Reversing Axonal Spheroids and Conduction Defects in Alzheimer's Disease

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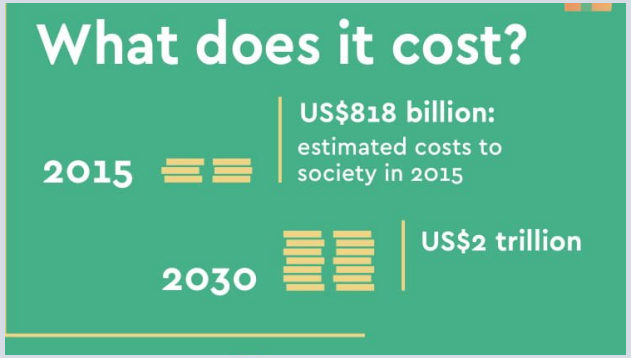
IP: Patents Pending
Related: OCR8237

Alzheimer's disease

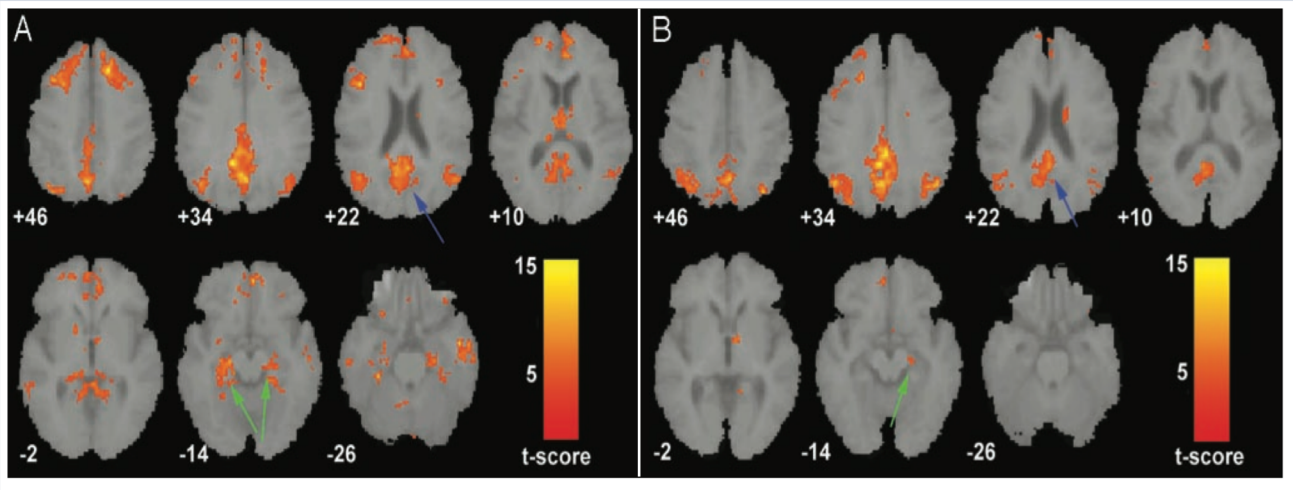
- The most common dementia (60-70% of cases)
- Current treatments are symptomatic memory enhancers (i.e. Aricept , Namenda).
- Aducanumab (Biogen)- First drug approved for disease modification, based on amyloid biomarker and borderline therapeutic effect on clinical trial. Raises questions about validity of amyloid removal as therapeutic strategy.
- Urgent need for therapies based on additional hypotheses (i.e. ameliorating deficits in neuronal function)



Widespread disruption in brain connectivity in Alzheimer's disease

Decrease brain connectivity

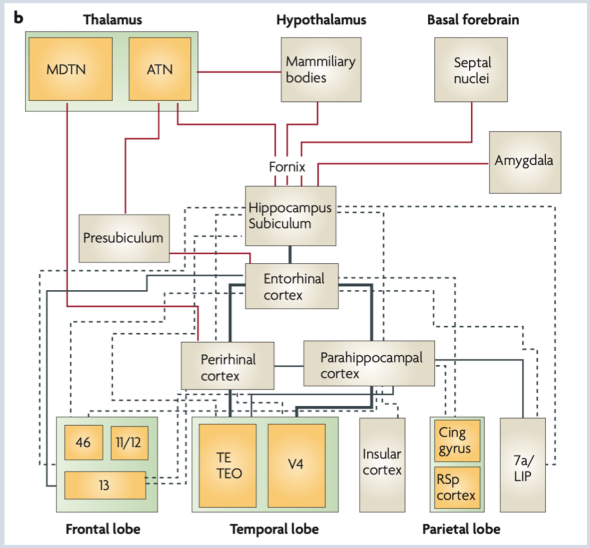
Normal Aging | **Alzheimer's disease**

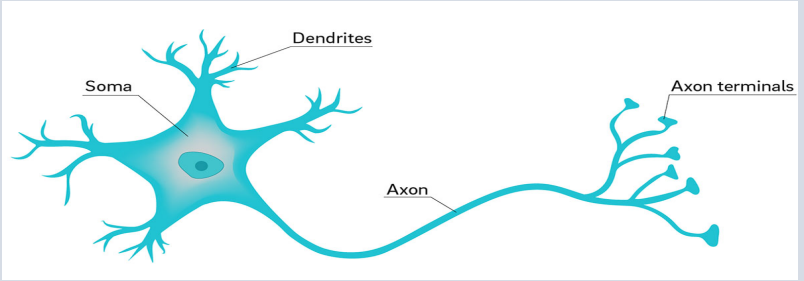


Functional Magnetic Resonance Imaging (resting state)

Greicius et al., 2004

Memory wiring diagram

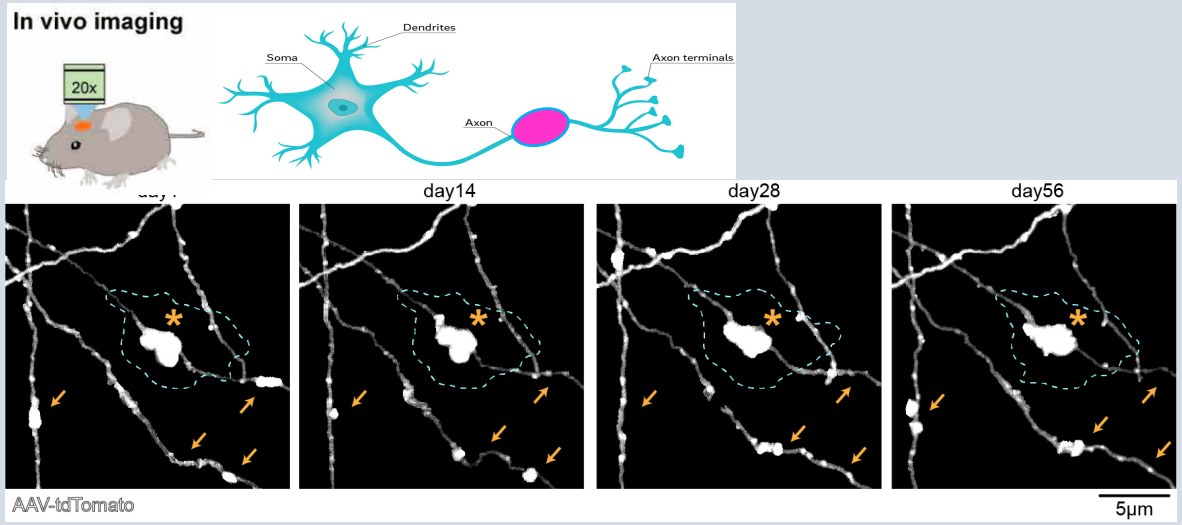




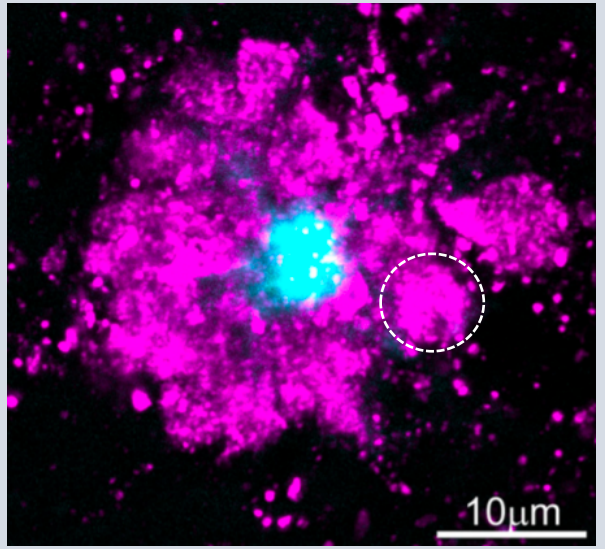
Connectivity between brain regions depends on axonal wiring

Axonal spheroids around amyloid plaques markedly disrupt electrical conduction

Live imaging shows axon spheroids in Alzheimer's mouse

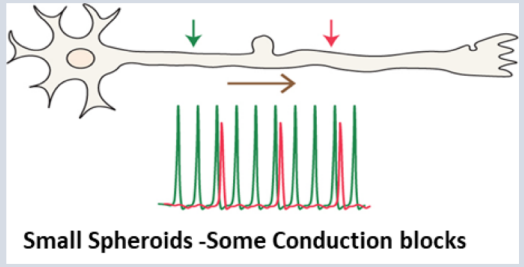


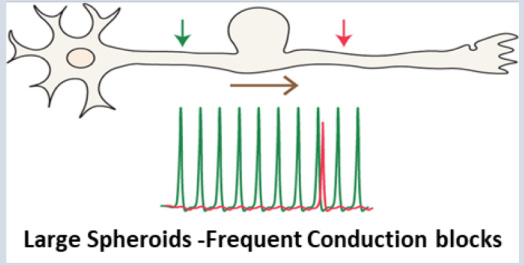
In mice and humans
Each Amyloid plaque
has 10^2 to 10^3 axon spheroids around them



(endo-lysosomal marker)

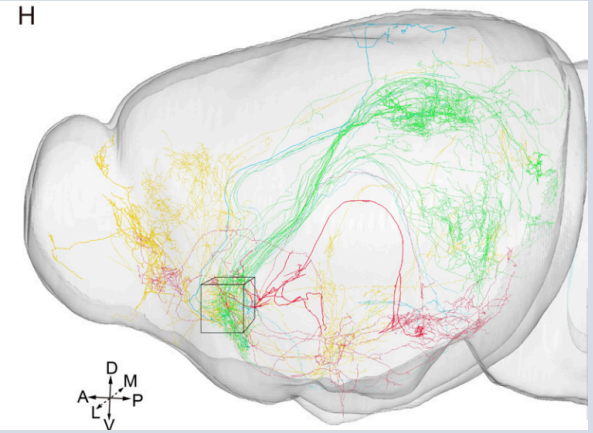
Spheroids act as capacitors/ current sinks that disrupt axonal conduction in a size-dependent manner





Yuan et. al., (2021) *in revision*

Disruption of single axons can affect thousands of interconnected neurons

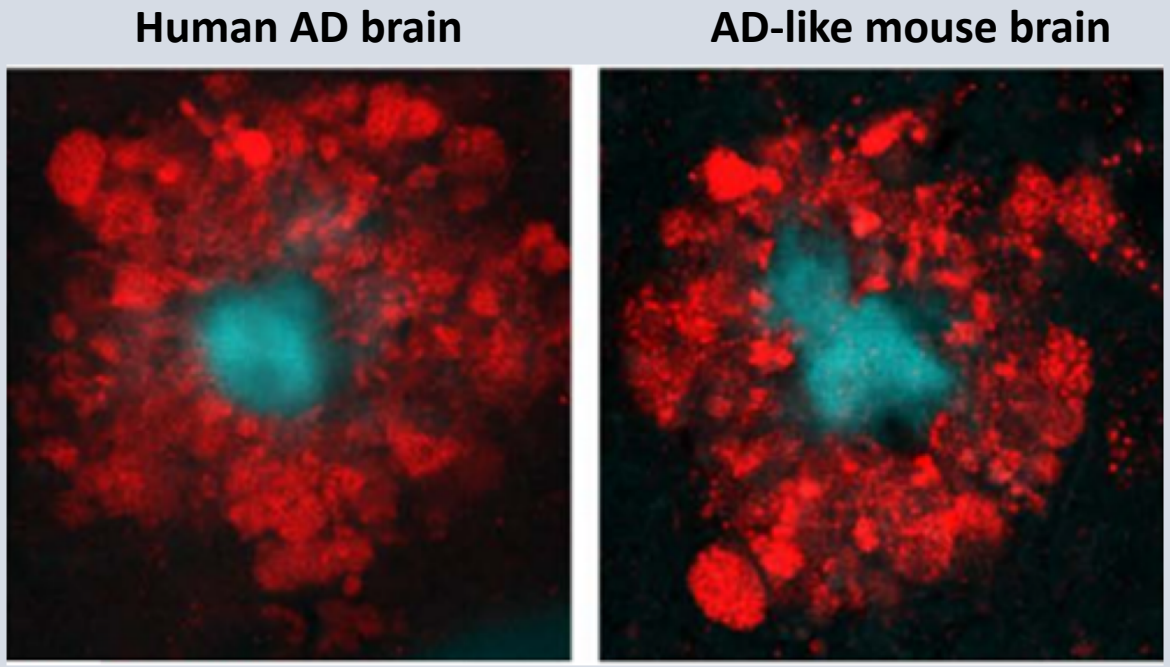


Novel therapeutic targets are shared between mice and humans

Axonal spheroid-enriched targets

Target 1: Neuronal endolysosomal protein

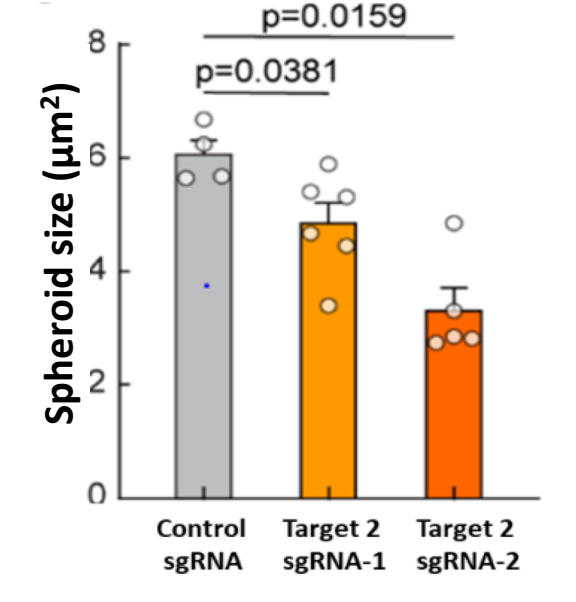
Target 2: Neuronal membrane receptor/ligand

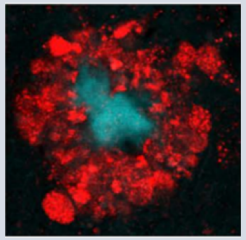


OCR8216-TARGET 1 (Red) is highly enriched in axonal spheroids (Red) around amyloid plaques (Thioflavin S, cyan).

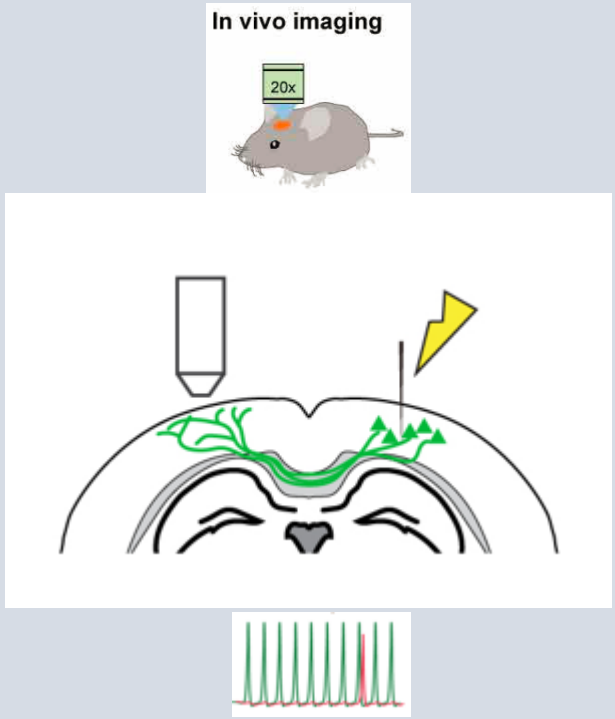
Target 1: *In vivo p*roof-of-concept CRISPR/Cas9 KO with AAV-gene therapy

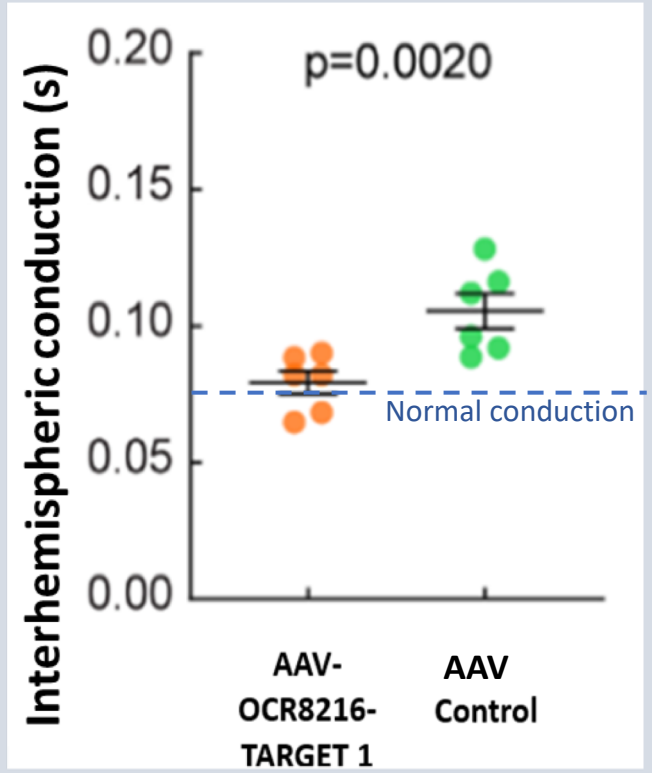
Reduces spheroid size





Normalizes axonal conduction in vivo





Blavatnik Target 1: Neuronal endolysosomal protein

✓ ***In vivo proof-of-concept* completed:** AAV-mediated CRISPR/Cas9

Blavatnik Goal:

Antisense oligonucleotide (ASO):

- Develop ASO as a therapeutic strategy to reduce target 1 levels (CRO).
- Test ASO in mouse model of Alzheimer's disease
- Evaluate effectiveness in reducing pathology, improving axonal conduction and behavioral outcomes (Grutzendler lab)
- Improve understanding of mechanisms related to Target 1

Budget request: $150K

Blavatnik Target 2: Neuronal receptor/ligand

✓ ***In vivo* proof-of-concept partially completed** ***:*** Neutralizing antibody against soluble ligand reduces axon spheroids

Blavatnik Goal:

New proprietary neutralizing Abs

- BBB penetrant bispecific Abs (CRO) and isotypes with limited immune activation
- Test antibodies in mouse model of Alzheimer's disease
- Evaluate effectiveness in reducing pathology, improving axonal conduction and behavioral outcomes (Grutzendler lab)
- Improve understanding of mechanisms related to Target 2

Budget request: $150K

Use of Blavatnik funds for value creation

18 MONTHS → **New Venture**
2 assets for 2 targets

Target 1 12 MONTHS $150K → POC for Anti-sense oligos

Target 2 12 MONTHS $150K → POC for Novel Antibodies