Development of Therapeutic Approaches and Agents for Alzheimer's Disease

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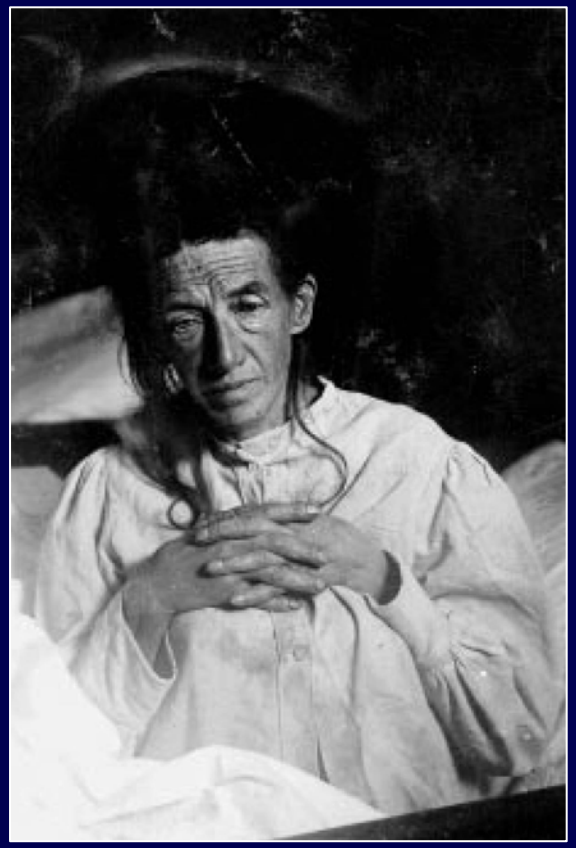
Alzheimer's Disease



Photograph dated Nov 1902
Lancet 349 (1997) 1546-1549

- 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)

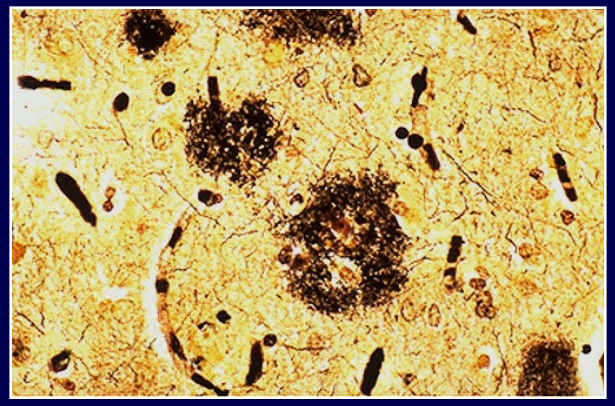
Donepezil (Aricept ™)
ENA-713 (Exelon ™)
Galantamine (Reminyl ™)
Tacrine (Cognex ™)
Memantine (Namenda ™)

} Acetylcholinesterase inhibitor

NMDA receptor antagonist

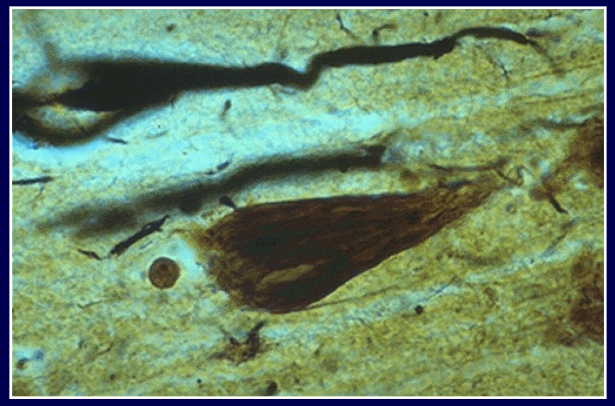
However, there is no disease-modifying therapy available.

Alzheimer's Disease -- Pathology



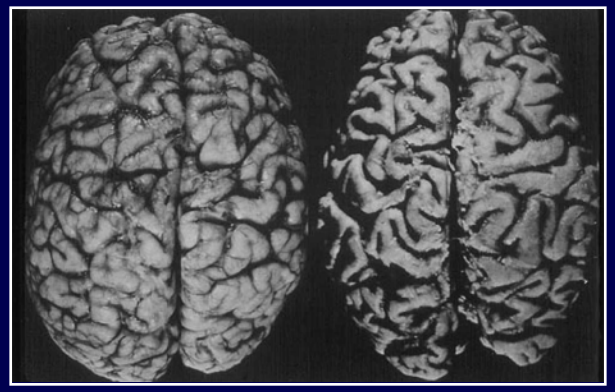
Abeta plaque

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

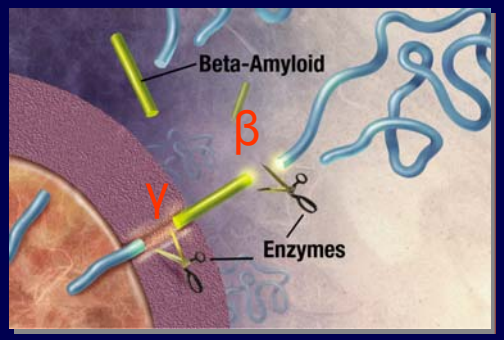
Why Abeta?

- 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

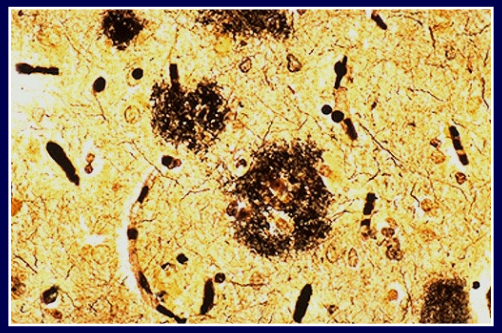
- Transgenic mice expressing APP induce hyperphosphorylation of tau.

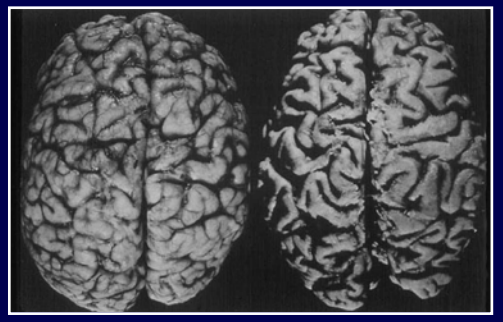
- Tau pathology was attenuated by Abeta-lowering approach in transgenic mouse recapitulating both plaque and tangle pathology.

Possible therapeutic targets in Abeta hypothesis



Soluble Abeta





STOP

STOP

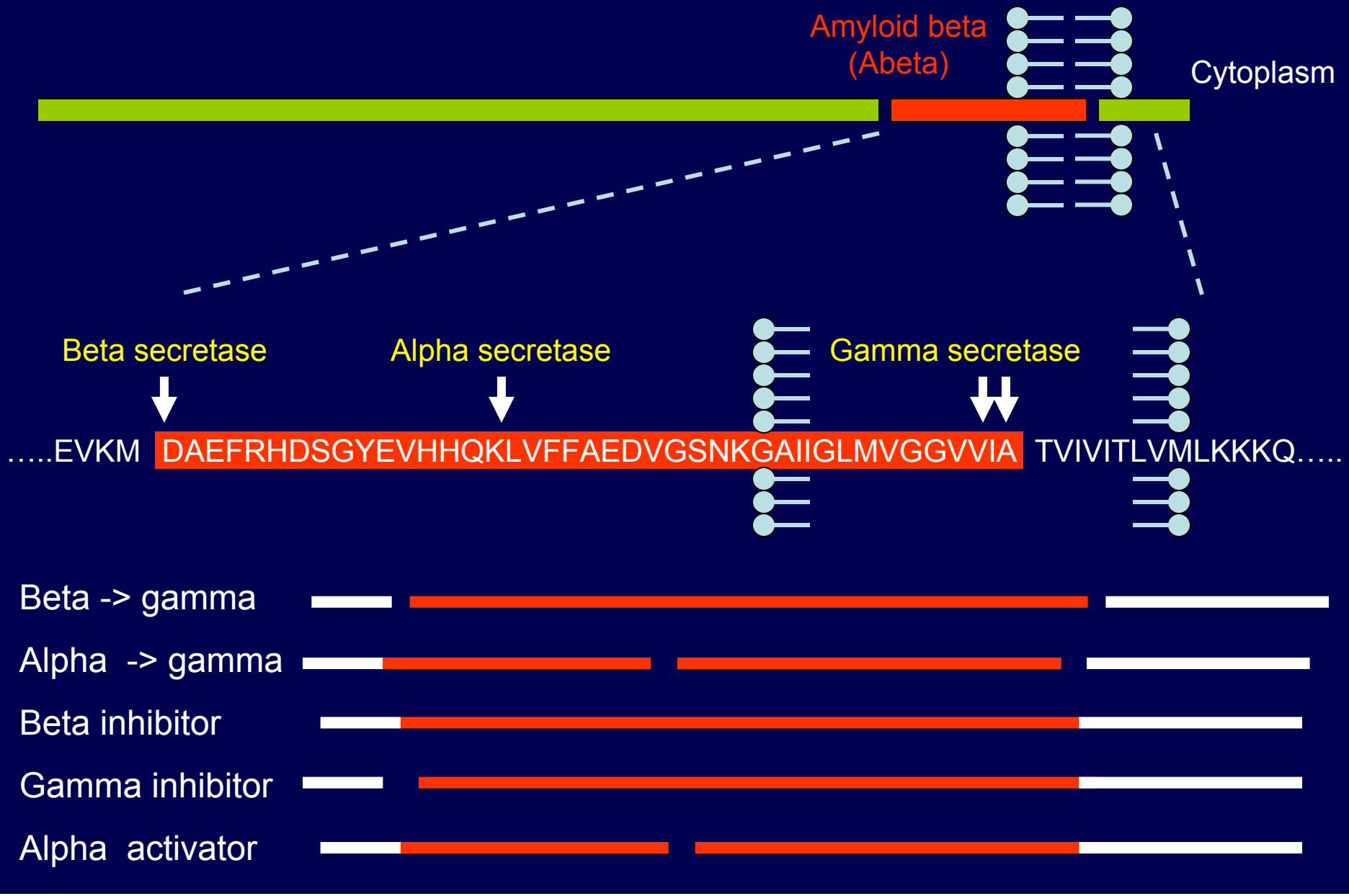
Secretase Modulators

Neuroprotectants

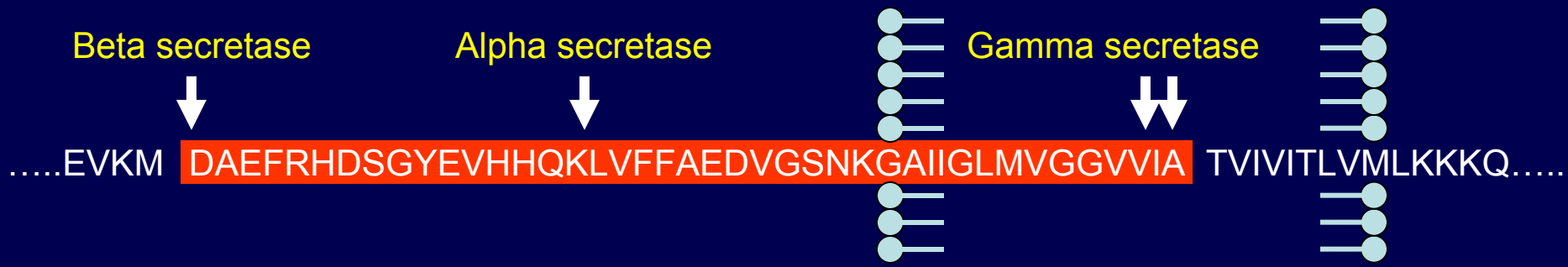
Clean up

Sequestration

APP cleavage and possible therapeutic targets



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

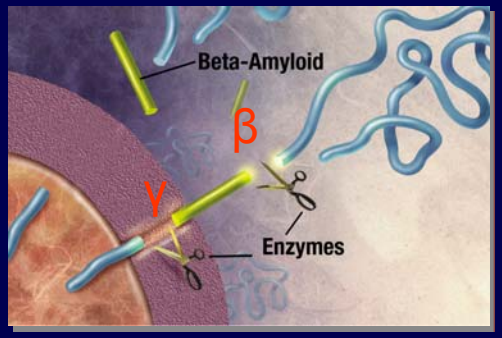
✓ Two BACE collaboration
(active in vivo, two independent structures)

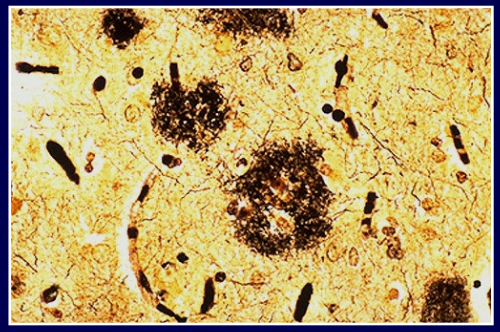
✓ One alpha secretase collaboration
(not yet active in vivo)

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

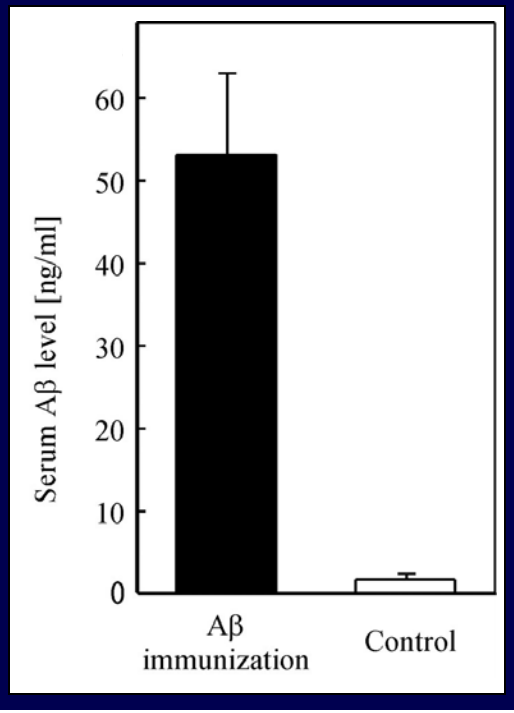
✓ Both cognitive impairment and brain Abeta load were attenuated

Mechanism originally proposed:

Anti-Abeta antibodies enhanced microglial phagocytosis in the brain.

Clinical trial (active immunization):

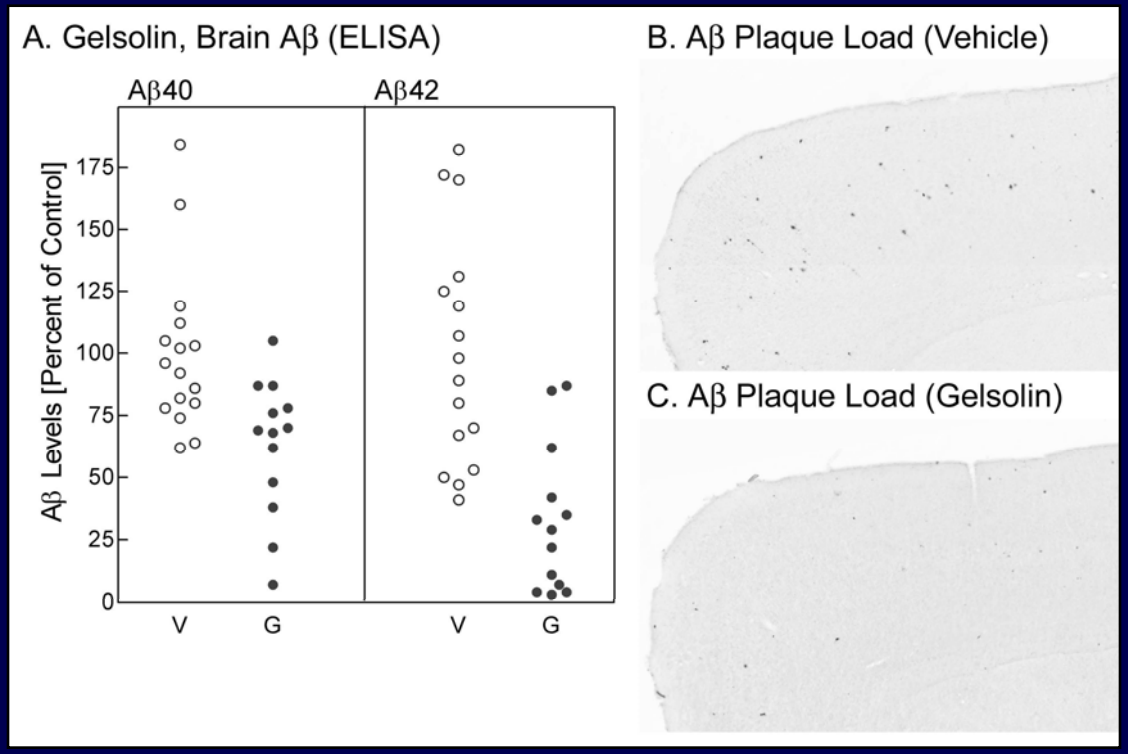
Enhancement of plasma Abeta after vaccination



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

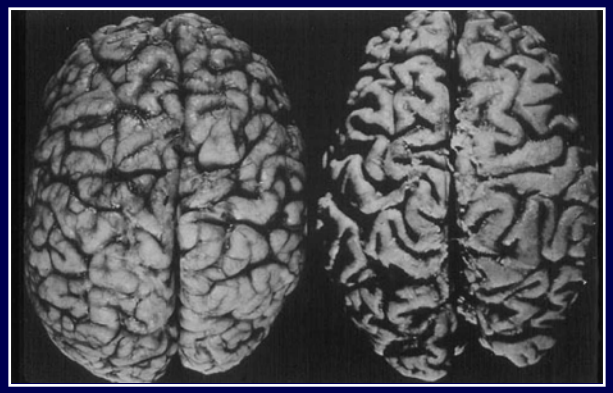
- Proof-of-concept compounds are extracted large proteins:
  Immunogenicity, Biological carry over,
  Impossible to apply chemical modification
- No need to cross the blood-brain barrier:
  Safer and more flexible for drug development
- No immune modulation:
  Less risk of side effect.

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

Neuroprotective Agents

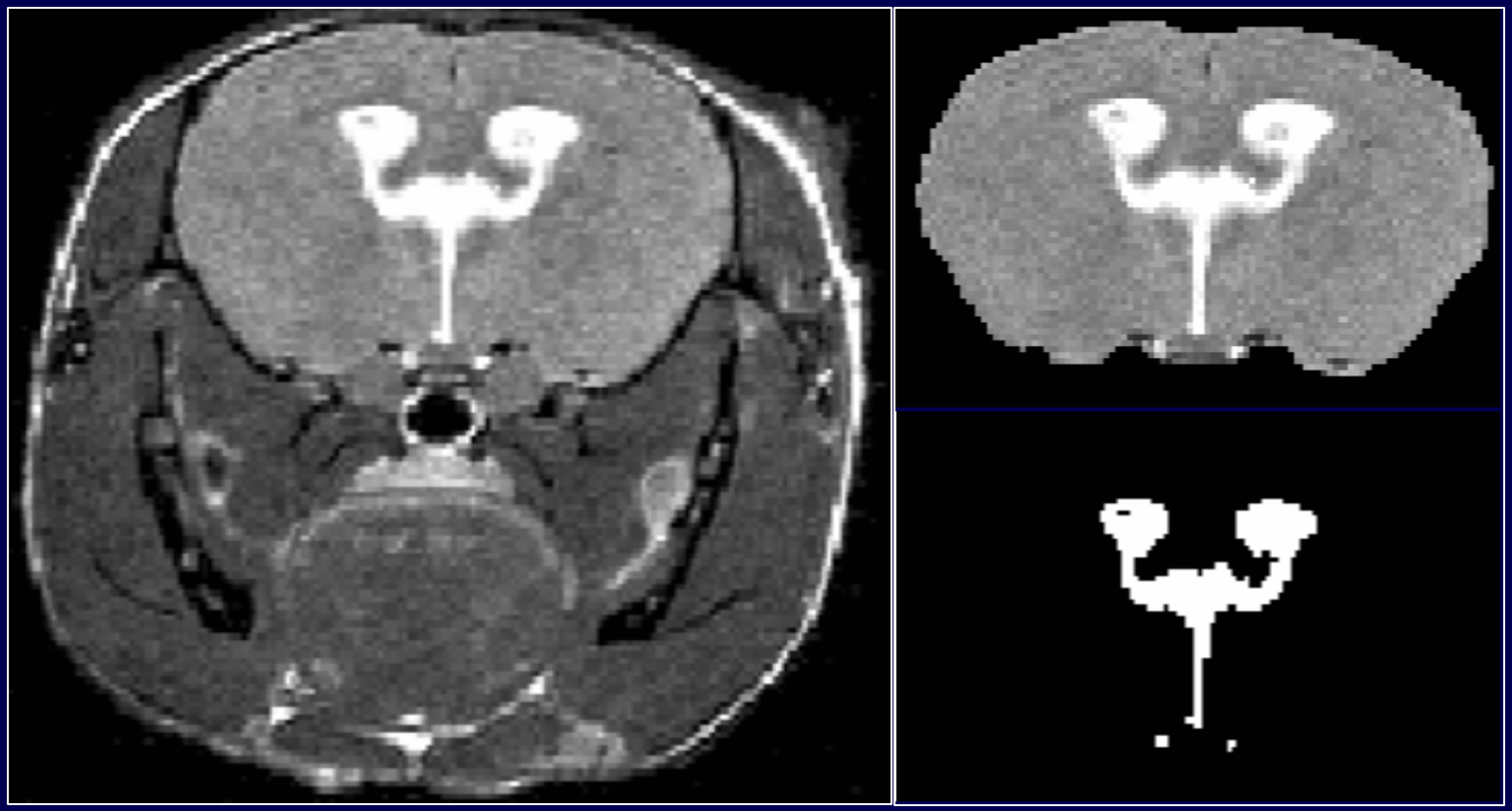


Neurodegeneration / neuronal cell loss and brain atrophy is commonly seen in Alzheimer's disease.

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

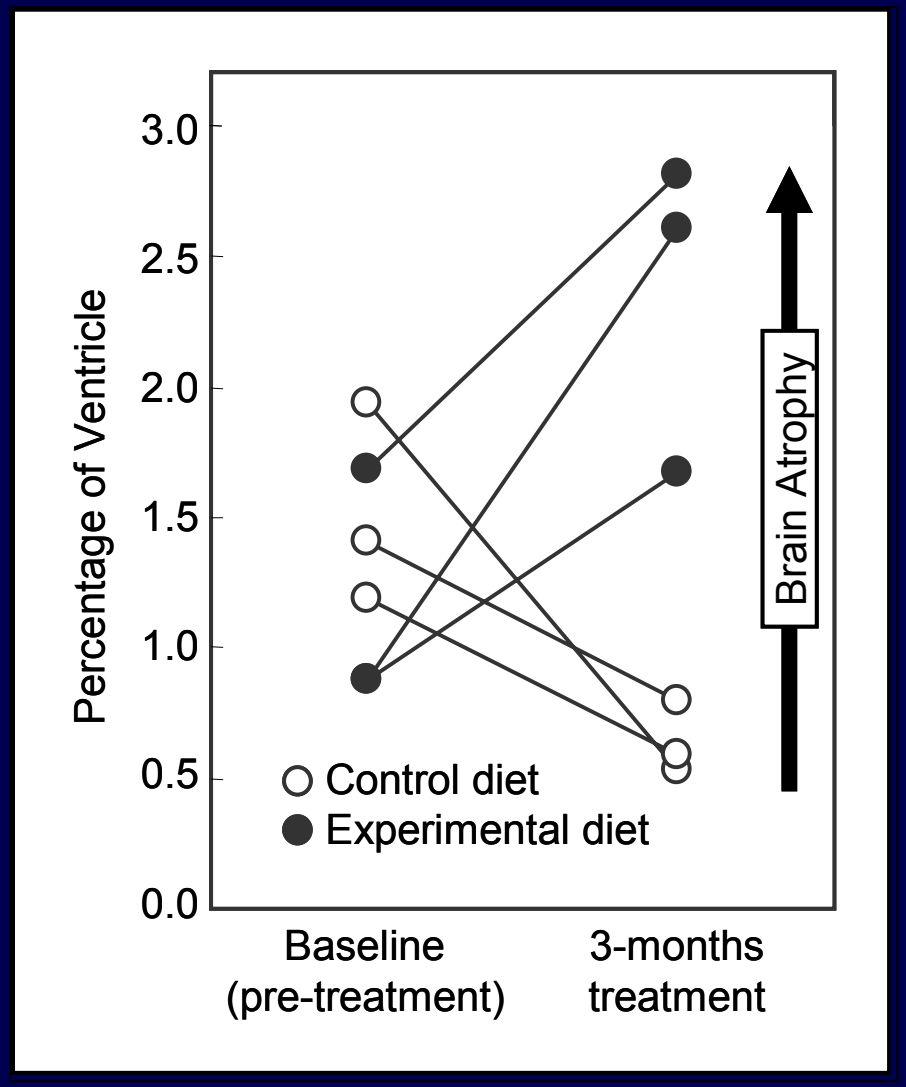
Model with Alzheimer-type neurodegeneration is desired to test neuroprotective agents.

Development of Alzheimer's mouse model with neurodegeneration and brain atrophy



Mouse MR imaging: Stan Fricke

Ventricle segmentation: John VanMeter


Percentage of Ventricle
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Brain Atrophy
Control diet
Experimental diet
Baseline
(pre-treatment)
3-months
treatment

Matsuoka Lab

Development of therapeutic approaches for Alzheimer's disease

Basic Neuroscience → **Pre-clinical Neuroscience** → Clinical Neuroscience

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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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