Asparagine Endopeptidase (AEP) Inhibitors for Treating Neurodegenerative Diseases

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OTT Breakfast Club, May 3rd, 2017
Alzheimer’s Disease

- Degeneration of cortex and cingulate
- 30M cases worldwide & 1.9M deaths annually
- 60-70% of all dementia
- One of most costly diseases (US = $100B/year)
- Increasing as population ages

Current Treatments

- Lifestyle changes, Behavioral interventions, Therapeutics
- Opportunity = therapeutics that slow/halt disease

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<th>Drug</th>
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<th>Effects</th>
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<td>NMDA antagonist</td>
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AEP – the missing link?

Alzheimer's Disease

β Amyloid

• APP miscut to Aβ
• Forms extracellular amyloid plaques
• Plaques disrupt tissue

AEP

• Over phosphorylation
• Forms intracellular neurofibrillary tangles
• NFTs lead to cellular death

Tau Protein

Asparaginyl endopeptidase (AEP) – cysteine protease

• Expression upregulated with age
• Capable of miscutting APP when overexpressed
• Overexpression leads to hyperphosphorylation of Tau
Drug Discovery

Screen for AEP inhibition in kidney lines

Validate hits against pure AEP

Analyze structural similarity for hits

ID top hits by IC$_{50}$ for each family

Specificity & cytotoxicity assays

Top candidate/lead

**Compound #11**
- IC$_{50}$ - 800nM
- Strong specificity to AEP

54,000 compounds

760 initial hits

46 hits

8 families

8 “best” compounds
#11 Improves Physiology & Behavior

**5XFAD Mice** = widely used genetic AD model – display phenotypes like $\alpha$β plaques and cognitive impairment

**Aβ Plaque Formation**

- Compound #11 reduces plaques
- Compound #11 improves memory

**Morris Water Maze Test**

- Compound #11 improves memory
Value proposition

• AD is a condition with a large number of potential patients and large unmet need
• Compounds target mechanism involved in both main disease pathways
• Early but promising proof of concept data
• AEP also known to play role in PD

Next Steps – Additional drug design & POC data

IP Status – Applications filed in the US, EP, & China

Commercialization – Actively seeking entrepreneur & funding
Thank you!
US Cases (Millions)

- Alzheimer's: 5.4
- Parkinson's: 1.5
- Multiple Sclerosis: 0.4
- ALS: 0.03
- Huntington's: 0.03

Legend:
- Alzheimer's
- Parkinson's
- Multiple Sclerosis
- Huntington's
- ALS
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