Promising Alzheimer's Treatment: Hope for CJD

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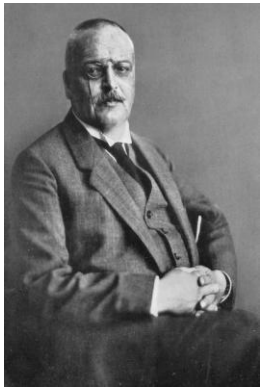
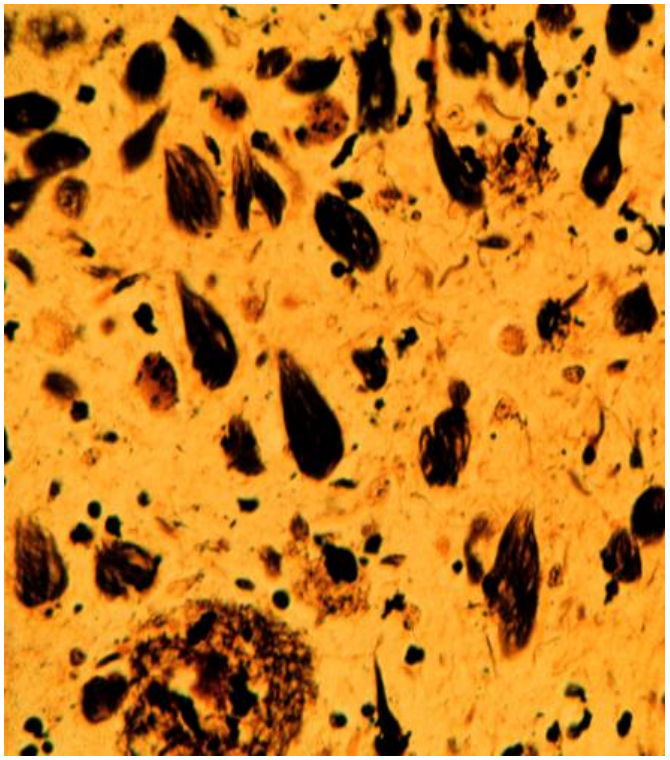
Alzheimer's Disease

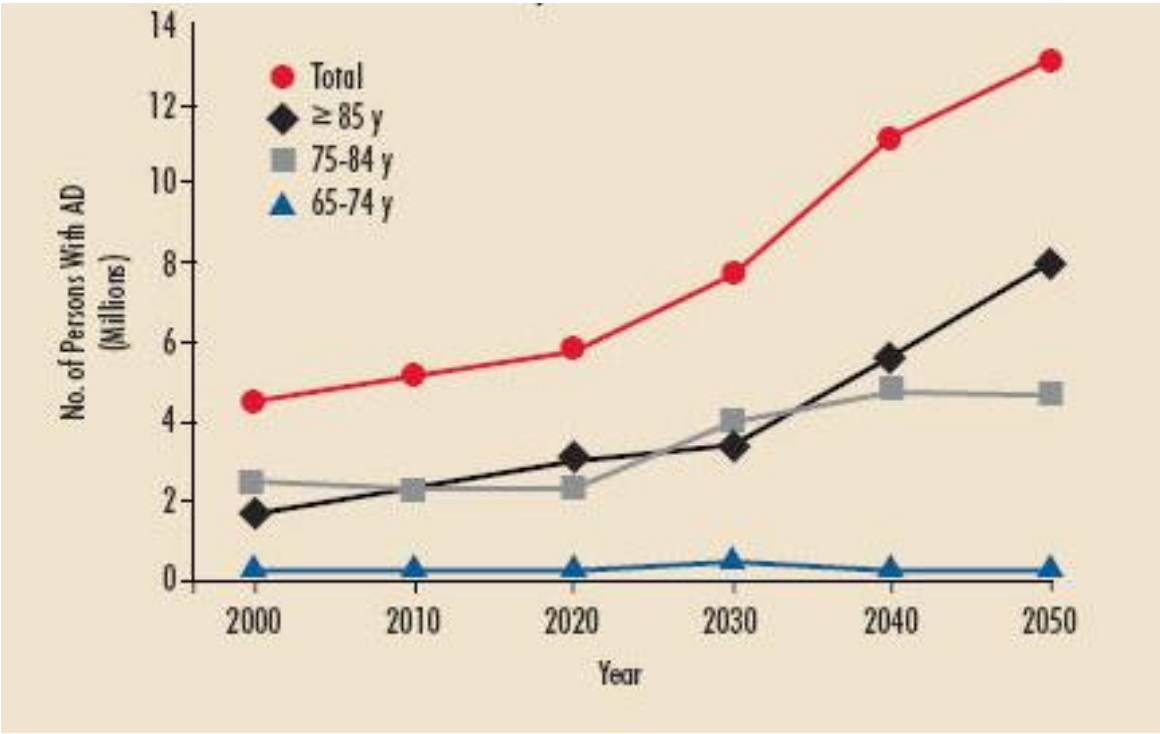


- First described by Dr. Alois Alzheimer in 1907.
- Most common cause of dementia in the elderly
- The 6th most common cause of death in the US
- Characterized by progressive loss of cognitive ability and dementia
- Extensive pathology-senile plaques and neurofibrillary tangles
- Average length between diagnosis and death is 8 years



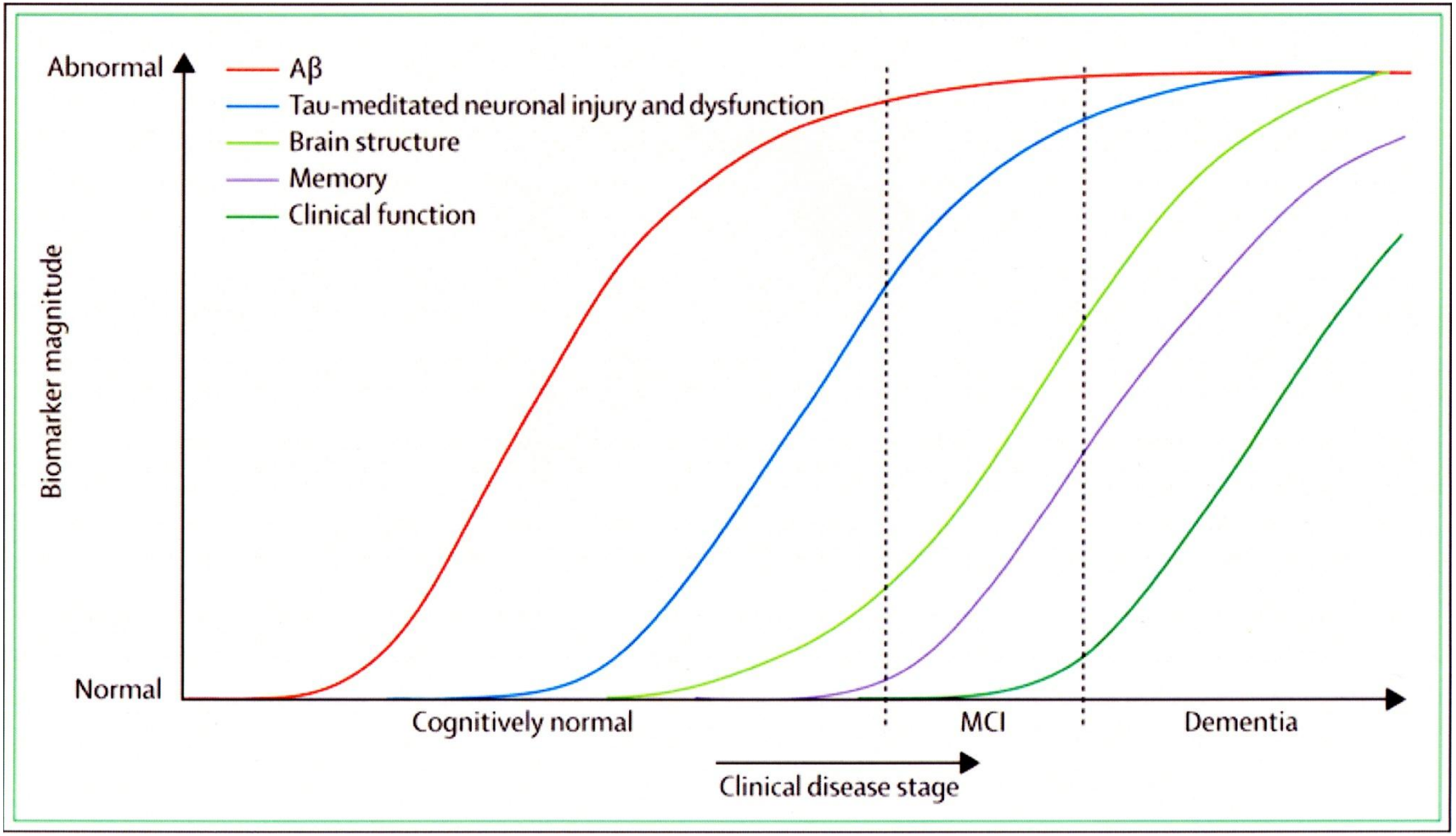
Alzheimer's Disease

- Presently ~5 million cases in the United States
- Prevalence in individuals >85 years old is estimated to be 40-50%
- Estimated Cost 2009 = $150B



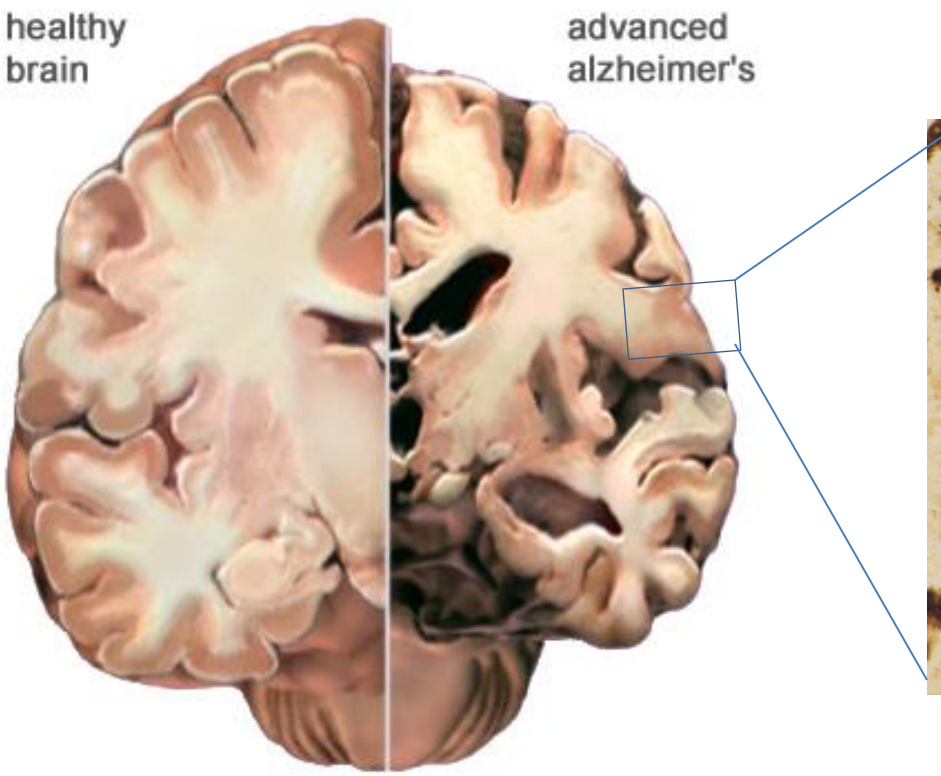
Alzheimer's Disease:

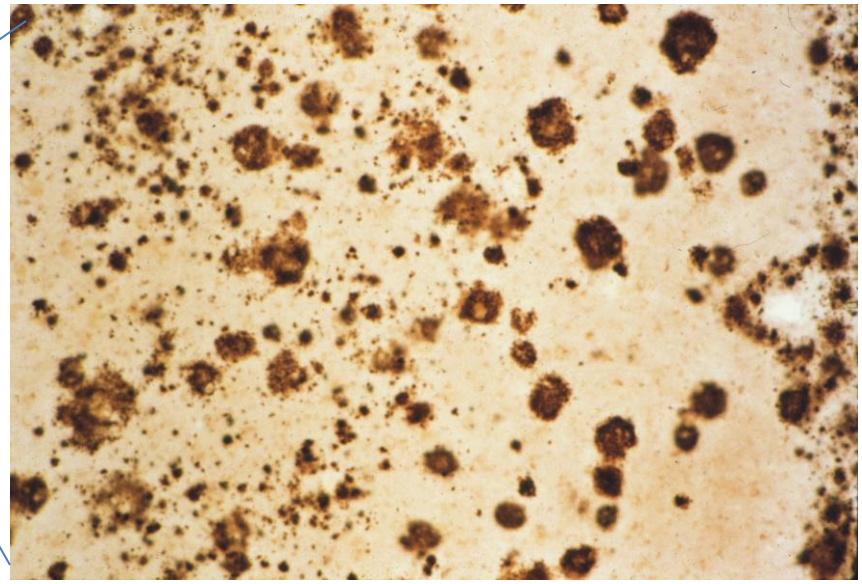
Pathological changes occur years before symptoms appear



Jacks et al., 2010

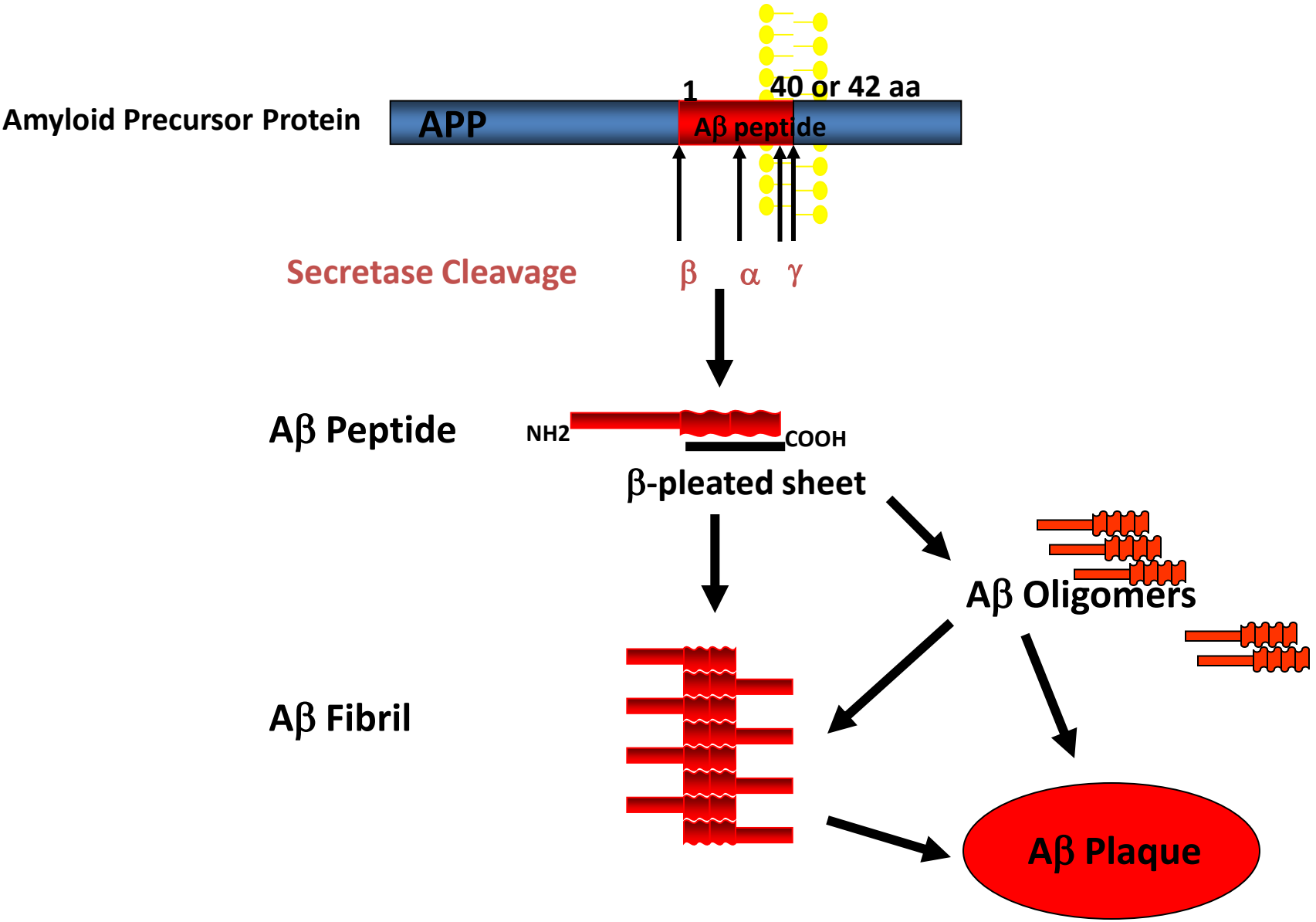
Alzheimer's Disease





One of the most prominent features of Alzheimer's disease is the extensive deposition of a waxy substance, termed beta amyloid within the brain.

Neuronal APP processing and amyloid fibril formation



Impaired Aβ clearance from the brain is responsible for late onset AD

Science *Vol. 330 :1774, Dec. 9, 2010*

The New York Times ON THE WEB

Dec. 13, 2010

The Vanishing Mind: Insights give hope for new attacks on Alzheimer's

Gina Kolata

For years, it seemed, the problem in Alzheimer's was that brain cells were making too much amyloid.

But now, a surprising new study has found that that view appears to be wrong. **It turns out that most people with Alzheimer's seem to make perfectly normal amounts of amyloid. They just can't get rid of it. It's like an overflowing sink caused by a clogged drain instead of a faucet that does not turn off**

Sporadic, late-onset AD is associated with impaired Aβ clearance from the brain

- Aβ is generated at high levels in the normal brain at a rate of 7.6%/hr
- Aβ is cleared from the brain at a rate of 8.3%/hr.

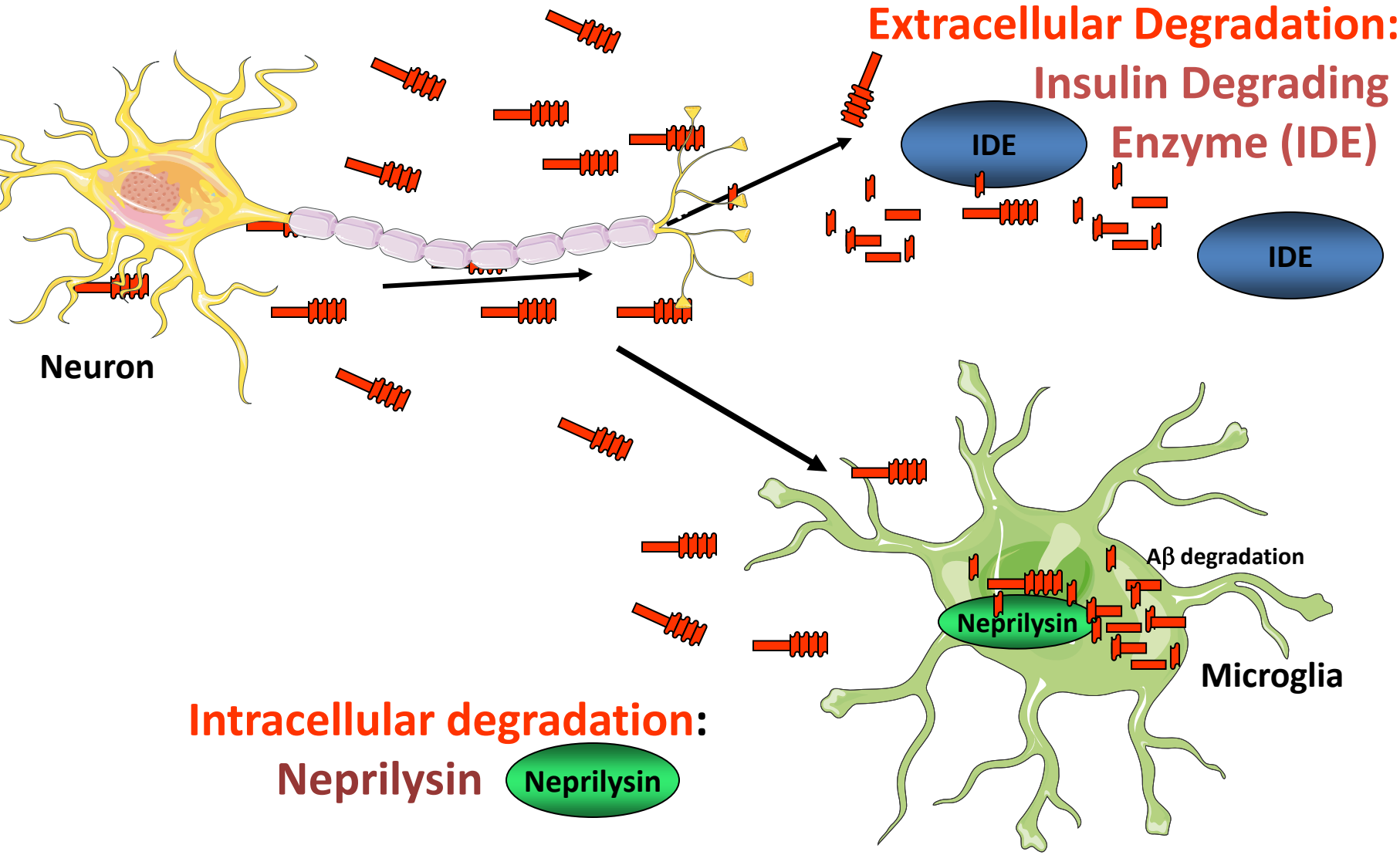
(Bateman et al. NatMed 12:856, 2006)

- **Small perturbations of clearance will result in accumulation of Aβ in the brain**

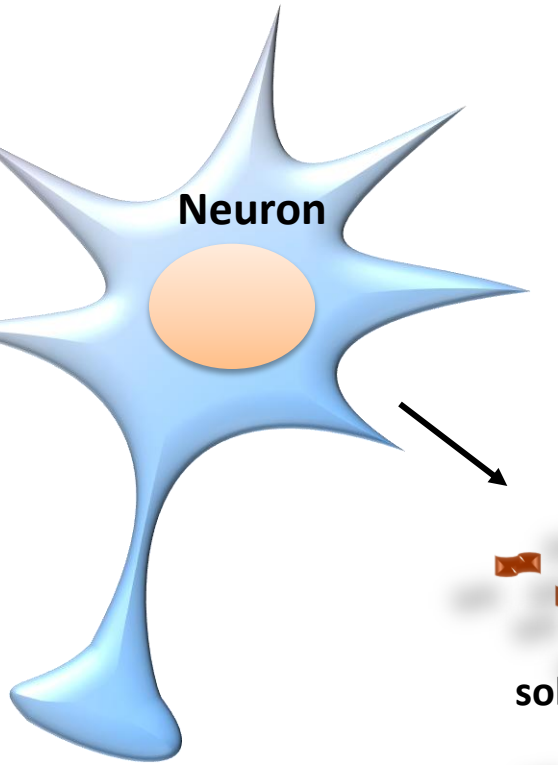
Aβ clearance from the CNS is reduced by appx. 30% in individuals with AD

(Mawuenyega et al. 2010)

Intrinsic Mechanisms of Aβ clearance



Alzheimer's Disease arises from the inability to clear amyloid from the brain



soluble Aß

Age-related Impairment

X

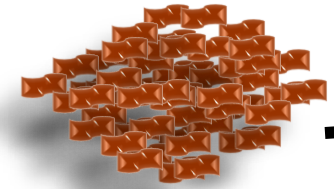
clearance

Degradation/ clearance

healthy brain

impaired

fibrillar Aß plaque

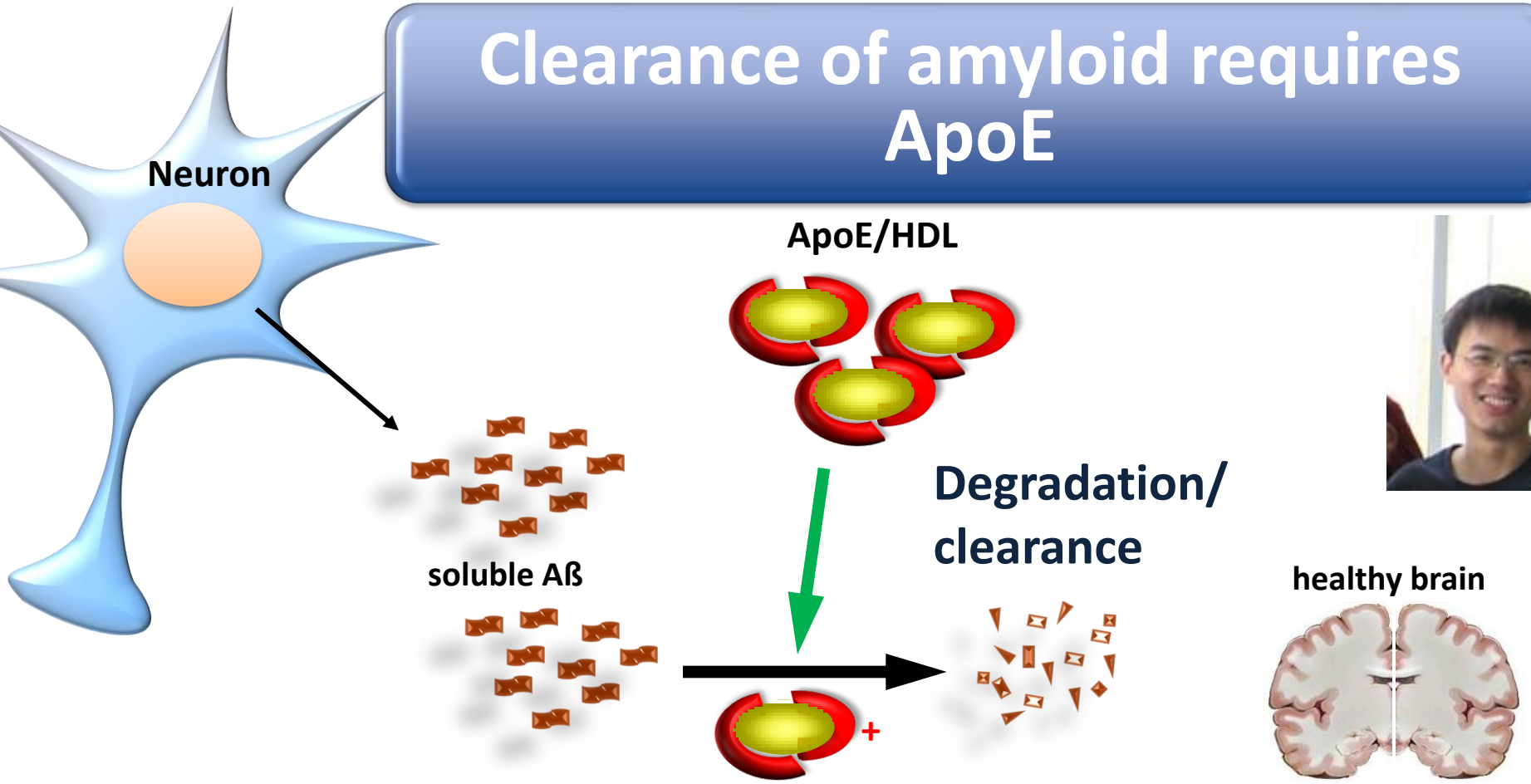


synaptic deficits

cognitive impairment

Alzheimer's Disease

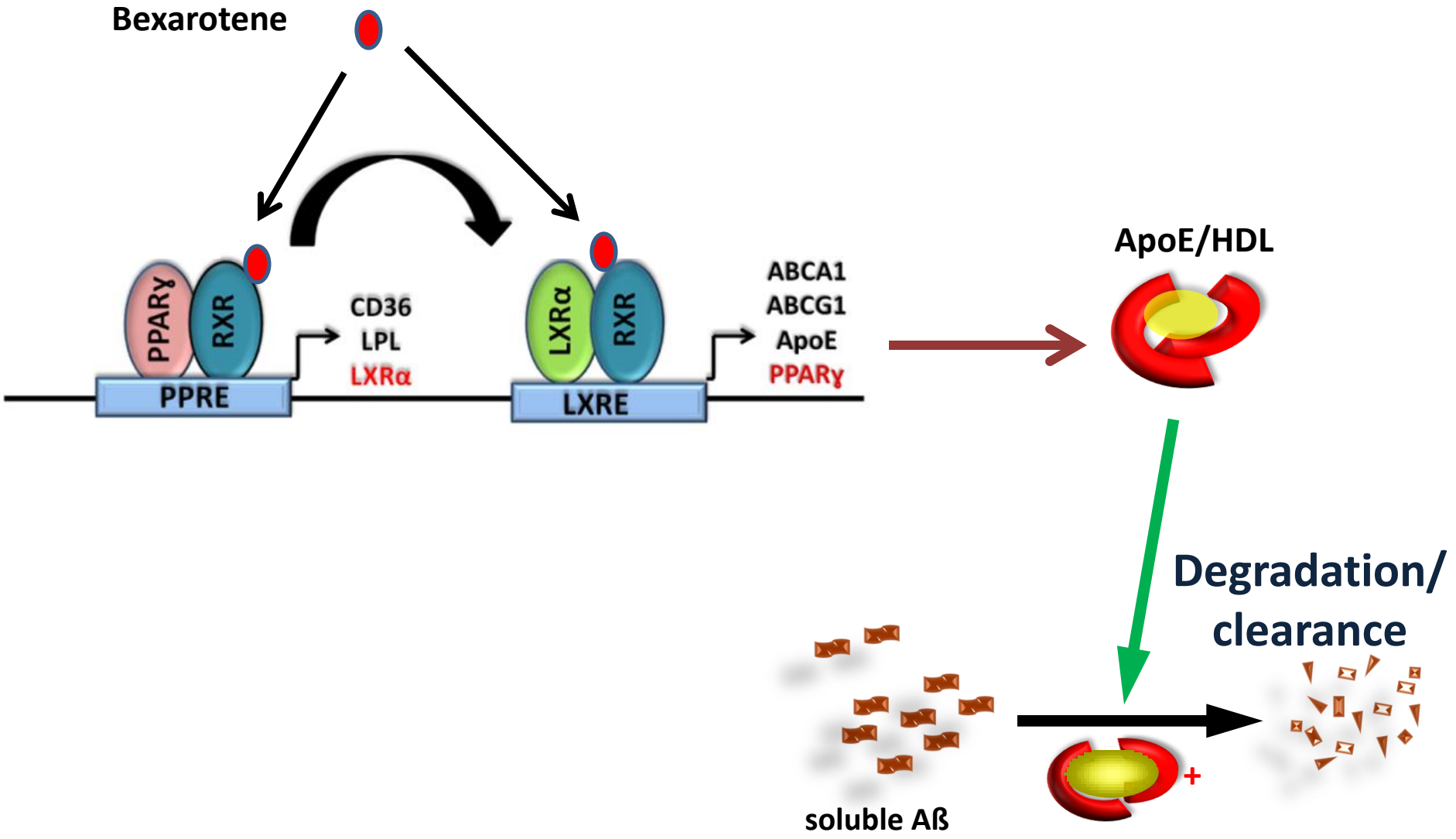
Clearance of amyloid requires ApoE



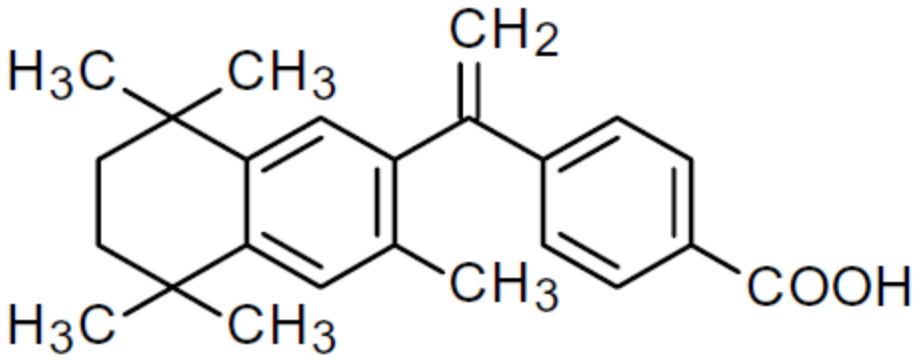
We discovered that ApoE is a critical component of the normal, physiological mechanism through which Aβ is cleared from the brain.

Thus, if ApoE levels in the brain can be elevated, this should stimulate the removal of Aβ from the brain, preserving cognition and memory.

Nuclear receptors in the brain act to stimulate the synthesis of ApoE and thus clearance of Aβ

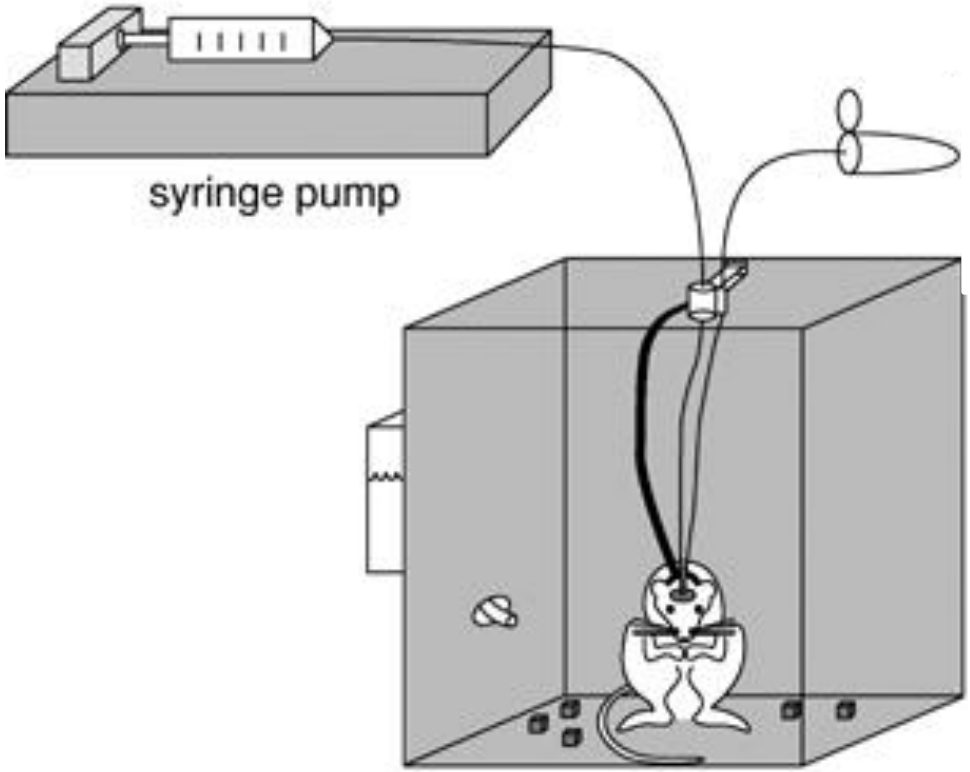


Bexarotene (Targretin™)



- Highly specific RXR agonist
- Bexarotene is fully BBB penetrant
- Orally delivered
- FDA approved for treatment of T cell lymphoma

In Vivo Microdialysis

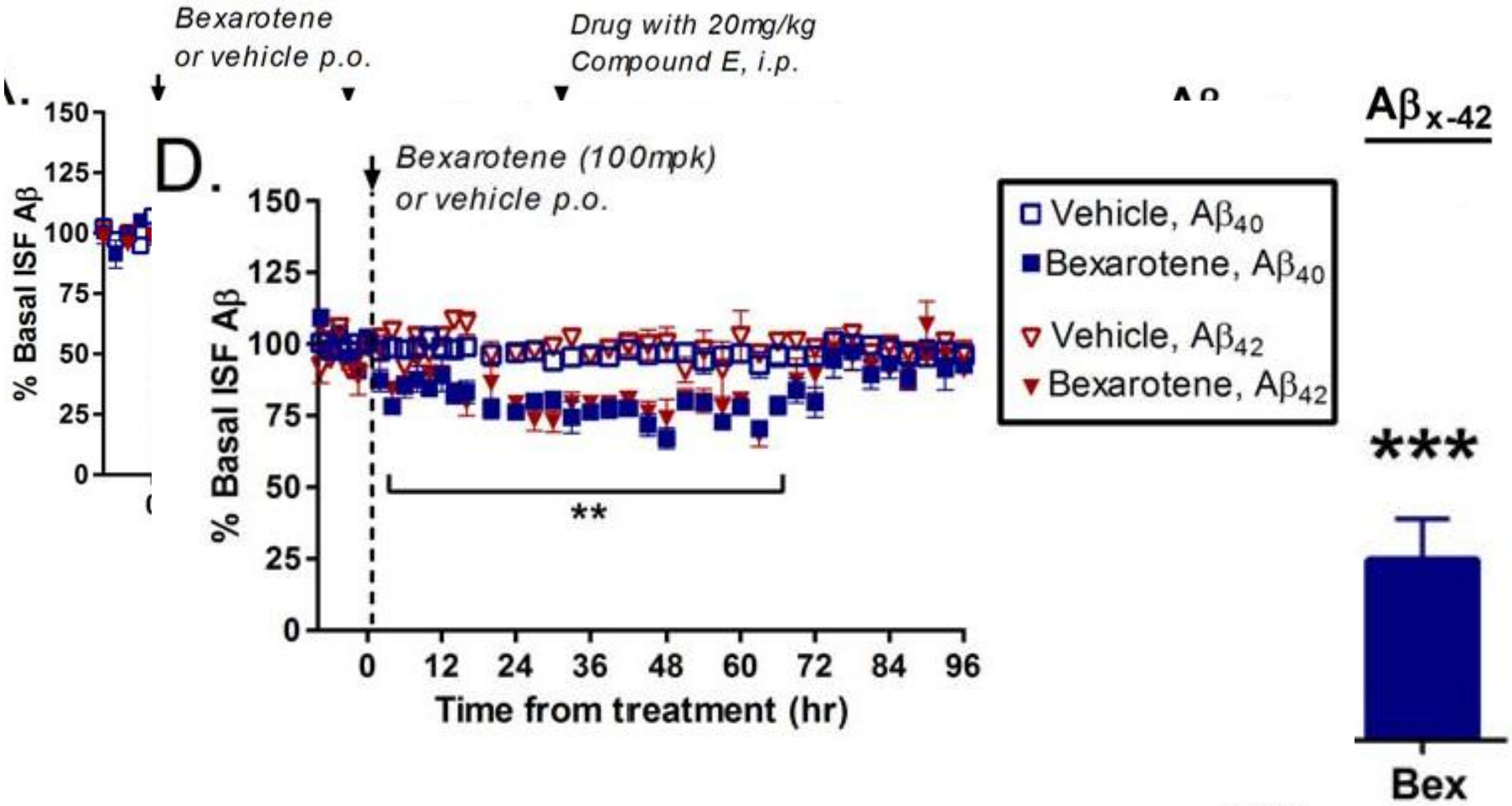


Measure Interstitial Fluid (ISF) levels of soluble Aβ

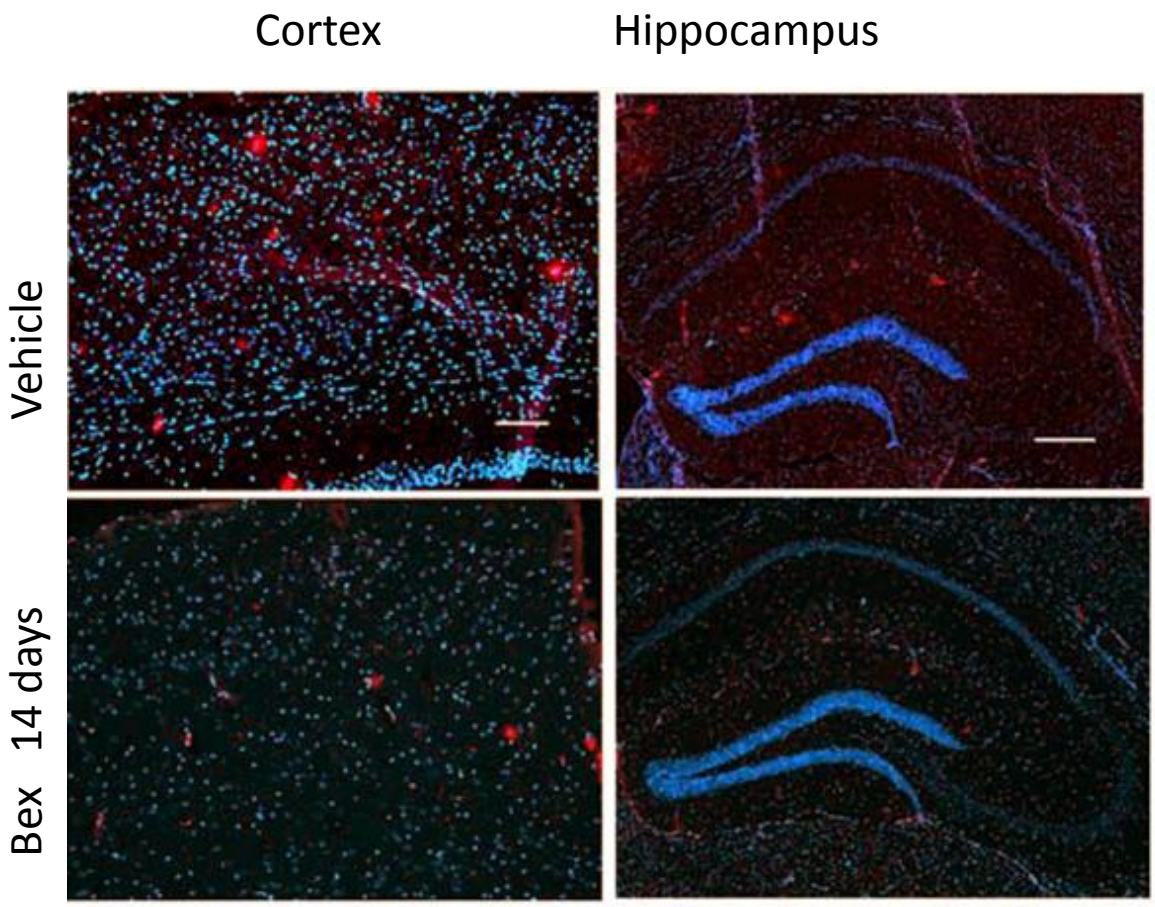
Modified from: http://www.currentprotocols.com/protocol/ns0702

Does Bexarotene clear soluble Aβ from the brains of an AD mouse model?

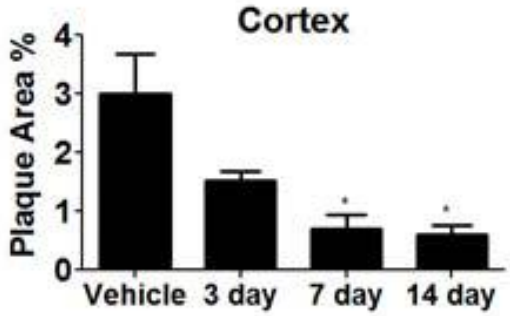
How long does 1 dose of bexarotene last?

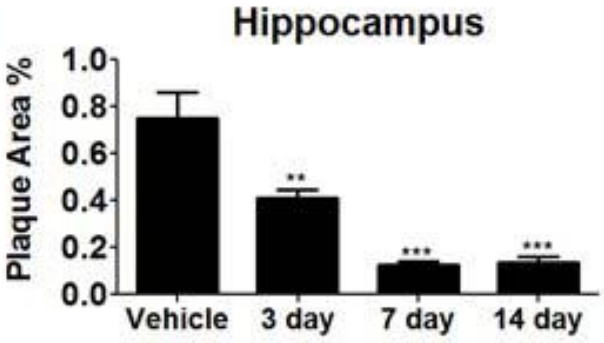


RXR agonist treatment rapidly clears preexisting plaques from the brain



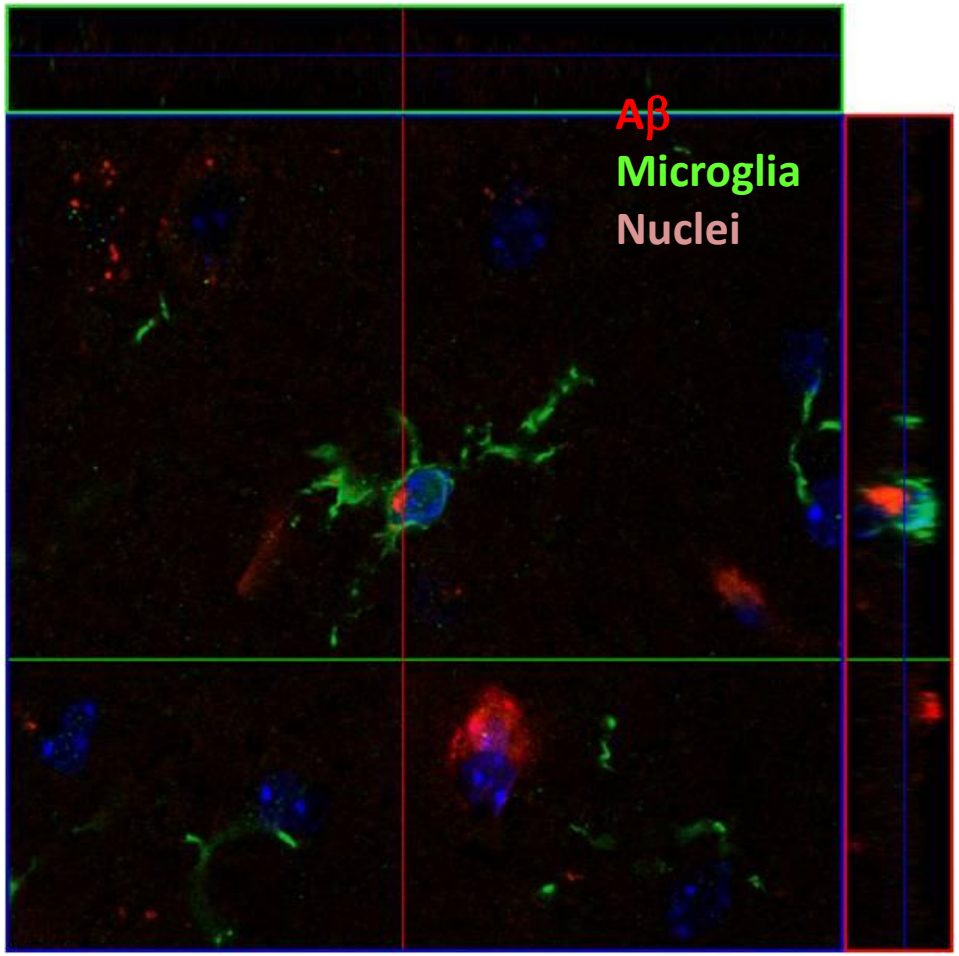
Thioflavin S





6 month old
APP/PS1

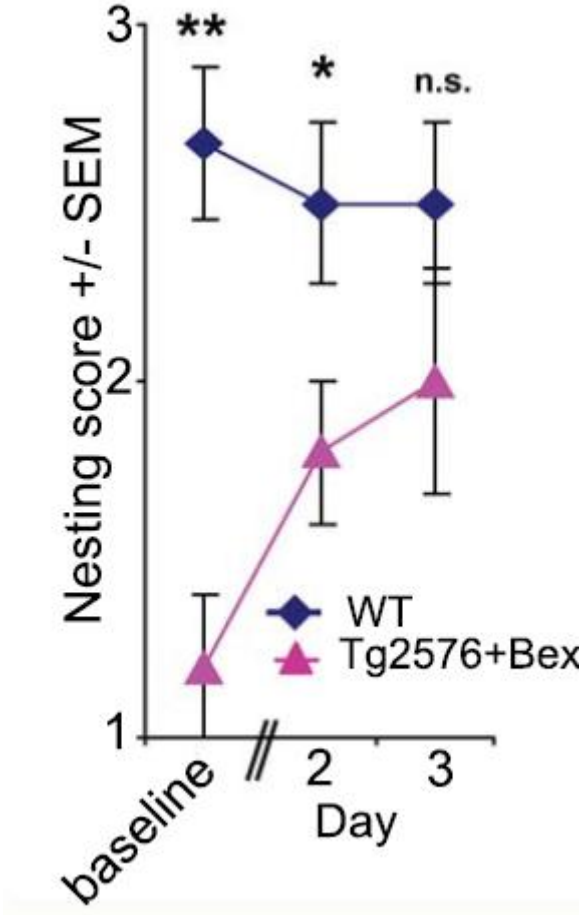
Bexarotene stimulates microglial phagocytosis of Aβ



9 month old APP/PS1 mice
72 hrs treatment with Bexarotene

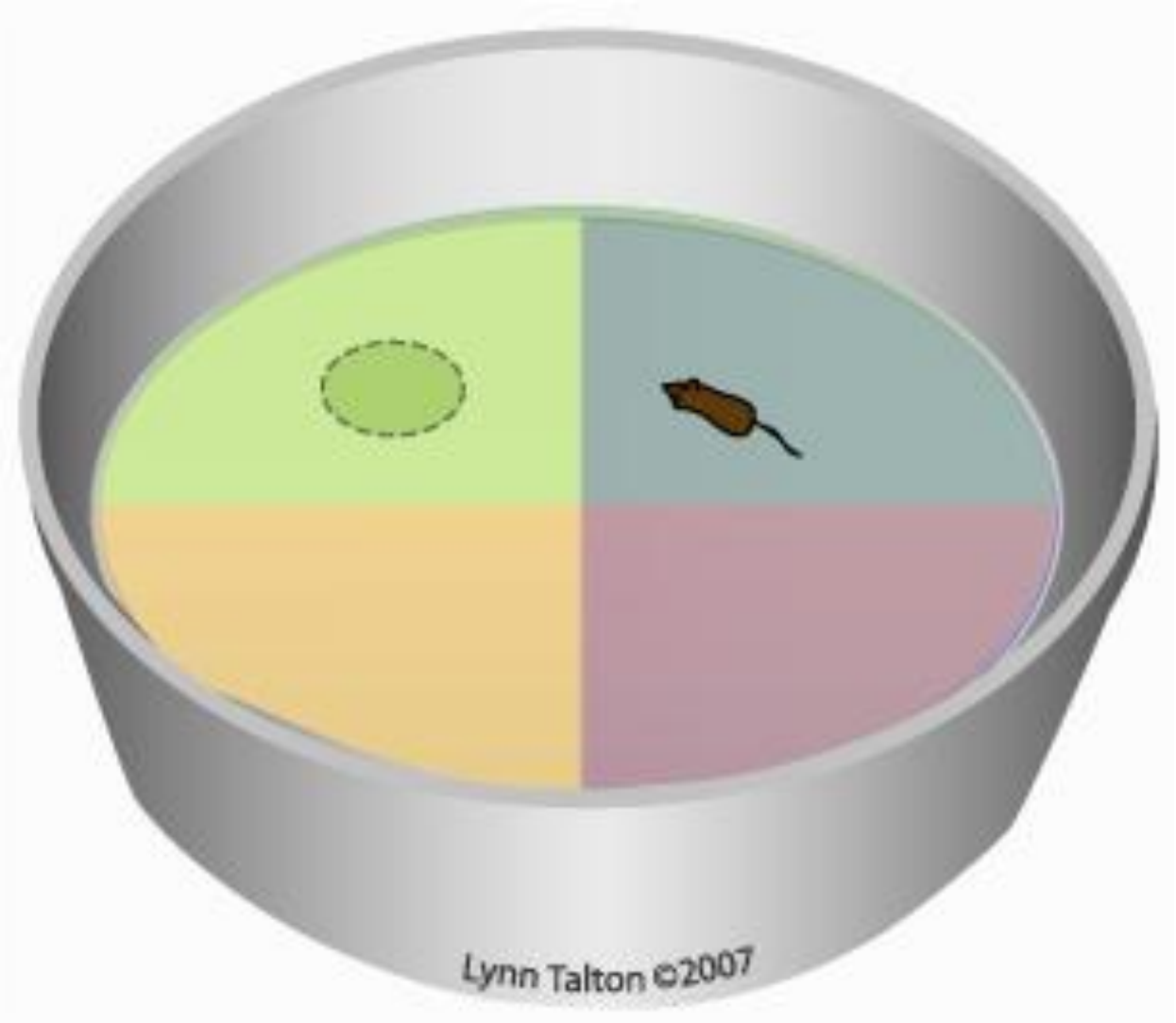
Bexarotene rapidly stimulates the phagocytic removal of amyloid plaques

Bexarotene Treatment Restores Nesting Behavior

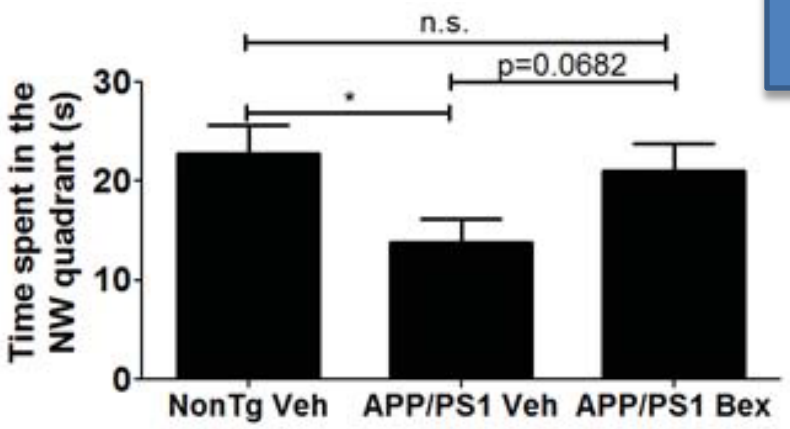


3 day treatment

Morris Water Maze



Bexarotene Treatment Improves Memory in Mouse Models of AD

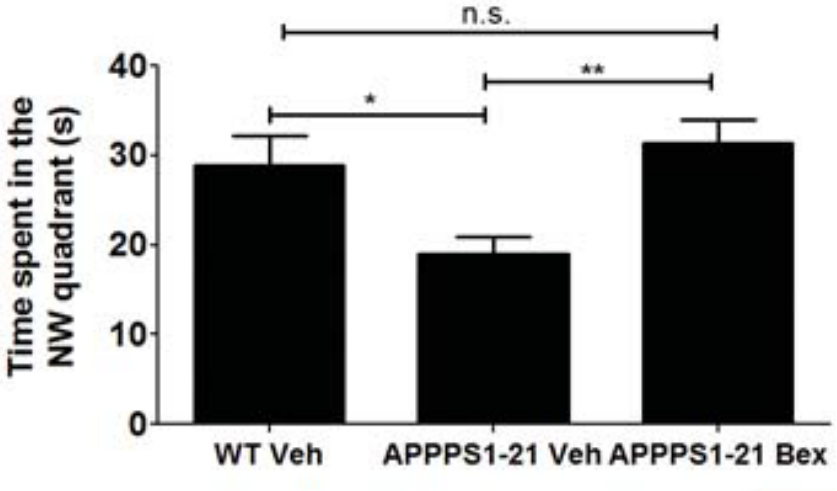


9 month APP/PS1

90 day treatment

7-8 month APPPS1-21

20 day treatment



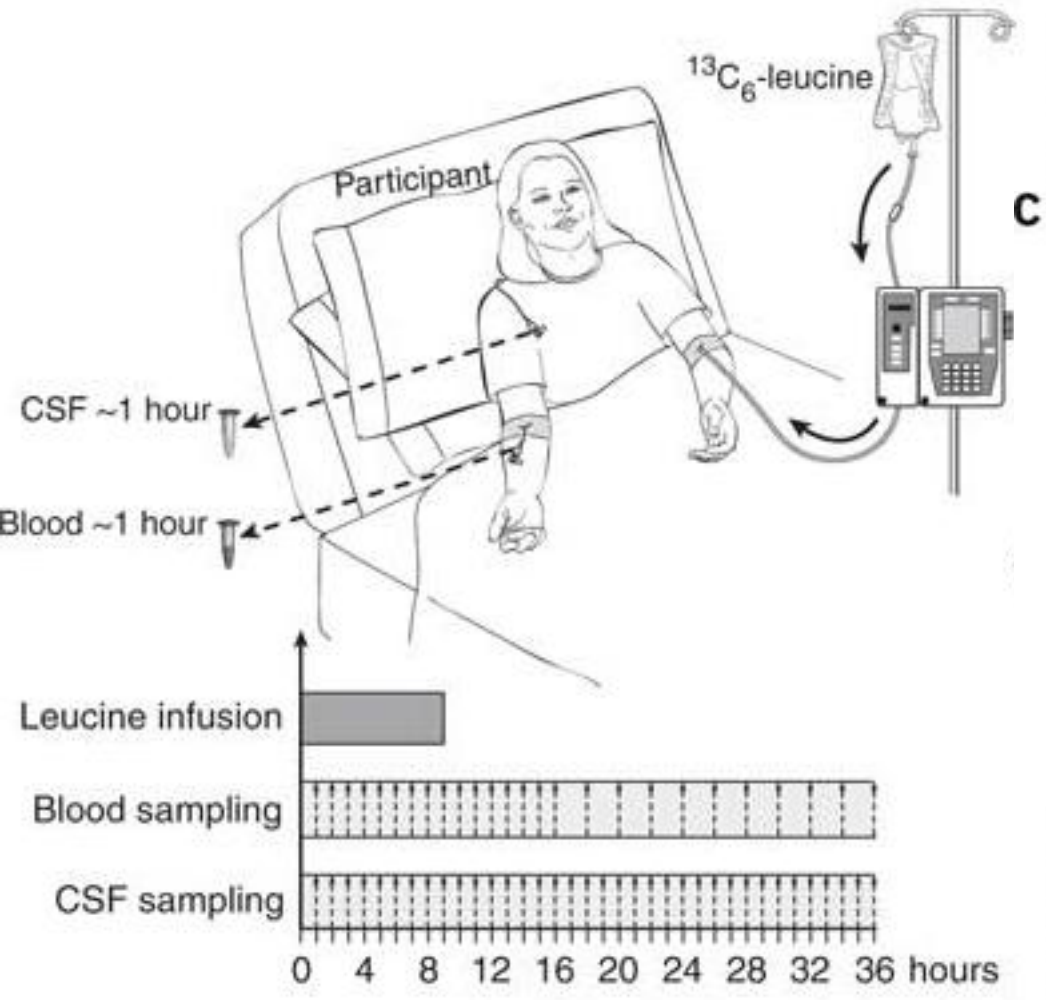
Translation into Clinical Trials

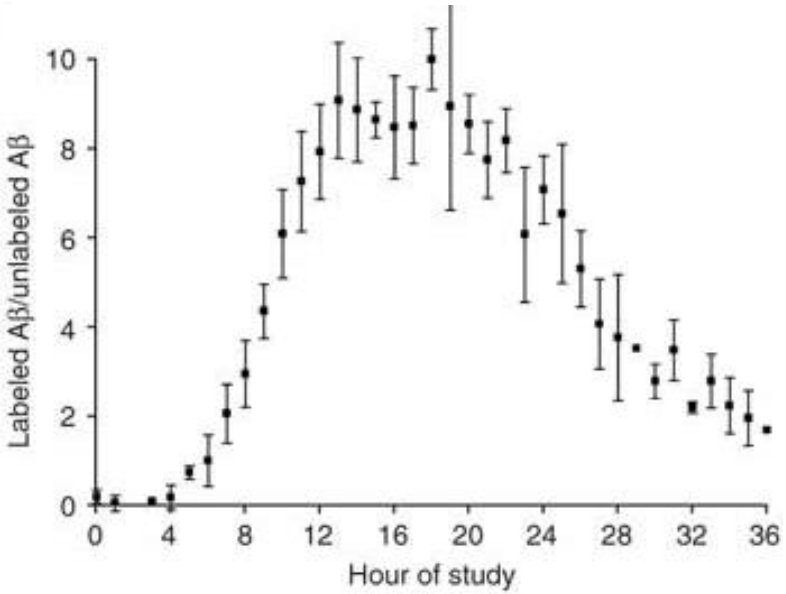
Proof of Mechanism Clinical Biomarker Trial of Bexarotene in Humans: A randomized, placebo-controlled study of Aβ and ApoE metabolism in the nervous system

Cost: $1.16M
100% of funding is in place.
Expect to initiate trial September, 2012
4 months to completion

C2N Diagnostics

SILK Technology



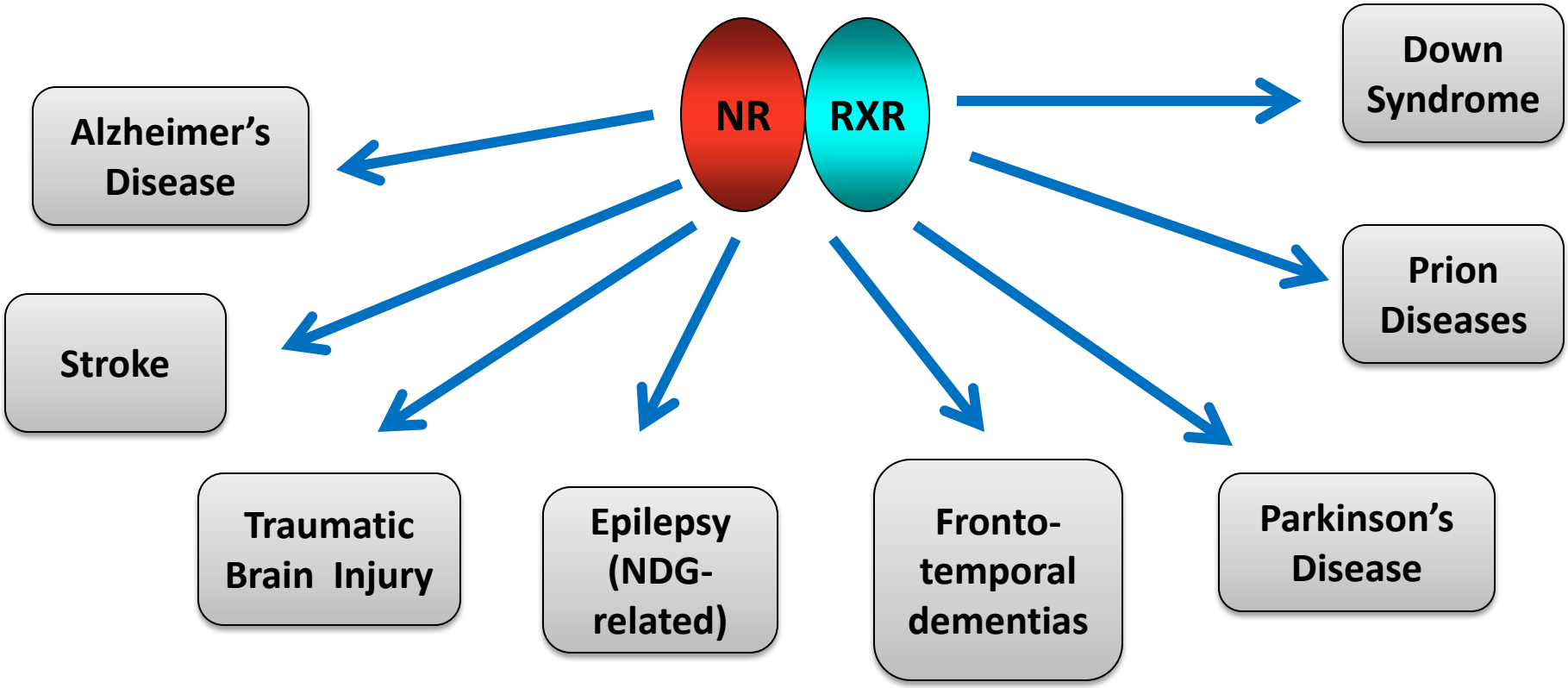


Trial Endpoints

- 12 Normal Subjects
- 6 subjects each on placebo or bexarotene
- Blood and CSF drawn hourly for 36 hrs
- Biomarkers:
  - Aβ clearance rate
  - ApoE biosynthesis rate
  - Brain and plasma levels of bexarotene

The use of an FDA-approved drug dramatically speeds the development of this therapy for AD

Discovery of new biological mechanisms and therapies will allow their application to other CNS disorders



Rationale for use in CJD

- Bexatrotene suppresses the glial inflammatory responses to neuronal dysfunction and death
- Bexarotene acts in neurons to promote the clearance of amyloid, thus it is possible that it may clear prion intraneuronal deposits
- Drug may promote microglial-mediated phagocytosis of extracellular prion deposits
- Drugs of this class exhibit broad neuroprotective actions