Development of Therapeutic Approaches and Agents for Alzheimer’s Disease

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Alzheimer’s Disease

- Progressive neurodegenerative disease. 
  - senile plaque, neurofibrillary tangle, 
  - neuronal cell loss, brain atrophy

- Most common form of dementia. 
  - impairment in cognition, activities of daily living and behavior

- Average life span following diagnosis is 7-10 yrs.

- No longer untreatable disease (symptomatic treatment)
  - Donepezil (Aricept™)
  - ENA-713 (Exelon™)
  - Galantamine (Reminyl™)
  - Tacrine (Cognex™)
  - Memantine (Namenda™)

  \[ \{ \text{Acetylcholinesterase inhibitor} \} \quad \{ \text{NMDA receptor antagonist} \} \]

However, there is no disease-modifying therapy available.
Alzheimer’s Disease -- Pathology

Abeta plaque
Deposit of Abeta peptides and other proteins in the extracellular space. Deposits change to insoluble form (senile plaque).

Neurofibrillary tangle
Hyper phosphorylation of tau (axonal transporter) in the intraneuronal accumulation. Hyper phosphorylated tau change to insoluble form (neurofibrillary tangle).

Neurodegeneration
Brain atrophy
Massive neuronal cell loss.
Abeta Hypothesis

Why Abeta?

- Genetic mutations found in Alzheimer’s disease link to Abeta and its processing.
  - Amyloid precursor protein (APP)
  - Presenilin (PS)-1 and 2 (γ secretase modules)
  - Down syndrome (trisomy 21) causes Alzheimer’s disease

- Transgenic mice expressing APP induce hyperphosphorylation of tau.

- Tau pathology was attenuated by Abeta-lowering approach in transgenic mouse recapitulating both plaque and tangle pathology.
Possible therapeutic targets in Abeta hypothesis

Soluble Abeta

Secretase Modulators

Clean up

Sequestration

STOP

Neuroprotectants

STOP

STOP
APP cleavage and possible therapeutic targets

Beta secretase

Alpha secretase

Gamma secretase

Beta -> gamma

Alpha -> gamma

Beta inhibitor

Gamma inhibitor

Alpha activator
Secretase modulators

- Beta secretase inhibitors
  - No Abeta in knockout mice
  - No abnormality in knockout mice

- Gamma secretase inhibitors
  - Gene deletion is lethal
  - Intramembrane cleavage
  - Enzyme is complex of module
  - Inhibits other signaling cascade

- Alpha secretase activators
  - Multiple enzymes

At Matsuoka lab

- Two BACE collaboration
  (active in vivo, two independent structures)
- One alpha secretase collaboration
  (not yet active in vivo)

We investigate the mechanism using developed compounds.
Abeta clearance

- Monomeric Abeta (Newly synthesized Abeta) ➔ Oligomeric Abeta ➔ Aggregated Abeta (plaques)

- Interfere Abeta oligomerization and/or fibrilization
  Alzmed, under clinical trial

- Enhancement of microglial phagocytosis
  Abeta vaccine – clinical trial was terminated due to encephalitis
  Passive immunization – under clinical trial.

- Active Abeta transfer to the periphery (sequestration)
Abeta sequestration approach

Active immunization with Abeta peptides reduces brain Abeta load

✓ Both cognitive impairment and brain Abeta load were attenuated

Mechanism originally proposed:
Anti-Abeta antibodies enhanced microglial phagocytosis in the brain.

Clinical trial (active immunization):
Enhancement of plasma Abeta after vaccination

Lemere et al. *Neurobiology of Disease*, 14: 10-18. Also confirmed by other groups.

Hypothesis: Simple Abeta binding agents capture Abeta in the periphery, alter CNS/periphery Abeta dynamics, and reduce CNS Abeta without entering the brain.
Abeta sequestration study -- proof-of-concept

Simple Abeta binding agents which unlikely enter the brain reduced brain Abeta load

Supportive evidences:
- Two other simple Abeta binding agents reduced brain Abeta load.
- Fab fragment of anti-Abeta antibody reduced brain Abeta load.
- Abeta active immunization reduced brain Abeta load in Fc receptor knockout mice
Abeta sequestration and other approaches for cure

- Proof-of-concept compounds are extracted large proteins:
  - Immunogenicity, Biological carry over,
  - Impossible to apply chemical modification

- No need to cross the blood-brain barrier:
  - Safer and more flexible for drug development

- No immune modulation:
  - Less risk of side effect.

High-throughput screening for Abeta sequesters

Mechanistic studies:
- Detail of Abeta responsive to this approach
- Cascade of Abeta transfer
- Transporters responsive at blood-brain barrier
Neurodegeneration / neuronal cell loss and brain atrophy is commonly seen in Alzheimer’s disease.

However, transgenic mouse models recapitulating Abeta and tau pathology do not show significant change.

Model with Alzheimer-type neurodegeneration is desired to test neuroprotective agents.
Development of Alzheimer’s mouse model with neurodegeneration and brain atrophy

Mouse MR imaging: Stan Fricke
Ventricle segmentation: John VanMeter
Development of therapeutic approaches for Alzheimer’s disease

Basic Neuroscience ➔ Pre-clinical Neuroscience ➔ Clinical Neuroscience

Mechanistic Studies ↔ Drug Development

- Abeta sequestration
- Beta-secretase inhibitors (two approaches)
- Alpha-secretase modulators
- Cholesterol efflux-mediated Abeta-lowering
- Neuroprotective agents (two approaches)
Wide range of knowledge

Wide range of lab skills

Current funding
NIH K01, PI, 2004 – 2009
NIH R01, Co-PI, 2005 – 2009
Contract from pharma, PI

Pending
1 R01, PI (5 years)
2 R21, PI (2 years)
Foundation grant (3 years)

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