Tau Mechanism in Dementia

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Major Therapeutic Objective in the Field: Inhibit Production and Aggregation of Aβ

Inhibiting β-Secretase
What Is the Risk of Side Effects?

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Selected BACE1 Substrates</th>
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</thead>
<tbody>
<tr>
<td>Aβ</td>
<td></td>
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<tr>
<td>APP</td>
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<tr>
<td>APP-like Proteins</td>
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<tr>
<td>Low Density Lipoprotein Receptor-Related Protein</td>
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<tr>
<td>Neuregulin-1</td>
<td></td>
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<tr>
<td>P-selectin Glycoprotein Ligand-1</td>
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<tr>
<td>STG6Gal I Sialyltransferase</td>
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<tr>
<td>Voltage-gated Sodium Channel β Subunit</td>
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</tbody>
</table>

# Inhibiting γ-Secretase

What Is the Risk of Side Effects?

## Table 2

<table>
<thead>
<tr>
<th>Selected γ-secretase Substrates</th>
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<tbody>
<tr>
<td>γ-protocadherin</td>
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<tr>
<td>APLP1</td>
</tr>
<tr>
<td>APLP2</td>
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<tr>
<td>APP</td>
</tr>
<tr>
<td>CD43</td>
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<tr>
<td>CD44</td>
</tr>
<tr>
<td>DCC</td>
</tr>
<tr>
<td>DELTA</td>
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<tr>
<td>E-Cadherin</td>
</tr>
<tr>
<td>ErbB-4</td>
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<tr>
<td>Jagged</td>
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<tr>
<td>Voltage-gated Sodium Channel β2 Subunit</td>
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<tr>
<td>N-Cadherin</td>
</tr>
<tr>
<td>Nectin-1α</td>
</tr>
<tr>
<td>Notch NRADD</td>
</tr>
<tr>
<td>P75</td>
</tr>
<tr>
<td>Syndecan-1</td>
</tr>
<tr>
<td>Tyrosinase</td>
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<tr>
<td>Tyrosinase-related</td>
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<tr>
<td>Proteins 1 and 2</td>
</tr>
</tbody>
</table>

Clearing Plaques
Efficacy and Risk of Side Effects?

NEP, IDE, ECE, CatB...

Aβ

Plaque

Microglia

Antibodies

Blood Vessel
Alternative or Complementary Targets in the Multifactorial Pathogenesis of Alzheimer’s Disease
SeveralTau Isoforms Are Derived from a Single Gene by Alternative Splicing

Modified from Buee et al., Brain Res Rev (2000)
Most Tau Phosphorylation Sites Surround the Microtubule Binding Domains
Does Tau Play the Same Role in AD and FTD?

Mutations

? -> Tau

? -> FTD

Post-translational Modification?
Aggregation?
NFT Formation?
Oligomers?
Other?

Aβ

? -> Tau

? -> AD

E4

Ashe, Binder, Cotman, Davies, Duff, Goetz, Huang, Hutton, Hyman, Lee, Mahley, Mandelkoff, Miller, Trojanowski, van Leuven,...
Is Tau Required for $A\beta$ to Elicit Cognitive Deficits?
Is Tau Required for Aβ to Elicit Cognitive Deficits?
Modulating Endogenous Tau Levels in hAPP Mice

- Normal Tau (2 copies)
  - Normal Aβ
  - Memory Deficits
  - Early Mortality

- Half Tau (1 copy)
  - Normal Aβ
  - ???

- No Tau (0 copies)
  - Normal Aβ
  - ???
Modulating Endogenous Tau Levels in hAPP Mice

- Normal Tau (2 copies)
- Half Tau (1 copy)
- No Tau (0 copies)

- Normal Aβ
- Normal Aβ
- Normal Aβ

- High Aβ
- High Aβ
- High Aβ

- Memory Deficits Early Mortality
- Normal Memory No Early Mortality
- Normal Memory No Early Mortality

Tau Reduction Prevents hAPP/Aβ-induced Premature Mortality

\[ p < 0.003 \]
Assessment of Navigational Deficits in Patients with Mild Cognitive Impairment (MCI) or Early AD

delpolyi et al, Neurology (2007)
Assessment of Navigational Deficits in AD Patients and hAPP Mice

AD Brain

Mouse Brain

NTG Control

hAPP Mouse
Tau Reduction Does Not Change Learning in the Morris Water Maze in the Absence of hAPP/Aβ
High Levels of Aβ Impair Learning in the Presence of Wildtype Tau Levels
Tau Reduction Ameliorates Aβ-induced Learning Deficits in the Morris Water Maze

![Graph showing escape latency by day of training for different groups.](image-url)
Tau Ablation Further Reduces Aβ-induced Learning Deficits in the Morris Water Maze

APP*Tau
$p < 0.02$
Tau Reduction Does Not Change Plaque Load But Makes the Brain Resistant Against Aβ-induced Functional Deficits

WT

hAPP (Tau+/+)

hAPP (Tau−/−)

Aβ Immunostain

Typical swim paths during probe trial in Morris water maze
Our Latest Version of the Aβ Cascade Hypothesis

Aβ

increased network excitability

compensatory inhibitory mechanisms

network dysfunction
High Levels of Human Aβ Elicit Nonconvulsive Epileptiform Activity in the Cortex and Hippocampus of hAPP Transgenic Mice

Palop et al, Neuron (2007)
High Levels of Human Aβ Elicit Intermittent Nonconvulsivive Seizures in hAPP Transgenic Mice
Clinical Evidence for Convulsive Seizures in AD

Pedigrees with familial AD onset ≤40 years of age
- 83% convulsive seizures
- 92% myoclonus

Seizure risk in sporadic AD (relative to ref. population)
- 87-fold increased at 50-59 years
- 3-fold increased at 85+ years

Amatniek et al, Epilepsia (2006)
Larner & Doran, J Neurol (2006)
Snider et al, Arch Neurol (2005)
Others
ALZHEIMER'S DISEASE AND EPILEPSY WORKSHOP

Does Epilepsy Play a Role in Alzheimer's Disease?

Discussion of the Evidence and Potential Pathogenic Mechanisms

Saturday
July 26, 2008
8:30am–5:30pm
PRECEDING THE INTERNATIONAL CONFERENCE ON ALZHEIMER'S DISEASE (ICAD)
Chicago, Illinois

The purpose of this meeting is to increase awareness and encourage further study of the potential link between Alzheimer's disease (AD) and epilepsy. This link is supported by both clinical and experimental evidence (see Reading List), but remains poorly understood. To improve this situation and fill pertinent knowledge gaps, we will bring together AD researchers with epilepsy researchers and ask them to critically discuss if aberrant neuronal activity might play a key role in AD pathogenesis and if this question deserves to be explored further in focused interdisciplinary basic and clinical investigations.

Host
Gladstone Institute of Neurological Disease

Organizers
Lennart Mucke Gladstone
Jeffrey Noebels Baylor
Dora Kovacs Harvard
Tau Reduction Increases Resistance to PTZ-induced Seizures in Nontransgenic Mice

![Graph showing latency (min) against seizure severity for Tau+/+, Tau+/-, and Tau-/- mice. The graph indicates a significant difference (p < 0.001) in resistance to seizures among the three groups.]
Novel Strategy to Block this Cascade

$A_\beta$

$\downarrow$

$\downarrow$ Tau

increased network excitability

compensatory inhibitory mechanisms

network dysfunction
Potential Roles of Tau in the Pathogenesis of Neurodegenerative Disease

- Abnormally Modified and/or Aggregated
- Gain of Function
  - DETRIMENTAL
- Loss of Function
  - DETRIMENTAL
- Toxicity
- Neuronal Death
Potential Roles of Tau in the Pathogenesis of Neurodegenerative Disease
Tau Is a Microtubule-associated Protein (MAP) that May Regulate Axonal Transport

Courtesy of Eva-Maria Mandelkow
Working Hypothesis

Aβ

 Tau-Exited

Other Effects
Neuronal Dysfunction
Working Hypothesis

Aβ

Other Effects

Neuronal Dysfunction

↓ Tau
Working Hypothesis

Aβ

↓ Tau

Neuronal Overexcitation

Other Effects

Neuronal Dysfunction
Microarray Analysis: Questions

- Other Effects
- Tau Effect
- Aβ τ

APP Effect

+/- +/ - -/ -
Gene Expression–Behavior Correlation as a Tool for Microarray Analysis
Summary

• Tau reduction ameliorates Aβ-induced deficits
  – Even partial tau reduction is effective
  – Prevents multiple adverse outcome measures
  – Works in different mouse models of AD
• Tau reduction creates resistance to Aβ
  – Does not change Aβ burden per se
  – Works downstream to uncouple Aβ from pathogenic mechanisms
• Tau reduction has an excitoprotective effect
  – Prevents EEG abnormalities in hAPP mice
  – Lowers susceptibility to seizures
  – Consistent with a permissive effect of tau for epileptiform activity
• Gene expression microarray
  – Behavioral correlation is a powerful adjunct to microarray analysis
  – Tau reduction modulates ~20% of hAPP/Aβ-induced gene expression changes
Excitotoxicity and aberrant network activity have been implicated in the pathogenesis of many neurological diseases.

Tau reduction may have broad therapeutic potential.
Acknowledgements

Gladstone/UCSF:
Erik Roberson
Jorge Palop

Baylor:
Jeffrey Noebels
Jong Yoo

Duke:
Hana Dawson
Michael Vitek

Supported by:
National Institutes of Health (NIA & NINDS);
S. Bechtel, Jr.; Giannini Foundation; McBean Foundation