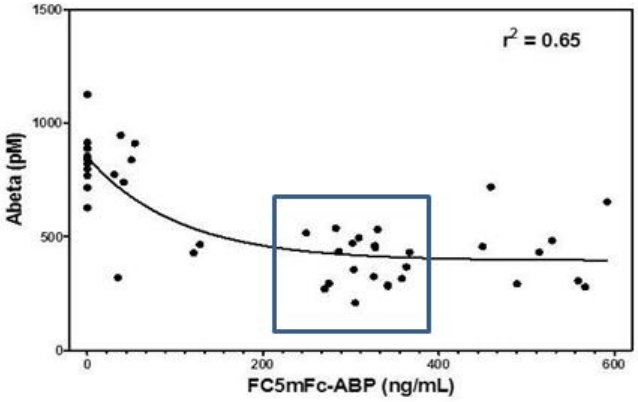
- KAL-ABP-BBB **serum PK** similar to that of a mAb
- **CSF exposure** 25-fold higher than that of a mAb



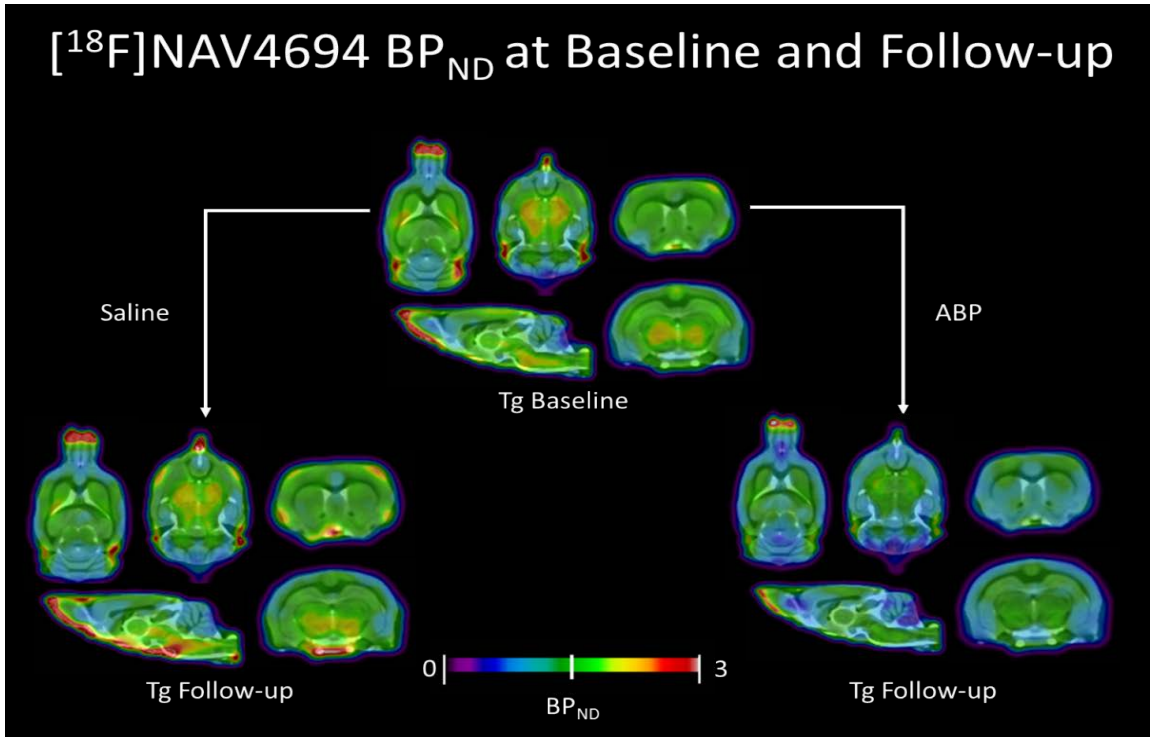
CSF levels of Aß inversely correlate with KAL-ABP-BBB levels in transgenic rats

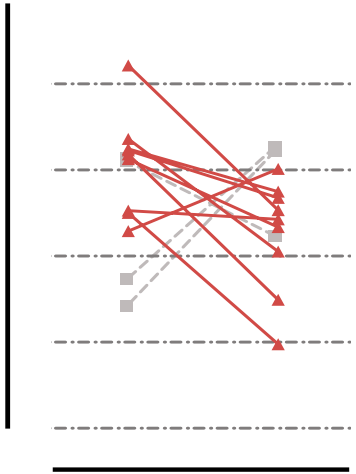






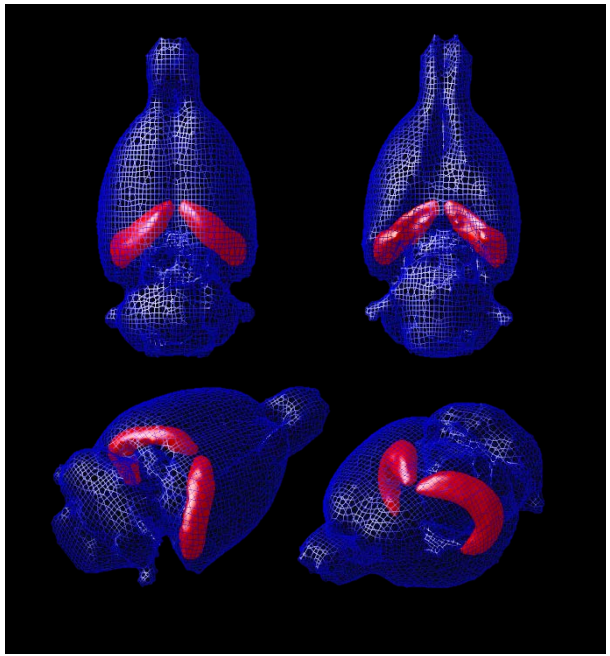
Drug Efficacy:
Aβ load is significantly reduced

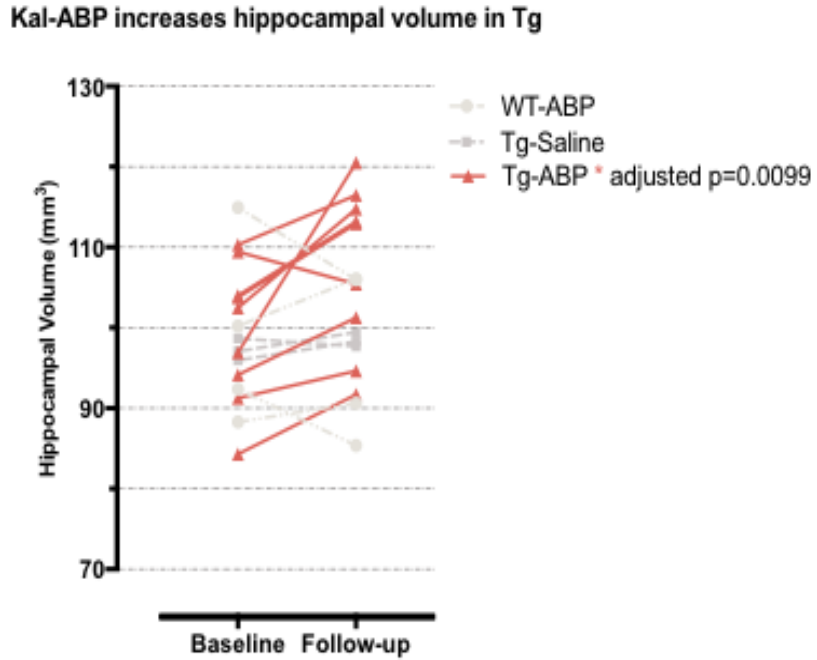




Drug Efficacy:
Hippocampal volume is increased

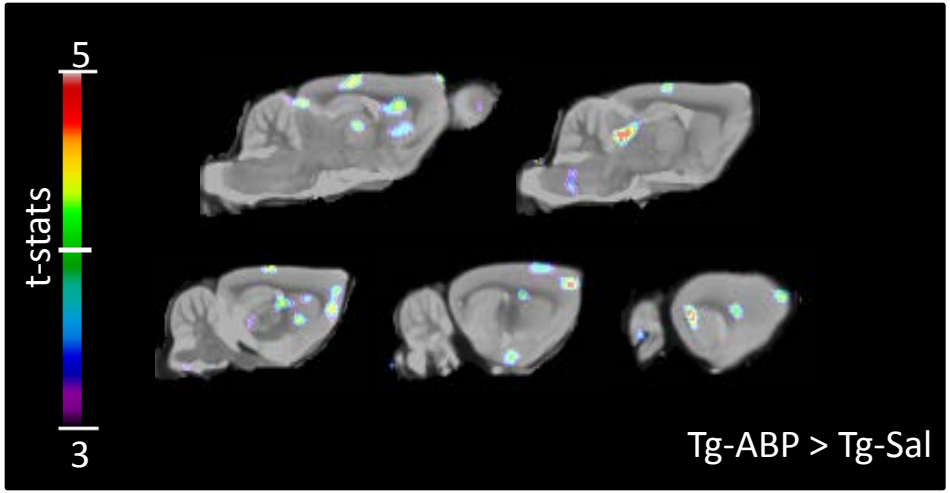
- Increased hippocampal volume only in Tg-ABP group





Secondary Drug Efficacy:
rs-fMRI ACC Connectivity

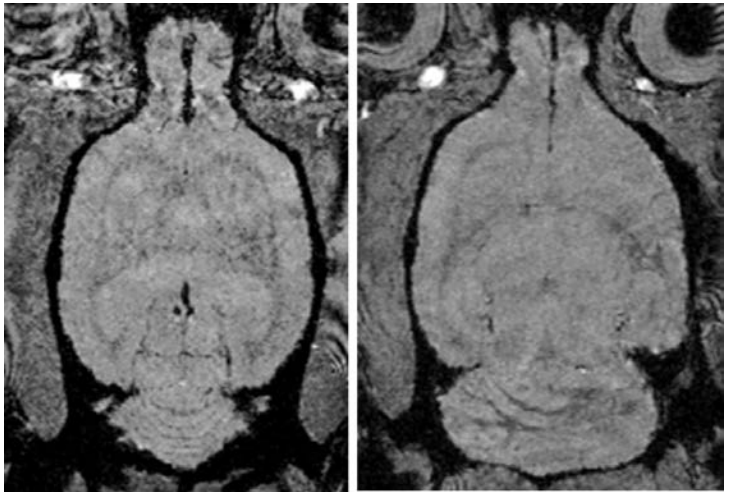
- Tg-ABP showed greater ACC connectivity compared to Tg-Sal treatment



Drug Safety:
Microhemorrhage

- No evidence of drug-induced microheamorrhage

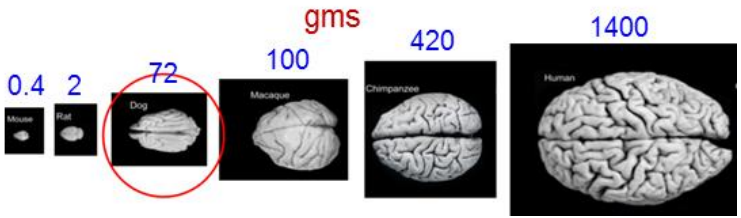
Before treatment | After treatment

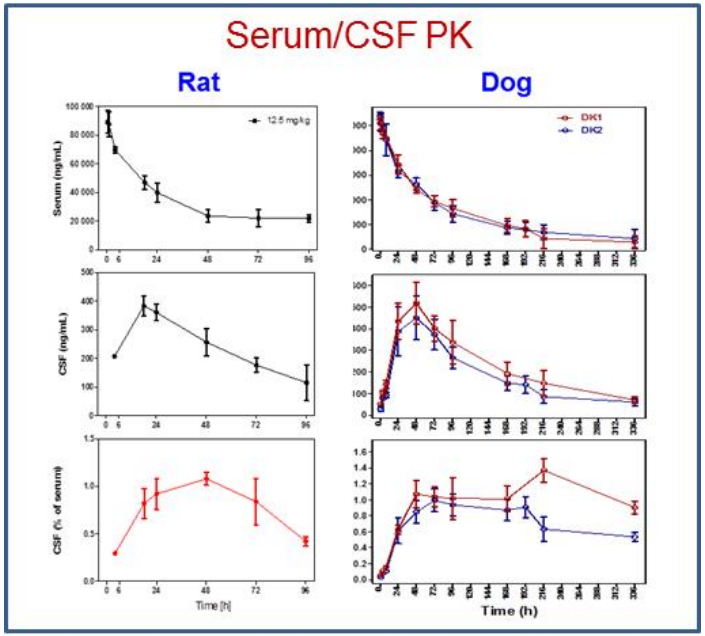


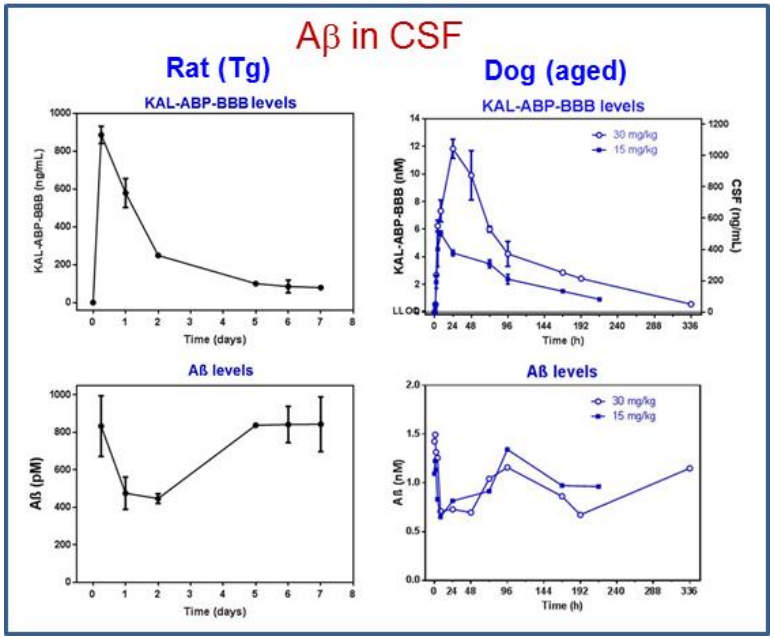
Summary of longitudinal studies in AD rat model

- 27% reduction in global amyloid load
- 7% Increased hippocampal volume
- Restoring rs-fMRI ACC Connectivity
- No evidence of microhaemorrhage

Translation from small to large brain







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