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

Normal Aging

Alzheimer’s disease

Decrease brain connectivity

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

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

Disruption of single axons can affect thousands of interconnected neurons

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

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

Target 2  12 MONTHS  $150K
POC for Novel Antibodies

New Venture
2 assets for 2 targets

Human AD brain
AD-like mouse brain