ADC Directors' Meeting

Saturday, April 12, 2008 – Sheraton V

Tau Mechanism in Dementia

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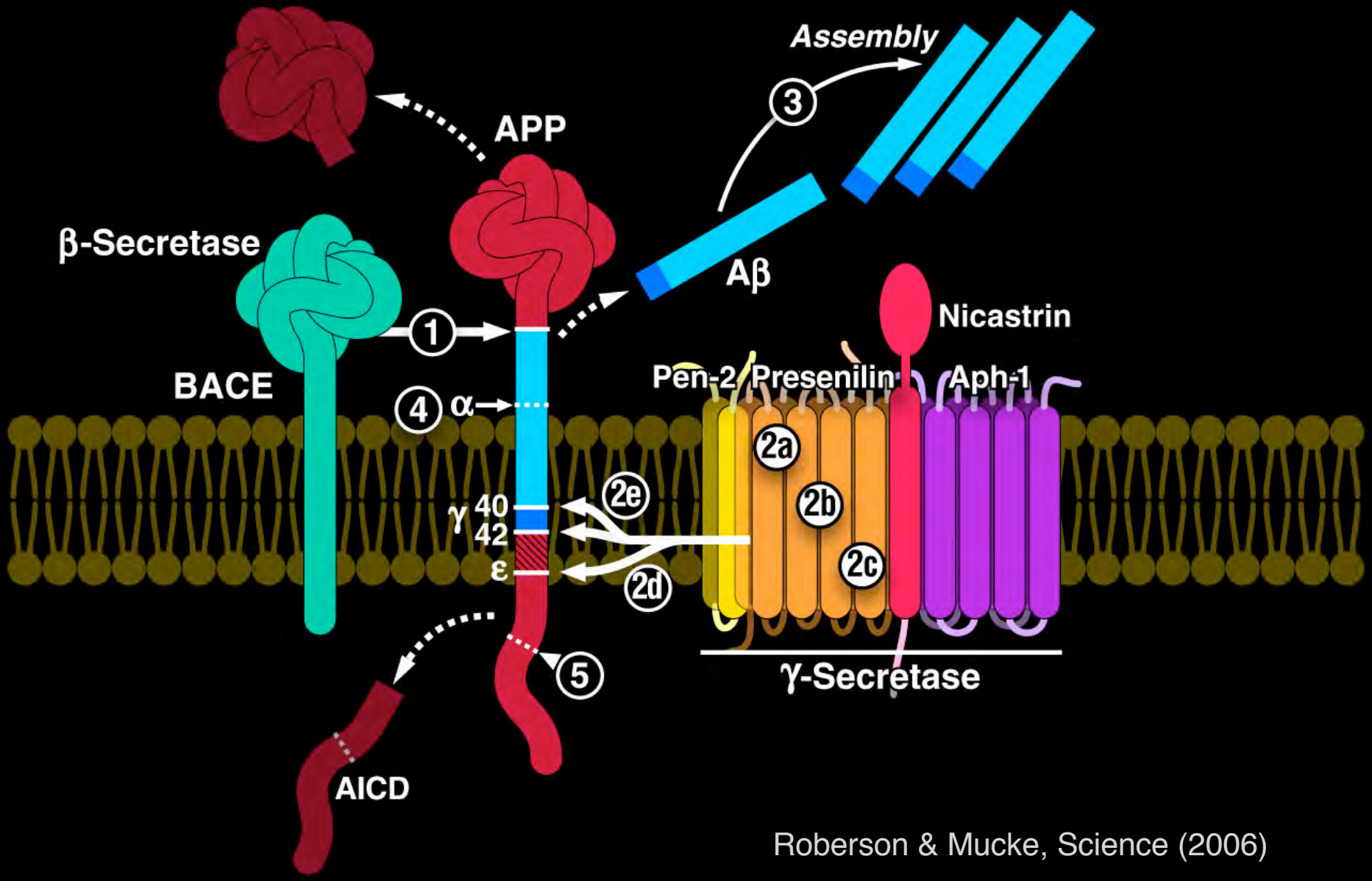
Joseph B. Martin Distinguished Professor
Department of Neurology
University of California, San Francisco

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



Roberson & Mucke, Science (2006)

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

Table 1	Selected BACE1 Substrates
Aβ	
APP	
APP-like Proteins	
Low Density Lipoprotein Receptor-Related Protein	
Neuregulin-1	
P-selectin Glycoprotein Ligand-1	
STG6Gal I Sialyltransferase	
Voltage-gated Sodium Channel β Subunit	

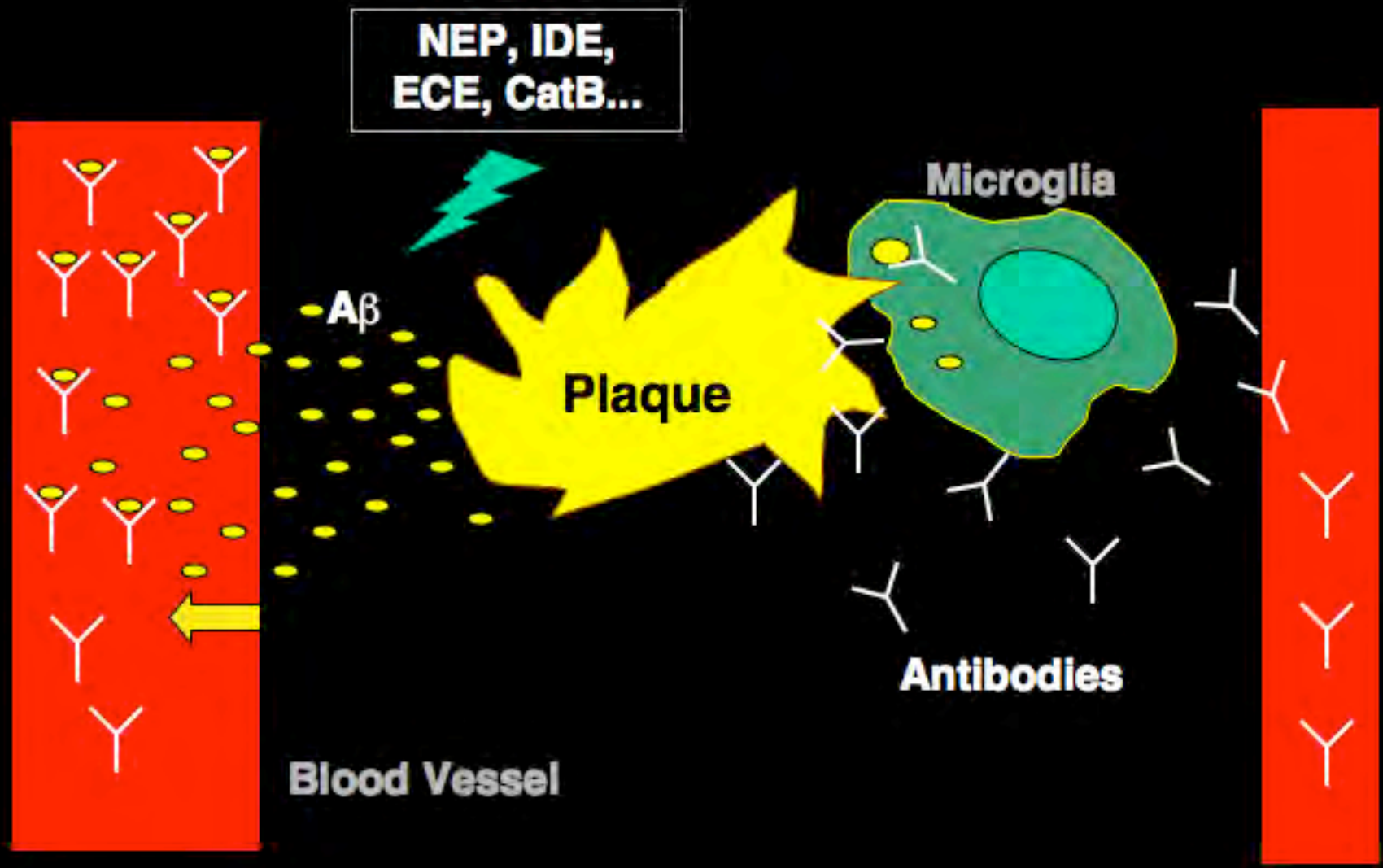
Adapted from Willem M, Garratt AN, Novak B, et al. (2006) Control of peripheral nerve myelination by the β-secretase BACE1. *Science* 314:664–666.

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

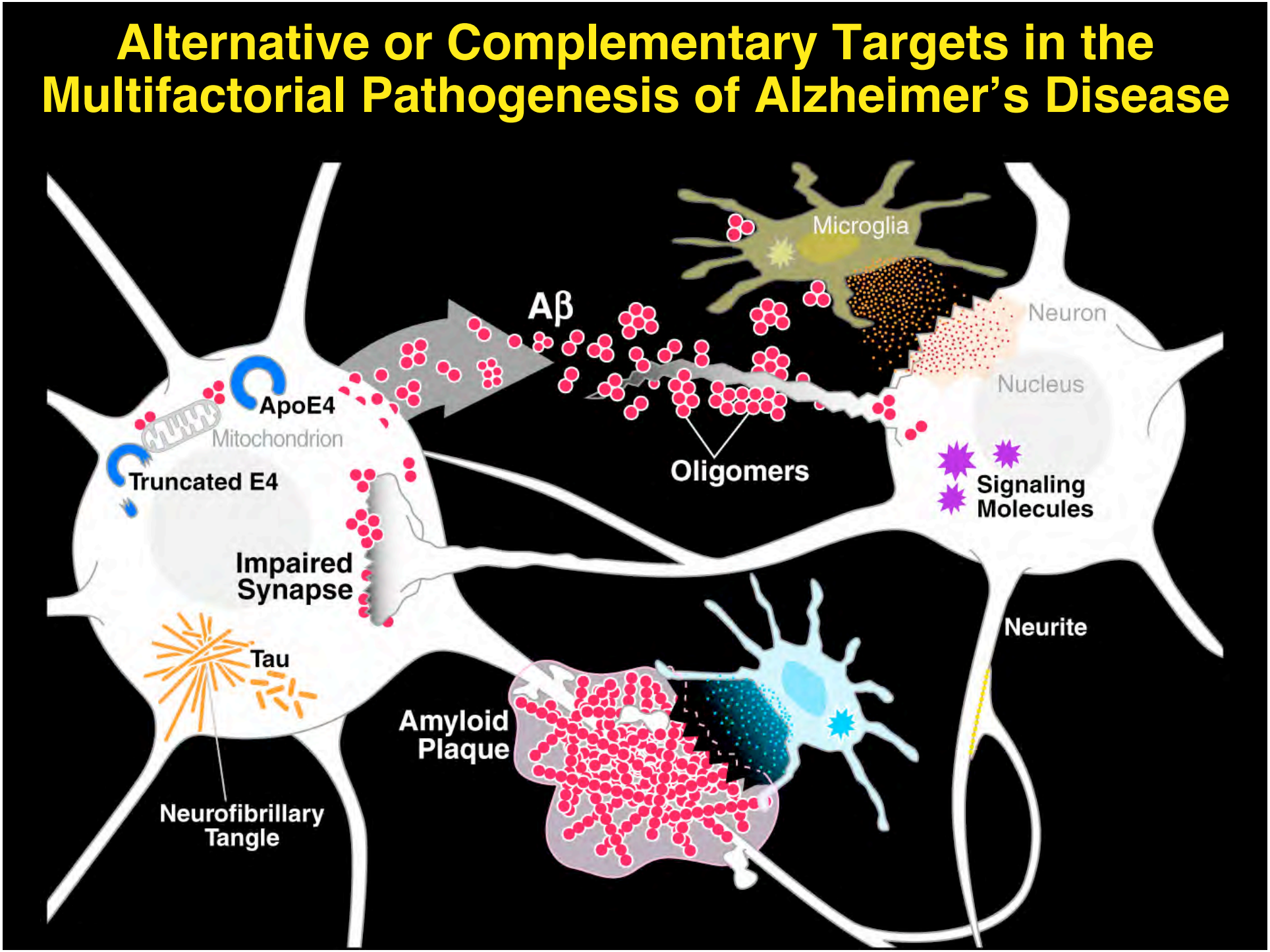
Table 2	Selected γ-secretase Substrates
γ-protocadherin	Voltage-gated Sodium Channel β2 Subunit
APLP1	N-Cadherin
APLP2	Nectin-1α
APP	Notch NRADD
CD43	P75
CD44	Syndecan-1
DCC	Tyrosinase
DELTA	Tyrosinase-related Proteins 1 and 2
E-Cadherin	
ErbB-4	
Jagged	

From Vetrivel KS, Zhang YW, Xu H, et al. (2006) Pathological and physiological functions of presenilins. *Mol. Neurodegener.* 1:4.

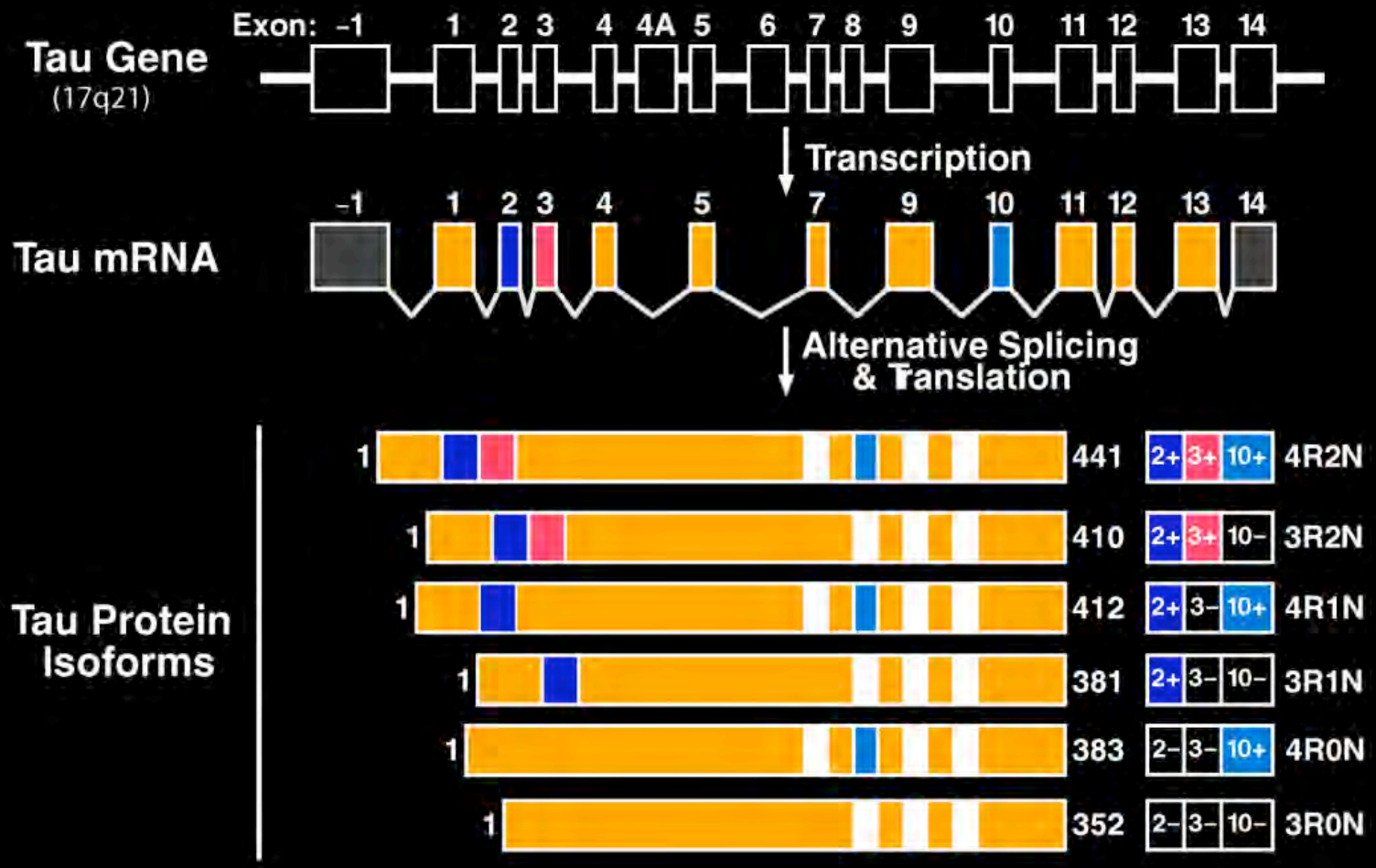
Clearing Plaques
Efficacy and Risk of Side Effects?



Alternative or Complementary Targets in the Multifactorial Pathogenesis of Alzheimer's Disease

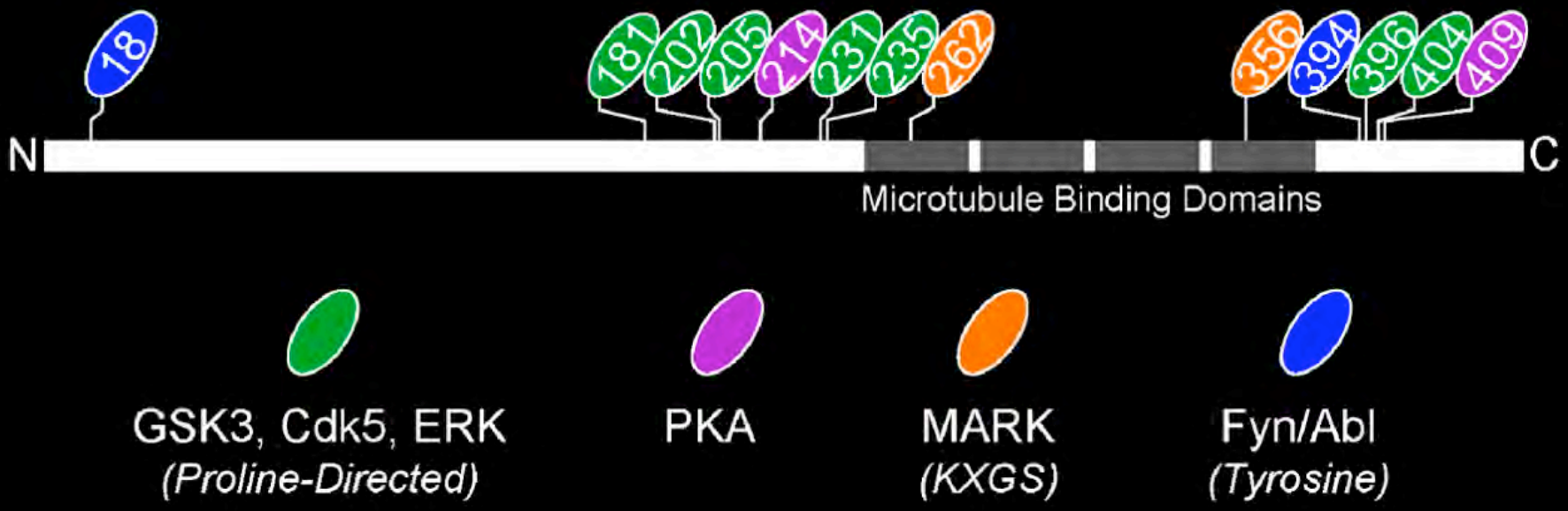


Several Tau Isoforms Are Derived from a Single Gene by Alternative Splicing

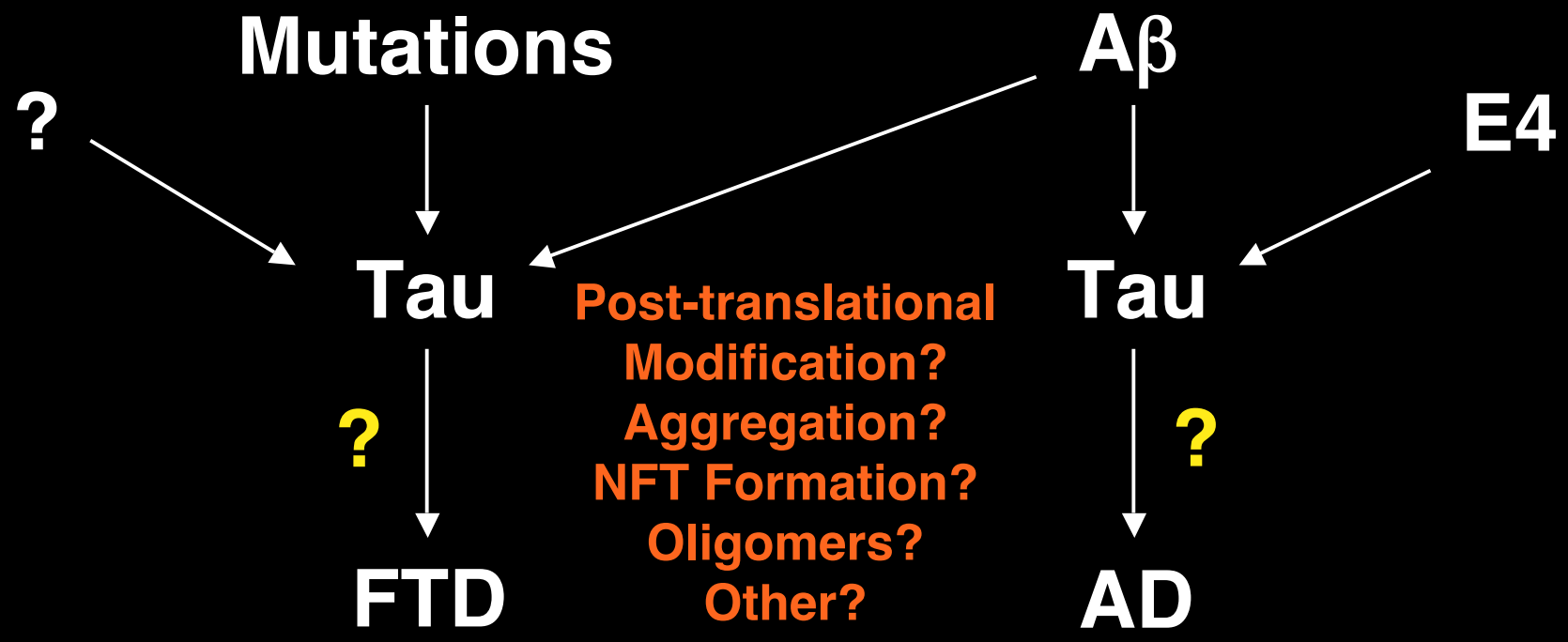


Modified from Buee et al., Brain Res Rev (2000)

Most Tau Phosphorylation Sites Surround the Microtubule Binding Domains

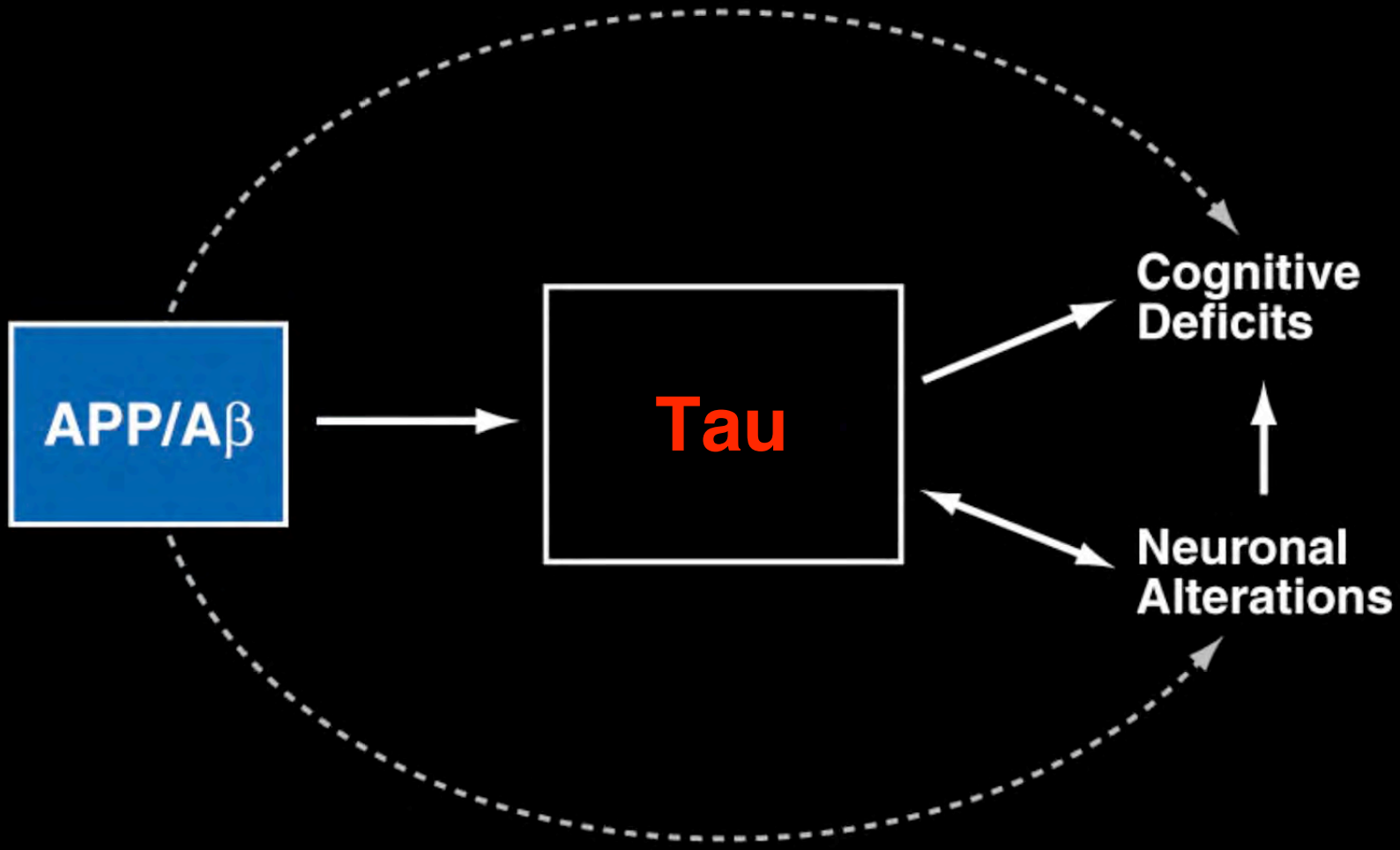


Does Tau Play the Same Role in AD and FTD?

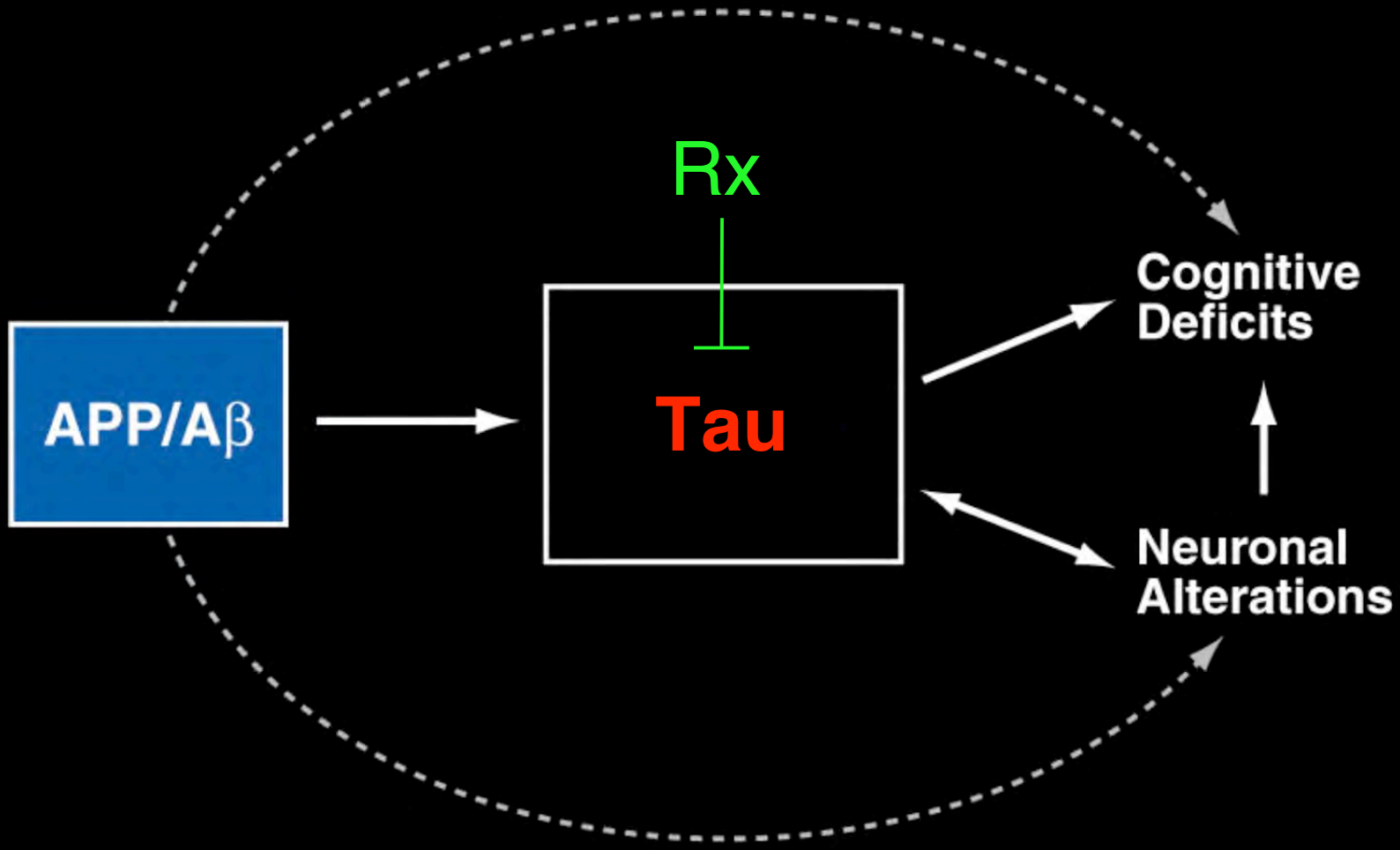


Ashe, Binder, Cotman, Davies, Duff, Goetz, Huang, Hutton, Hyman, Lee, Mahley, Mandelkoff, Miller, Trojanowski, van Leuven,...

Is Tau Required for Aβ to Elicit Cognitive Deficits?



Is Tau Required for Aβ to Elicit Cognitive Deficits?



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

Memory Deficits
Early Mortality

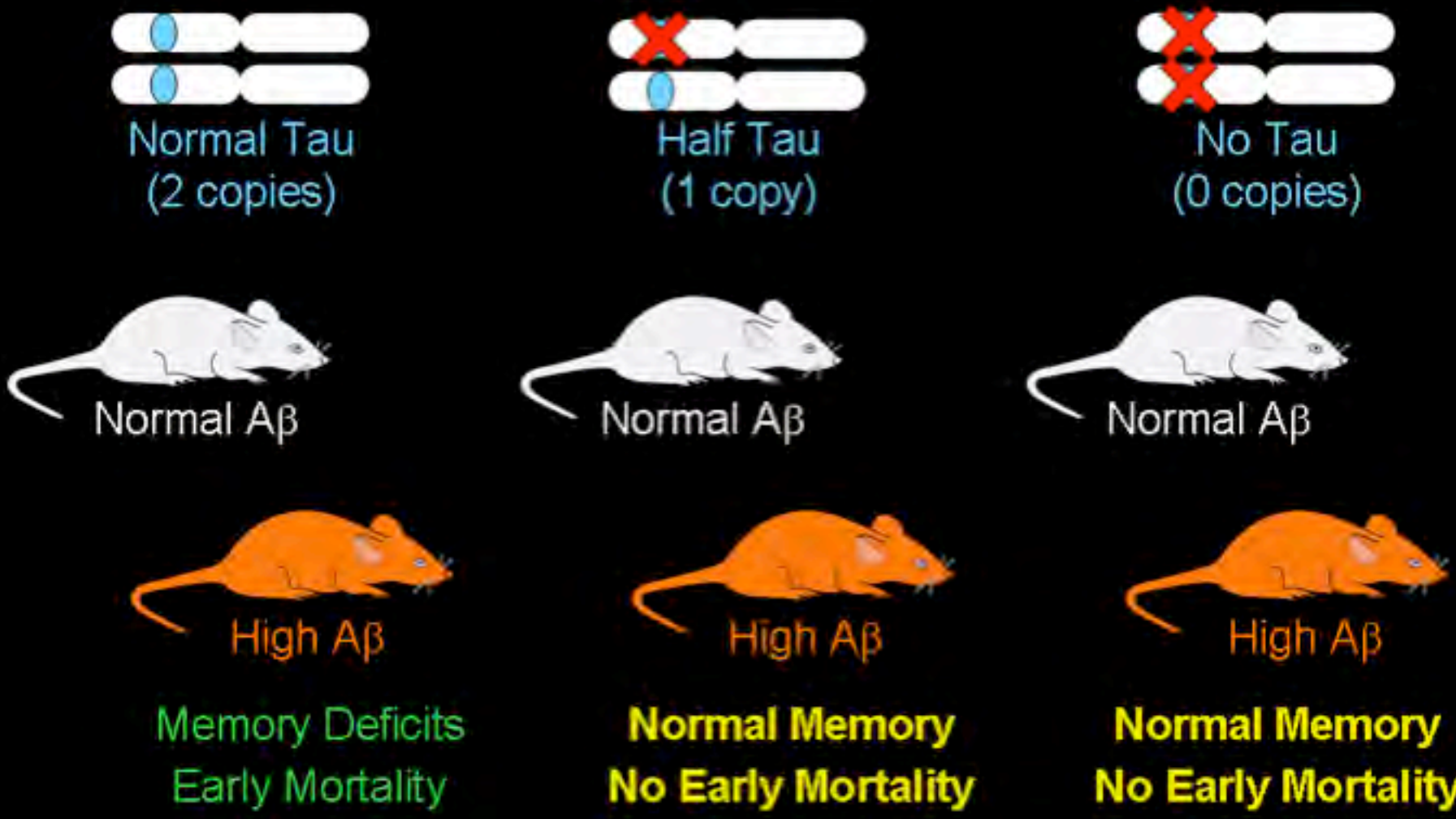
High Aβ

???

High Aβ

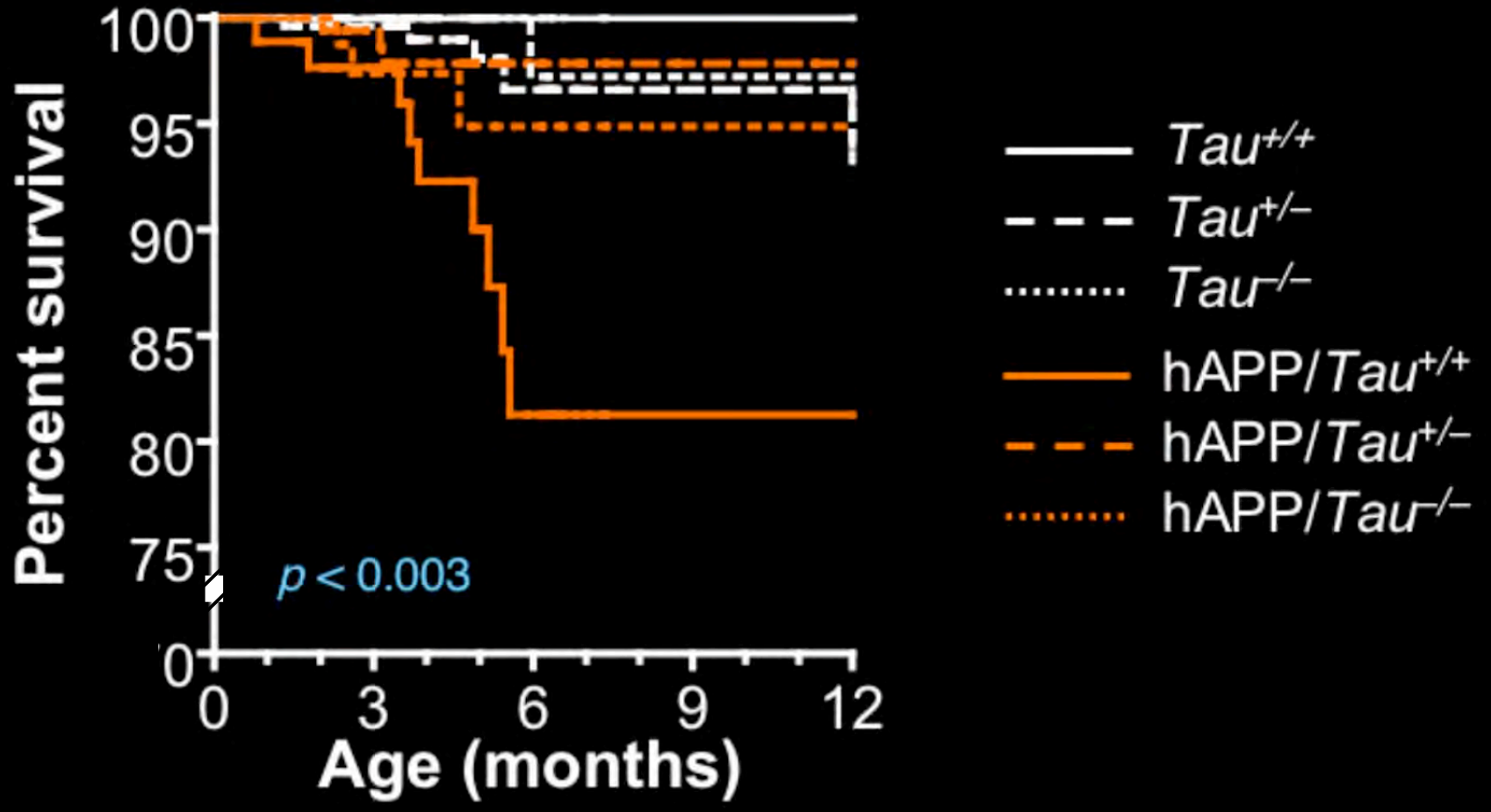
???

Modulating Endogenous Tau Levels in hAPP Mice

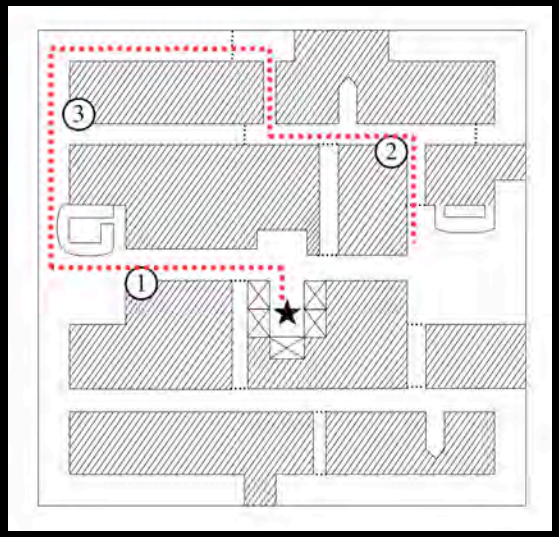


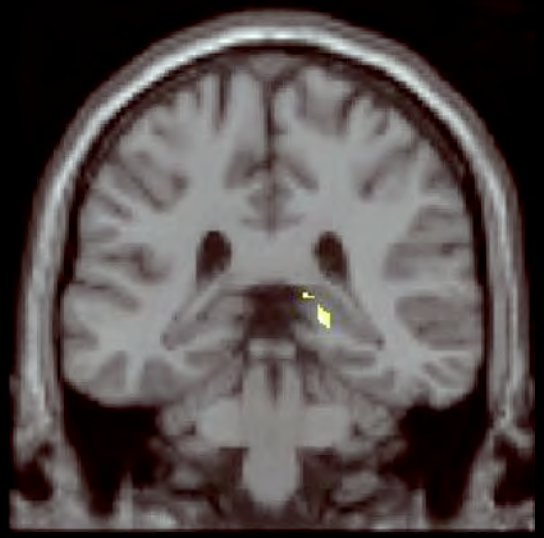
Roberson et al, Science (2007)

Tau Reduction Prevents hAPP/Aβ-induced Premature Mortality

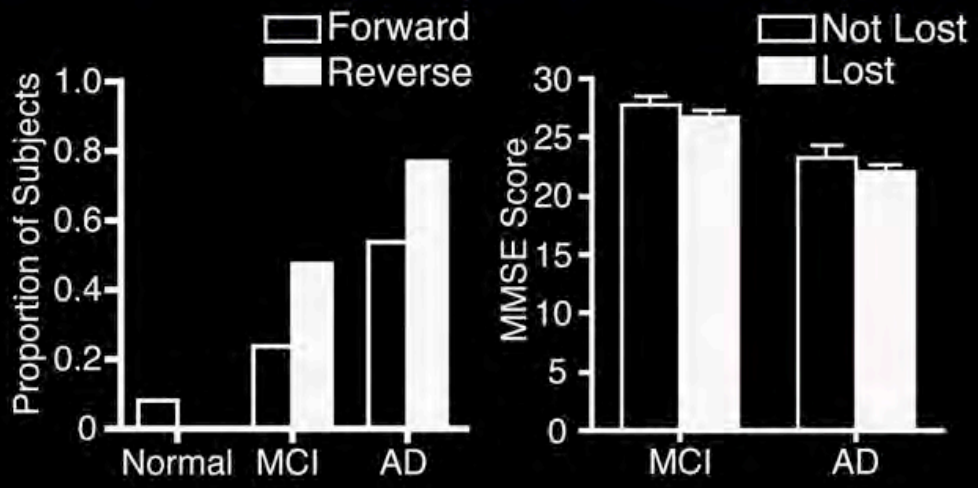


Assessment of Navigational Deficits in Patients with Mild Cognitive Impairment (MCI) or Early AD





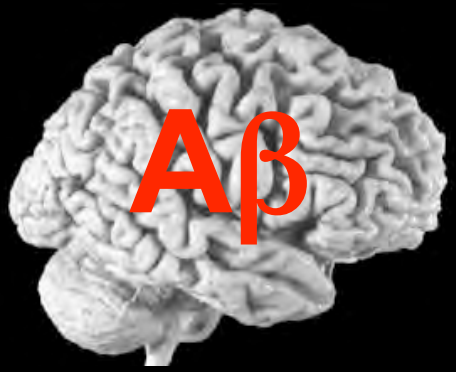
Proportion of subjects that got lost on forward or reverse route

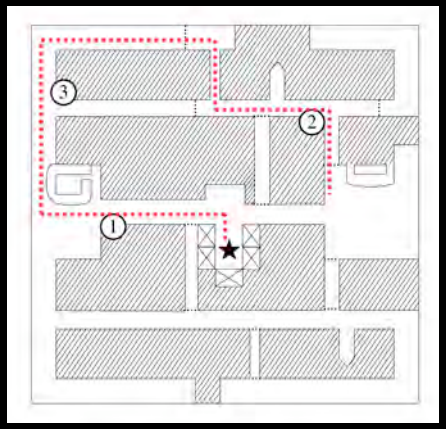


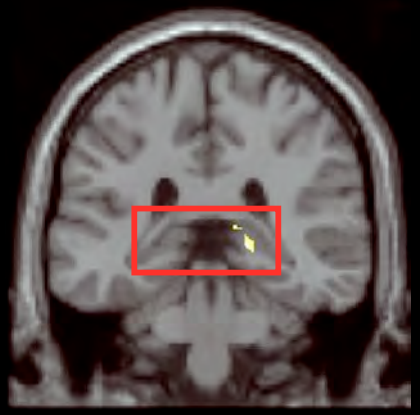
delpolyi et al, Neurology (2007)

Assessment of Navigational Deficits in AD Patients and hAPP Mice

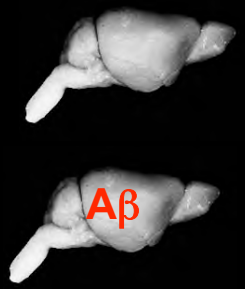
AD Brain



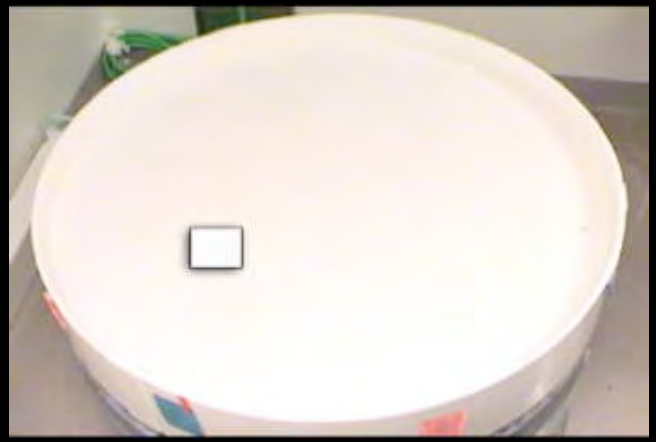




Mouse Brain

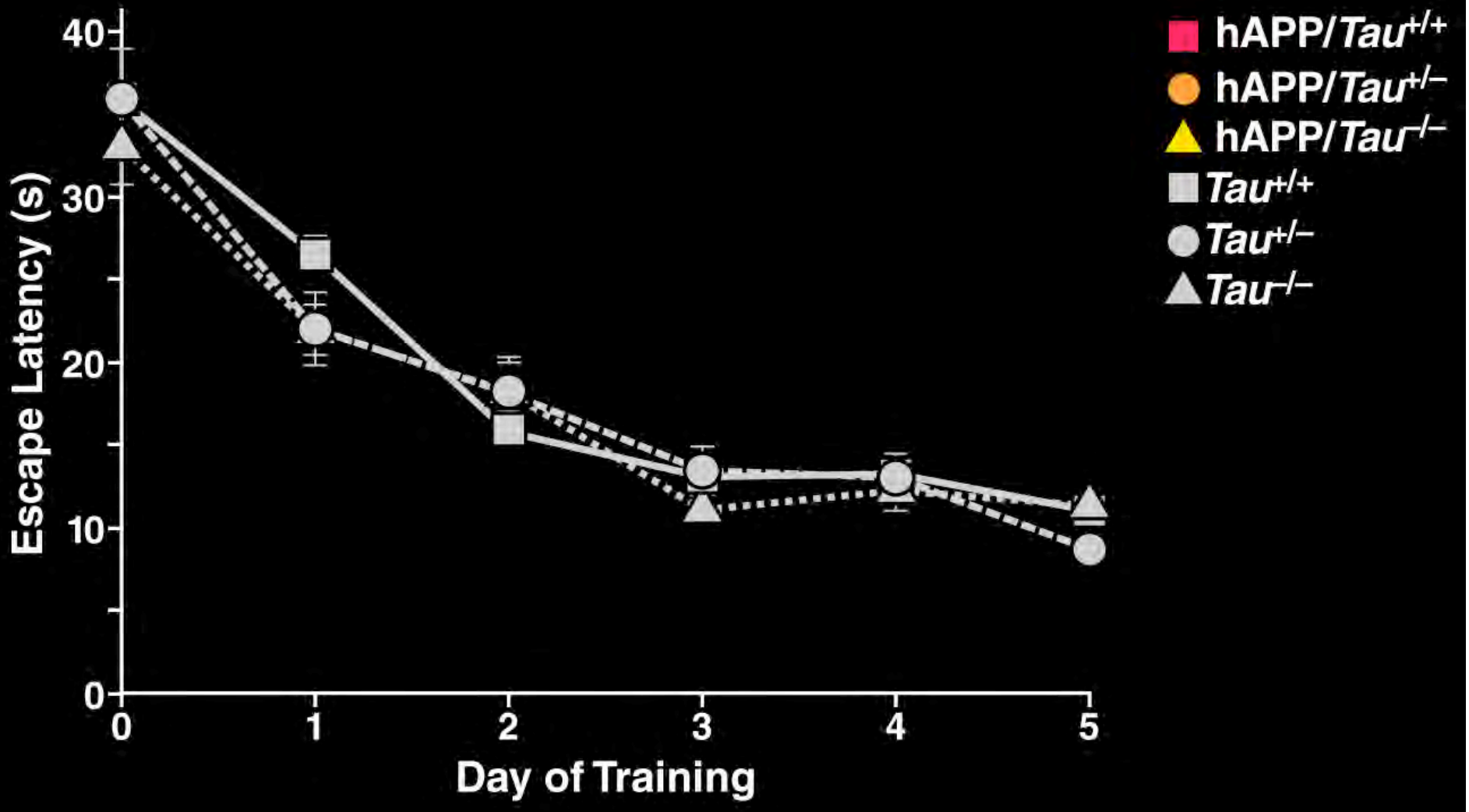


NTG Control

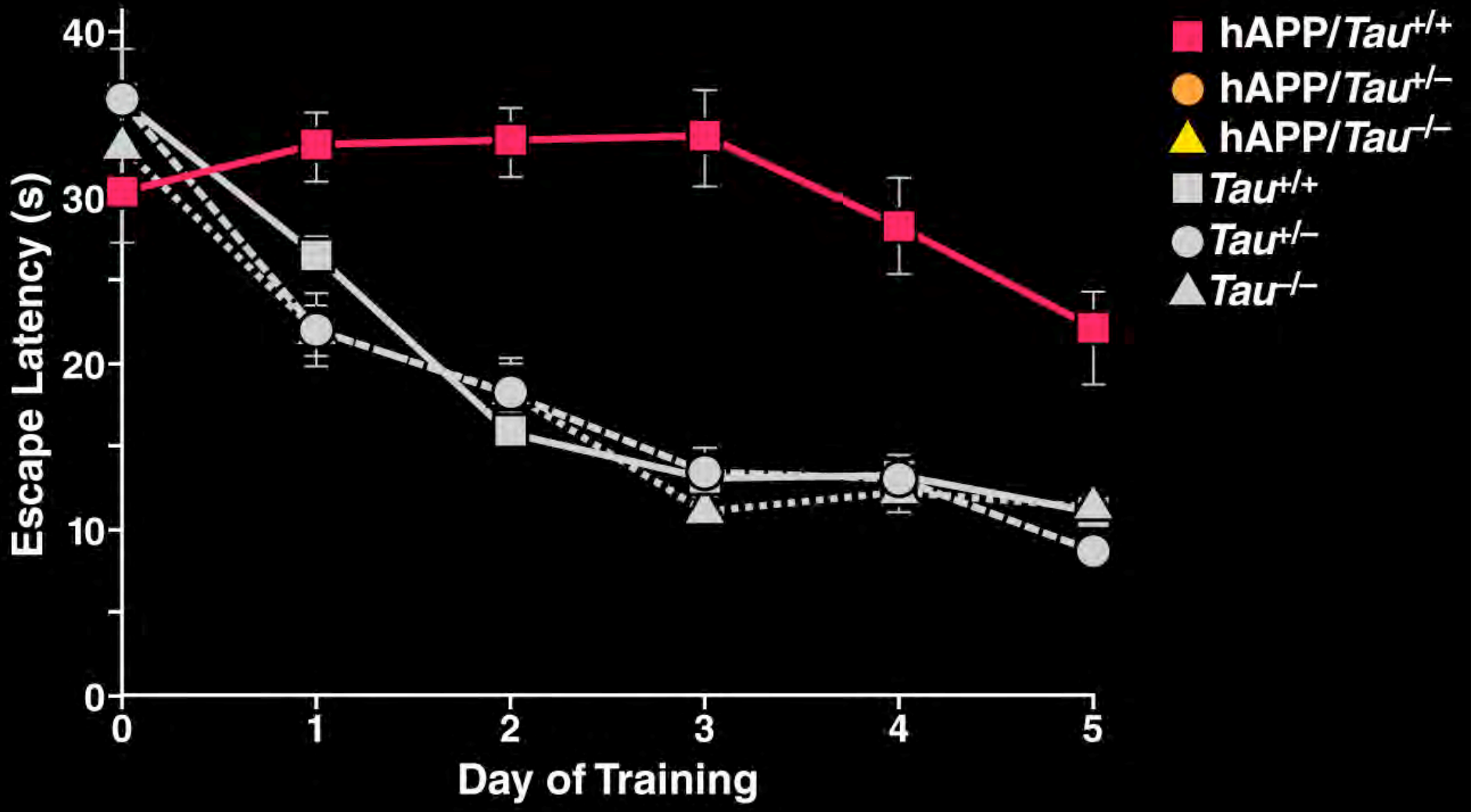


hAPP Mouse

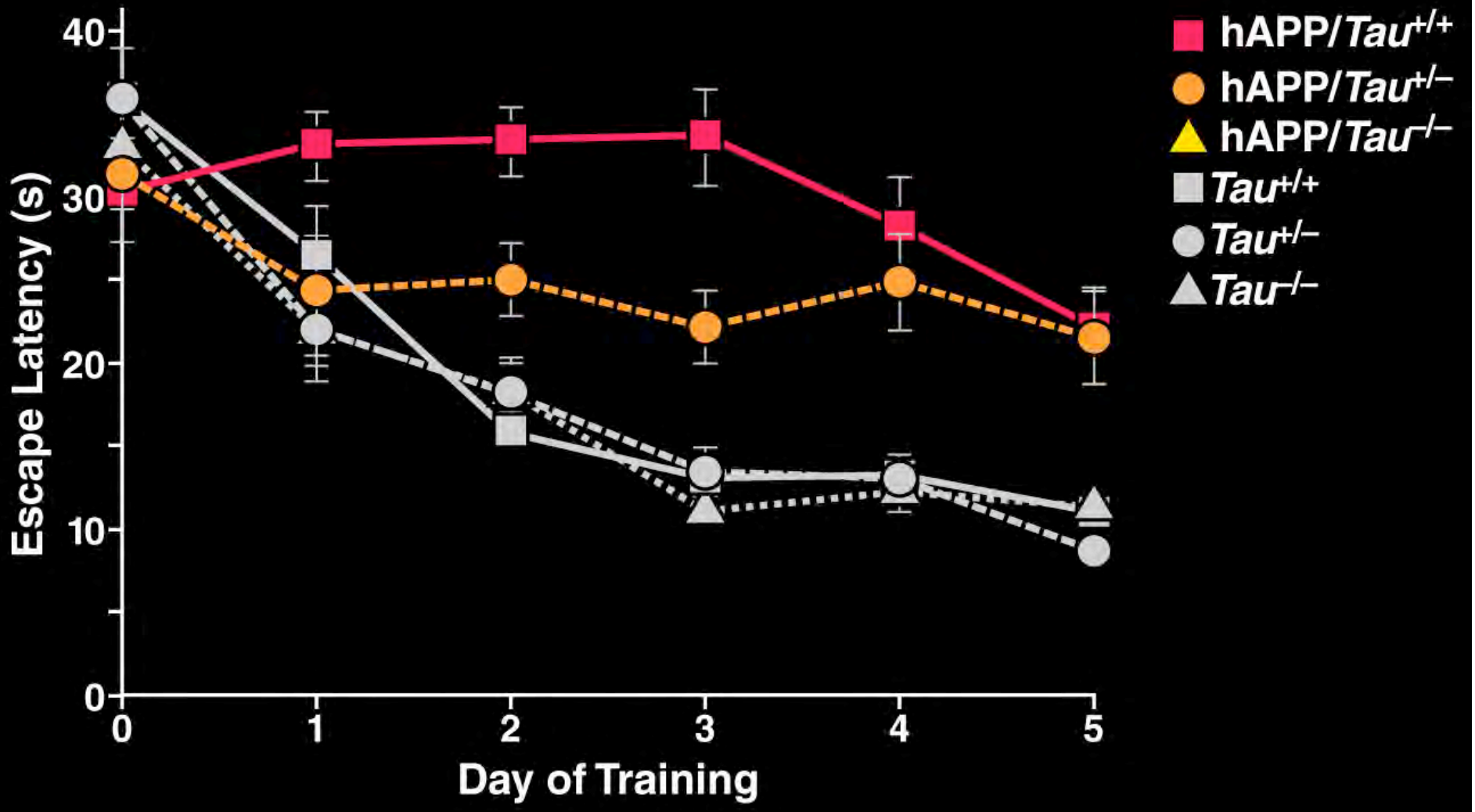
Tau Reduction Does Not Change Learning in the Morris Water Maze in the Absence of hAPP/Aβ



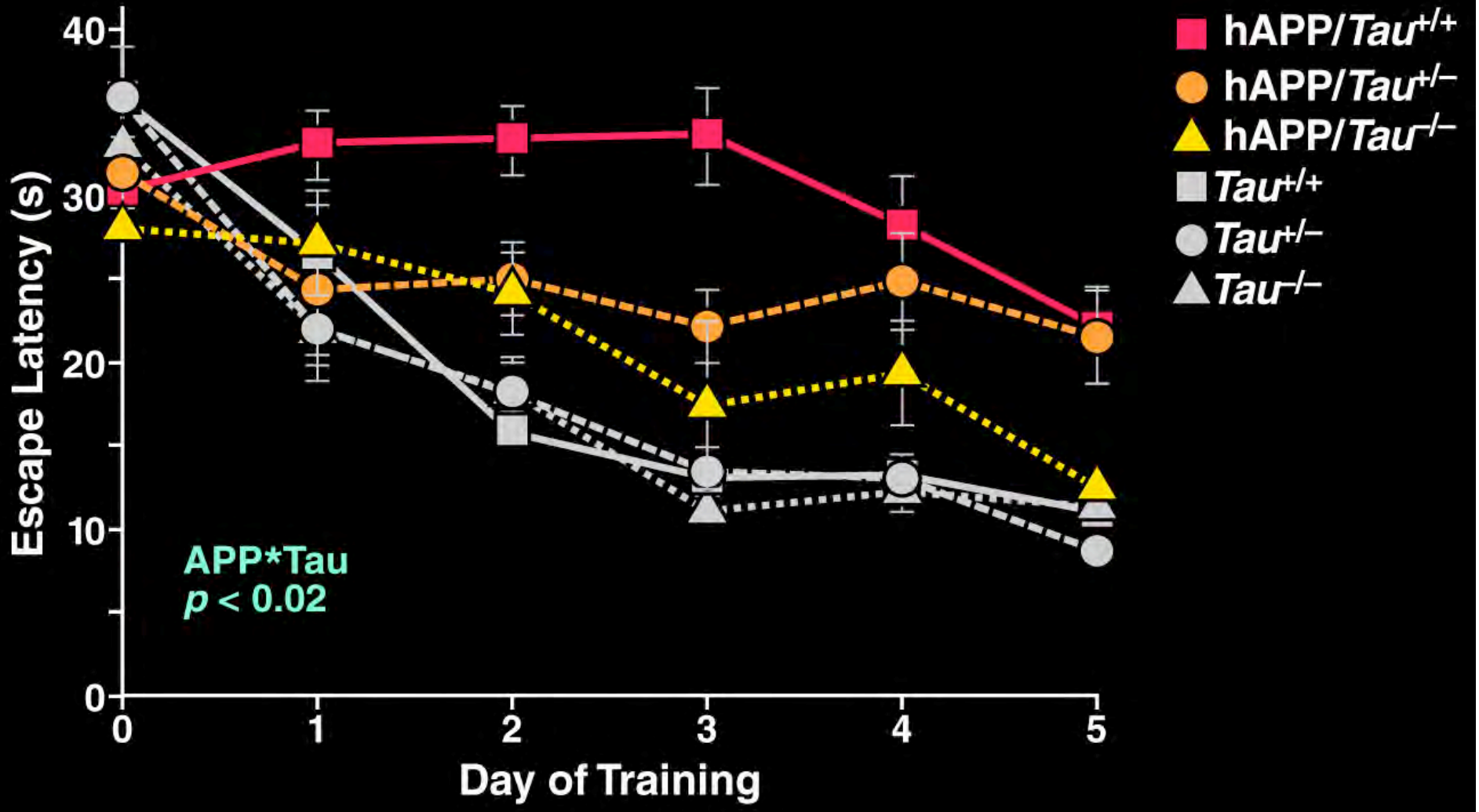
High Levels of Aβ Impair Learning in the Presence of Wildtype Tau Levels



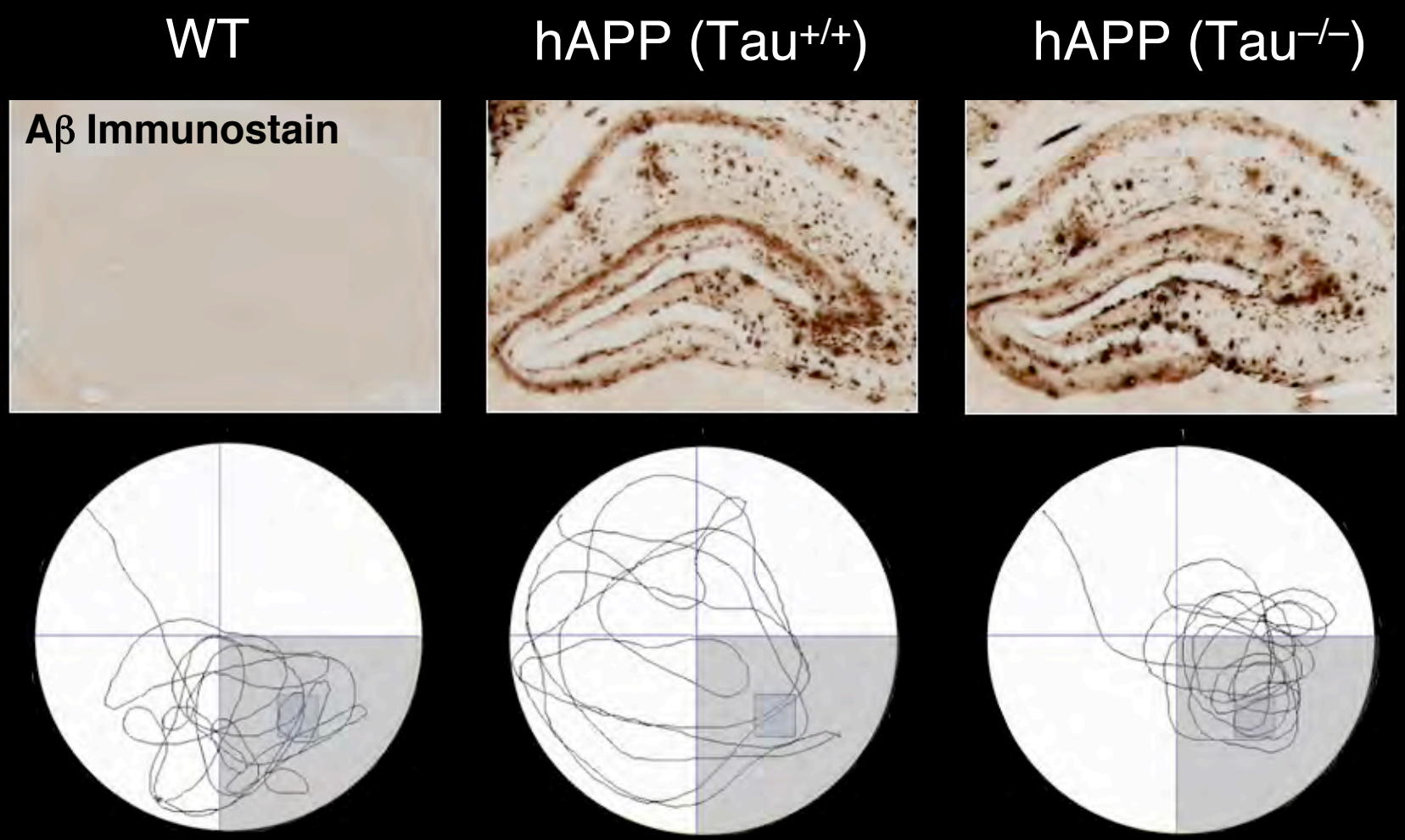
Tau Reduction Ameliorates Aβ-induced Learning Deficits in the Morris Water Maze



Tau Ablation Further Reduces Aβ-induced Learning Deficits in the Morris Water Maze

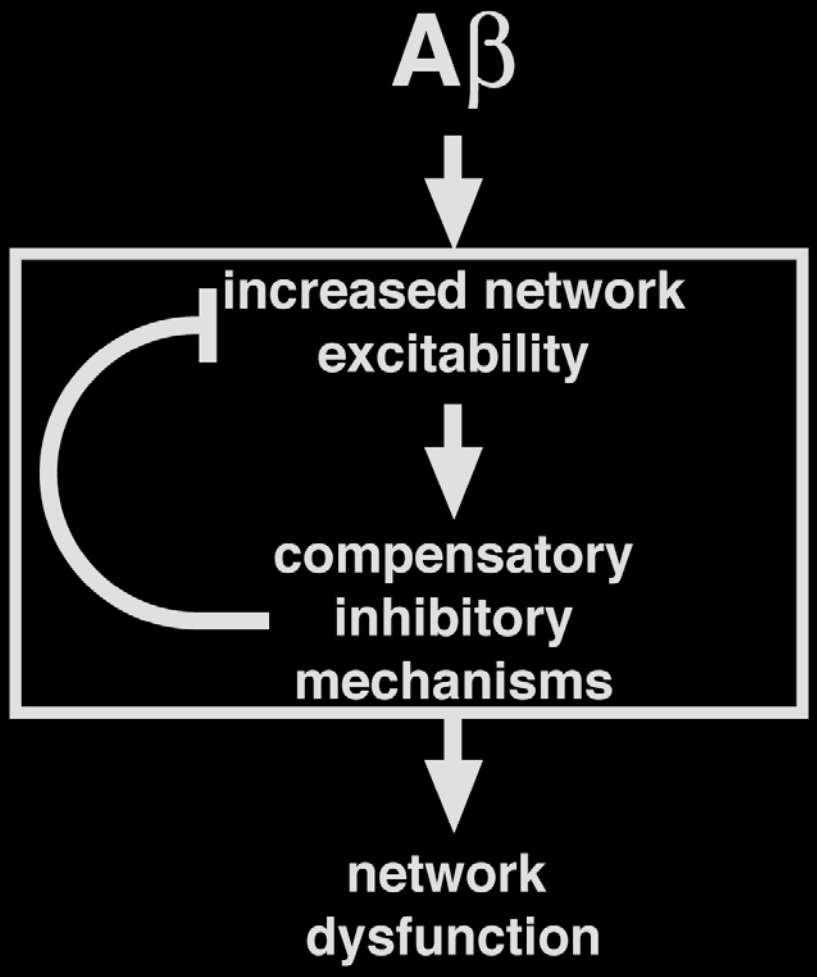


Tau Reduction Does Not Change Plaque Load But Makes the Brain Resistant Against Aβ-induced Functional Deficits

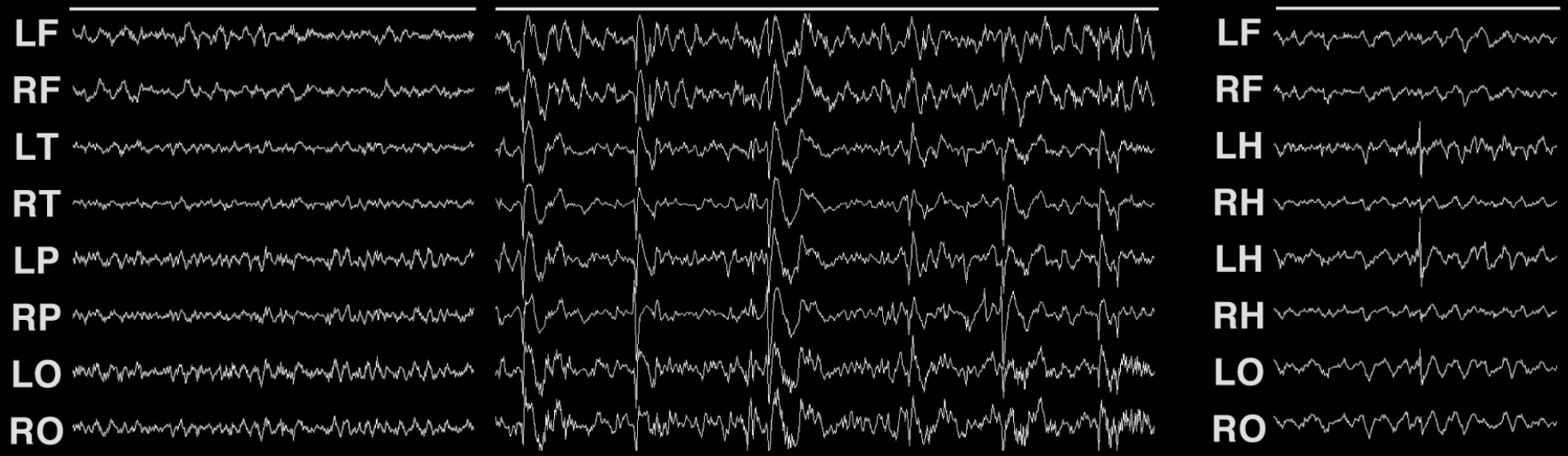


Typical swim paths during probe trial in Morris water maze

Our Latest Version of the Aβ Cascade Hypothesis

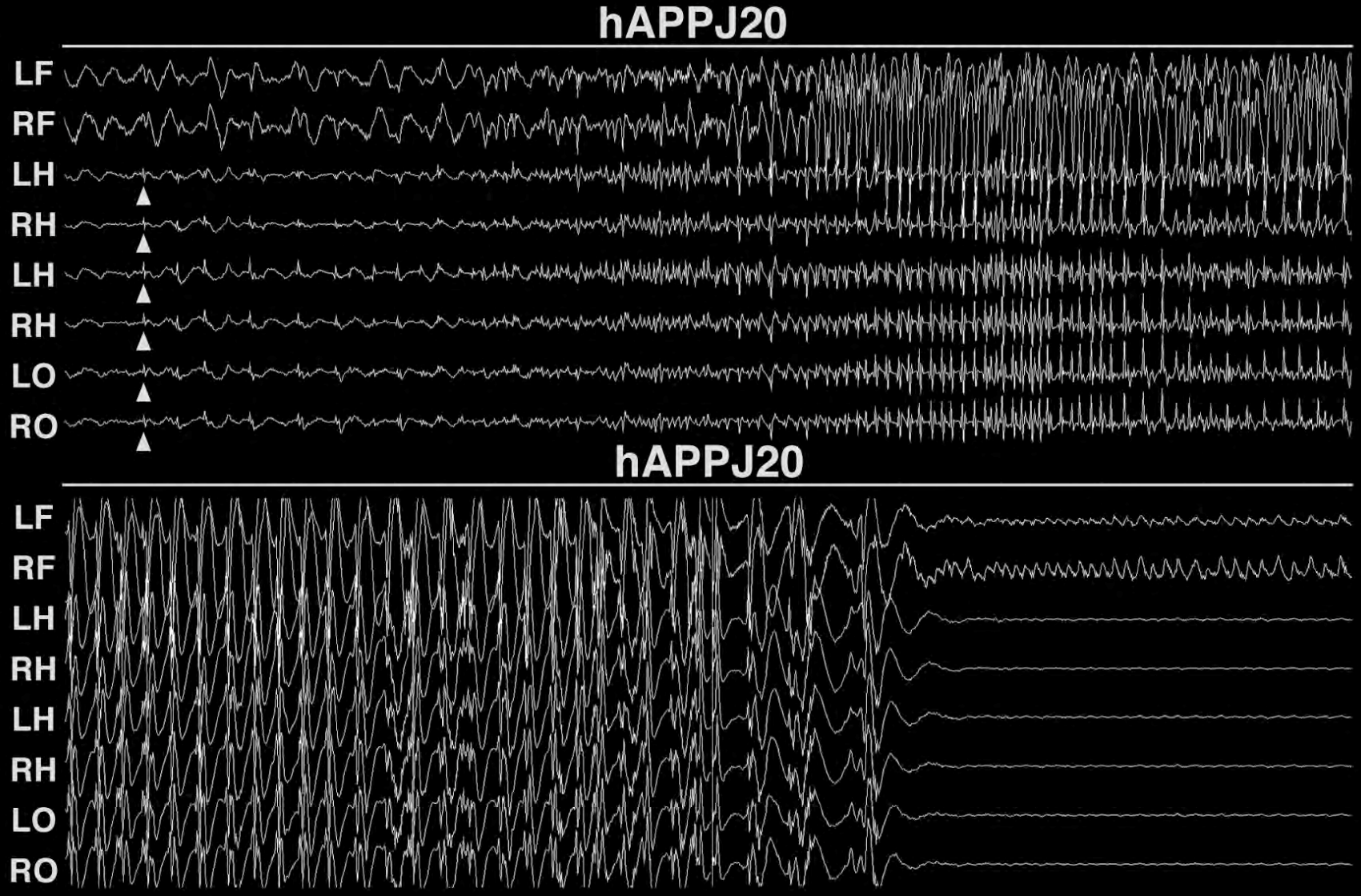


High Levels of Human Aβ Elicit Nonconvulsive Epileptiform Activity in the Cortex and Hippocampus of hAPP Transgenic Mice



Palop et al, Neuron (2007)

High Levels of Human Aβ Elicit Intermittent Nonconvulsive 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

http://adepi-icad.ucsf.edu/

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

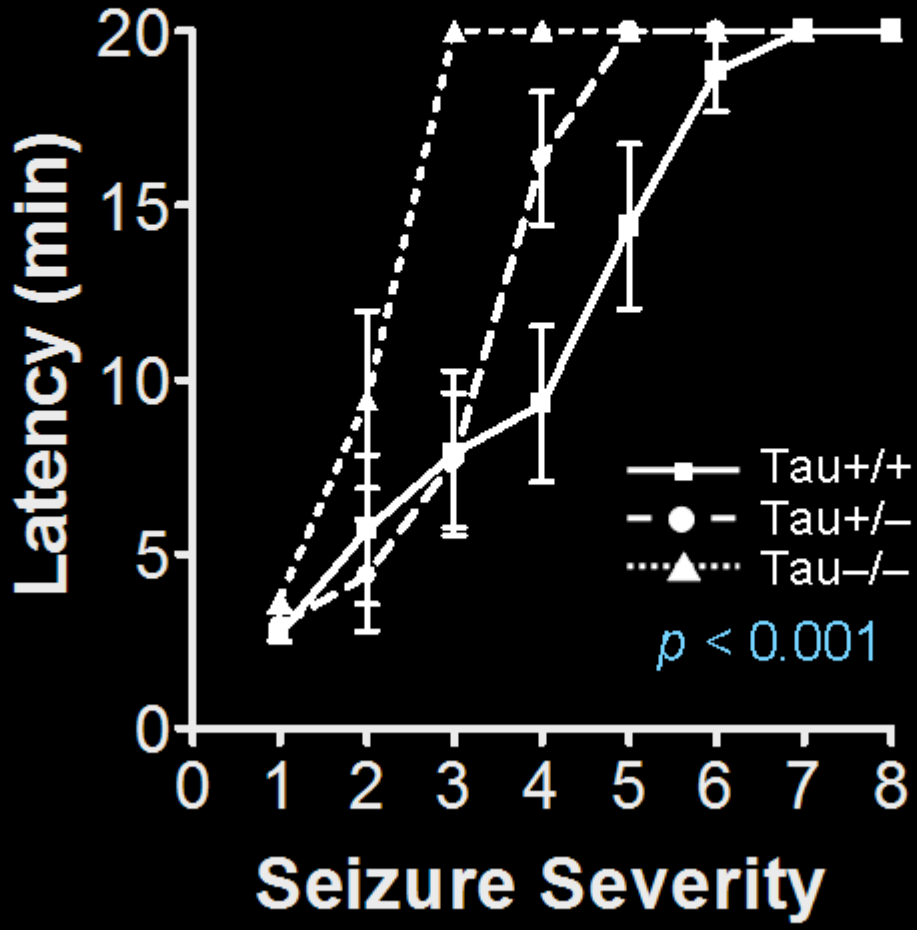
The purpose of this meeting is to increase awareness and encourage further study of the potential link between Alzheimer's disease (AD) and epilepsy. This link is supported by both clinical and experimental evidence (see Reading List), but remains poorly understood. To improve this situation and fill 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.

Registration · Program Schedule · Reading List

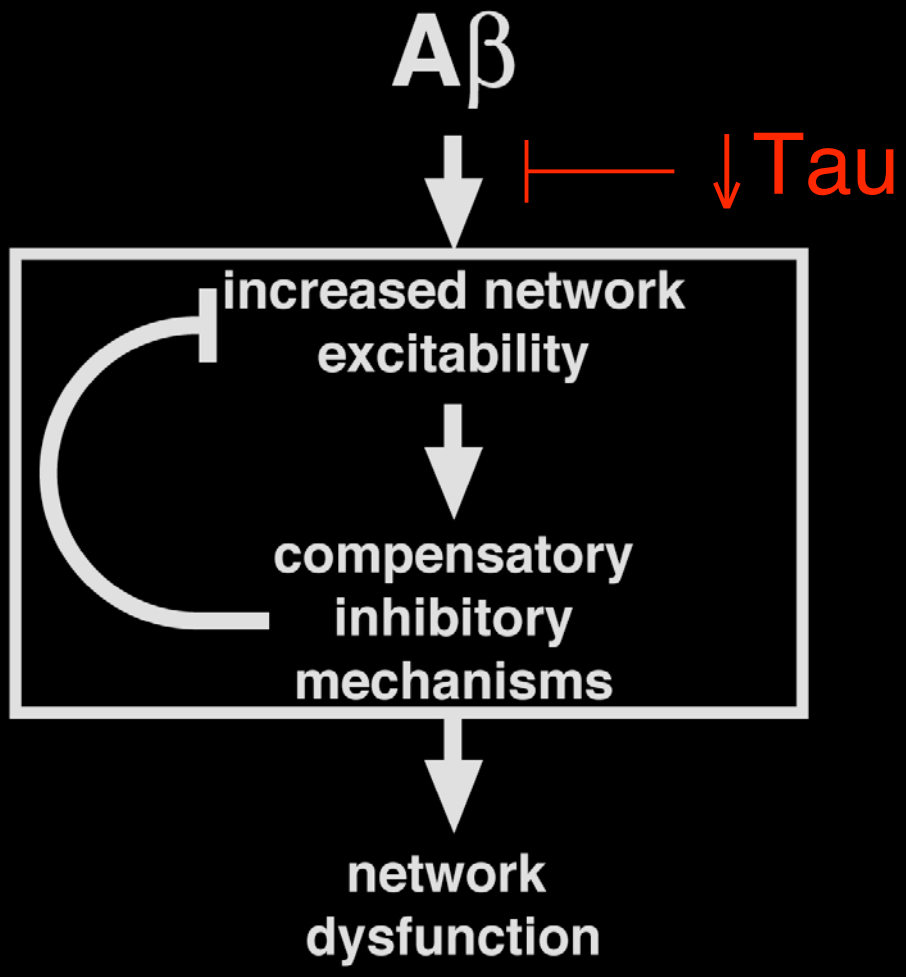
Host
Gladstone Institute of Neurological Disease

Organizers
Lennart Mucke Gladstone
Jeffrey Noebels Baylor
Dora Kovacs Harvard

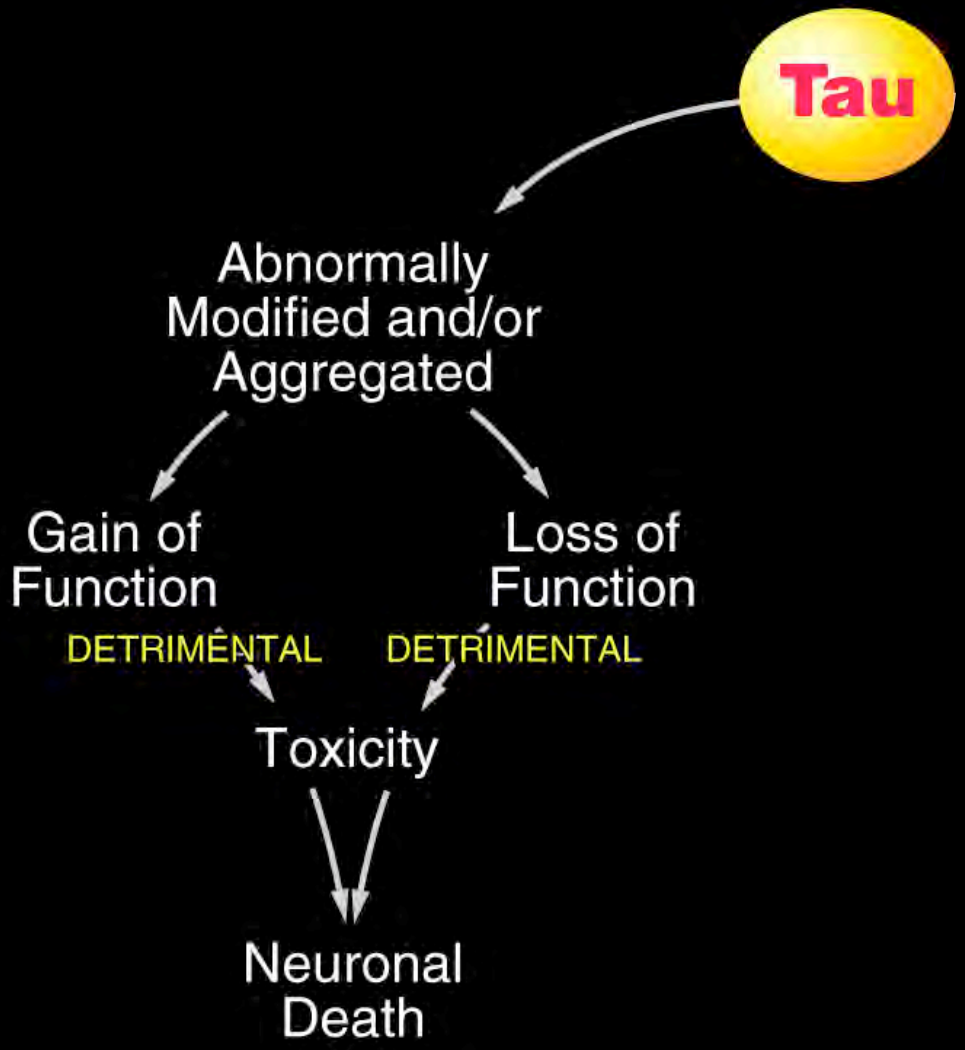
Tau Reduction Increases Resistance to PTZ-induced Seizures in Nontransgenic Mice



Novel Strategy to Block this Cascade



Potential Roles of Tau in the Pathogenesis of Neurodegenerative Disease



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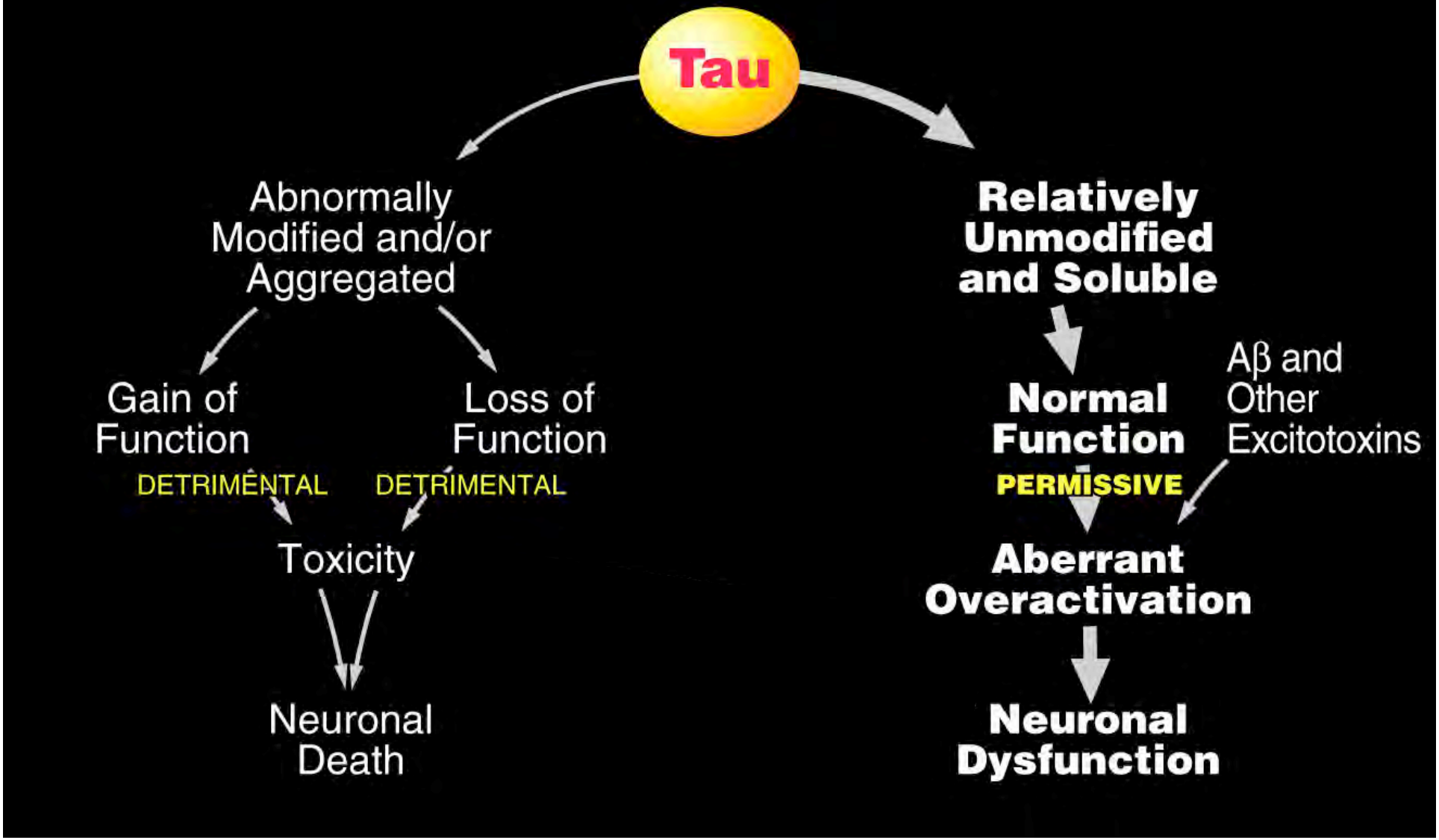
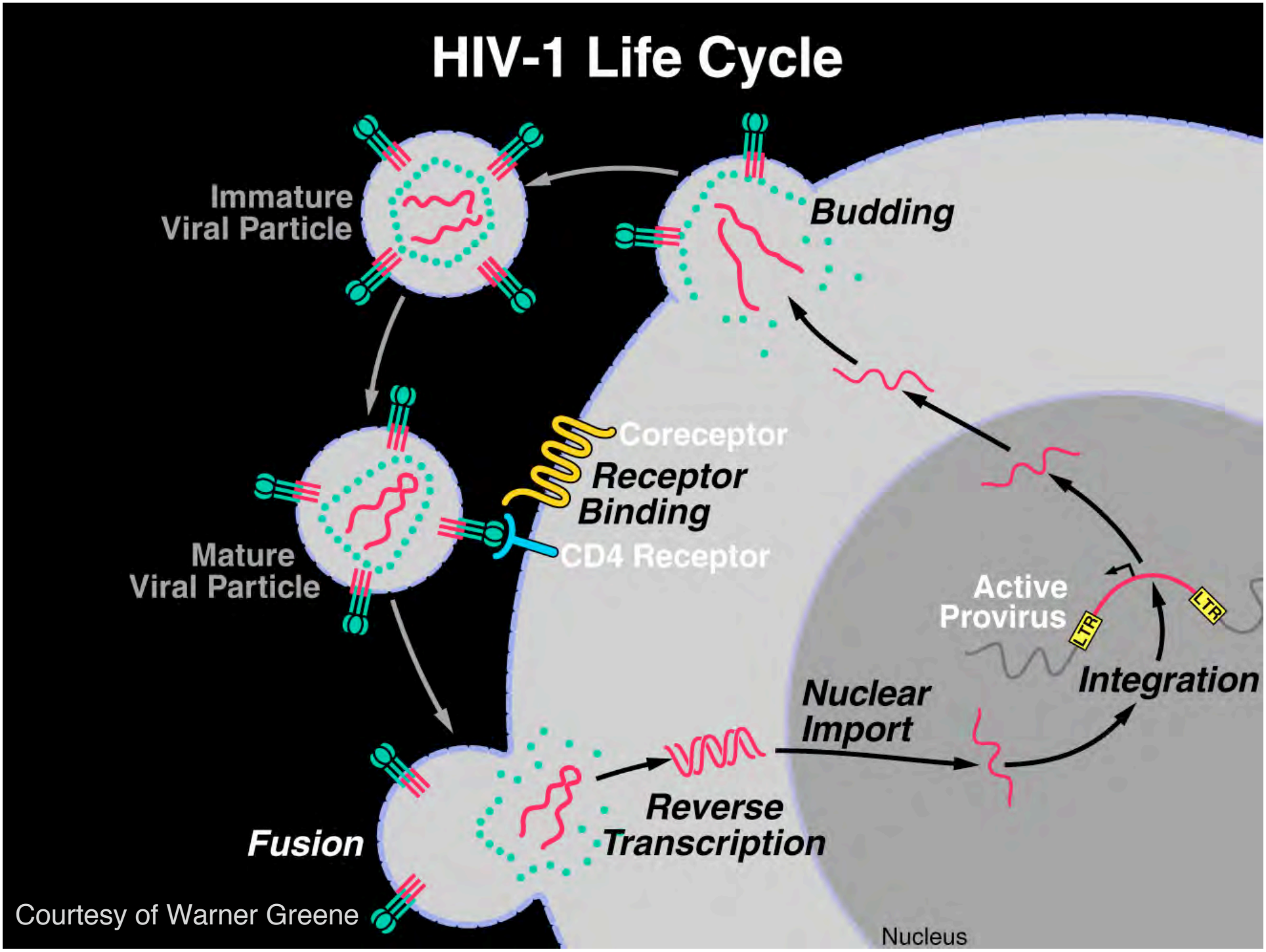
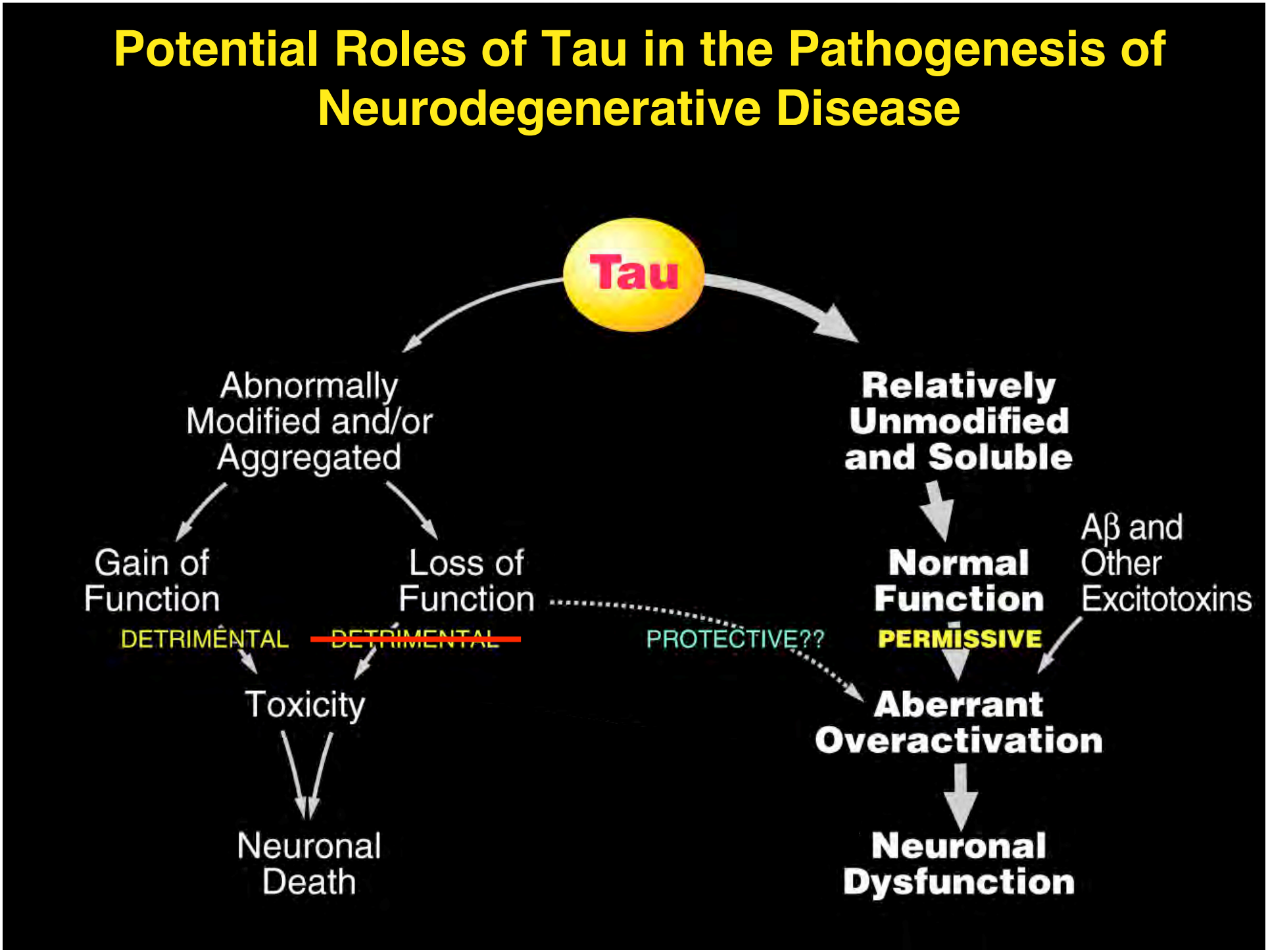



HIV-1 Life Cycle
Immature Viral Particle
Budding
Coreceptor
Receptor Binding
CD4 Receptor
Mature Viral Particle
Active Provirus
LTR
LTR
Integration
Nuclear Import
Reverse Transcription
Fusion
Nucleus
Courtesy of Warner Greene

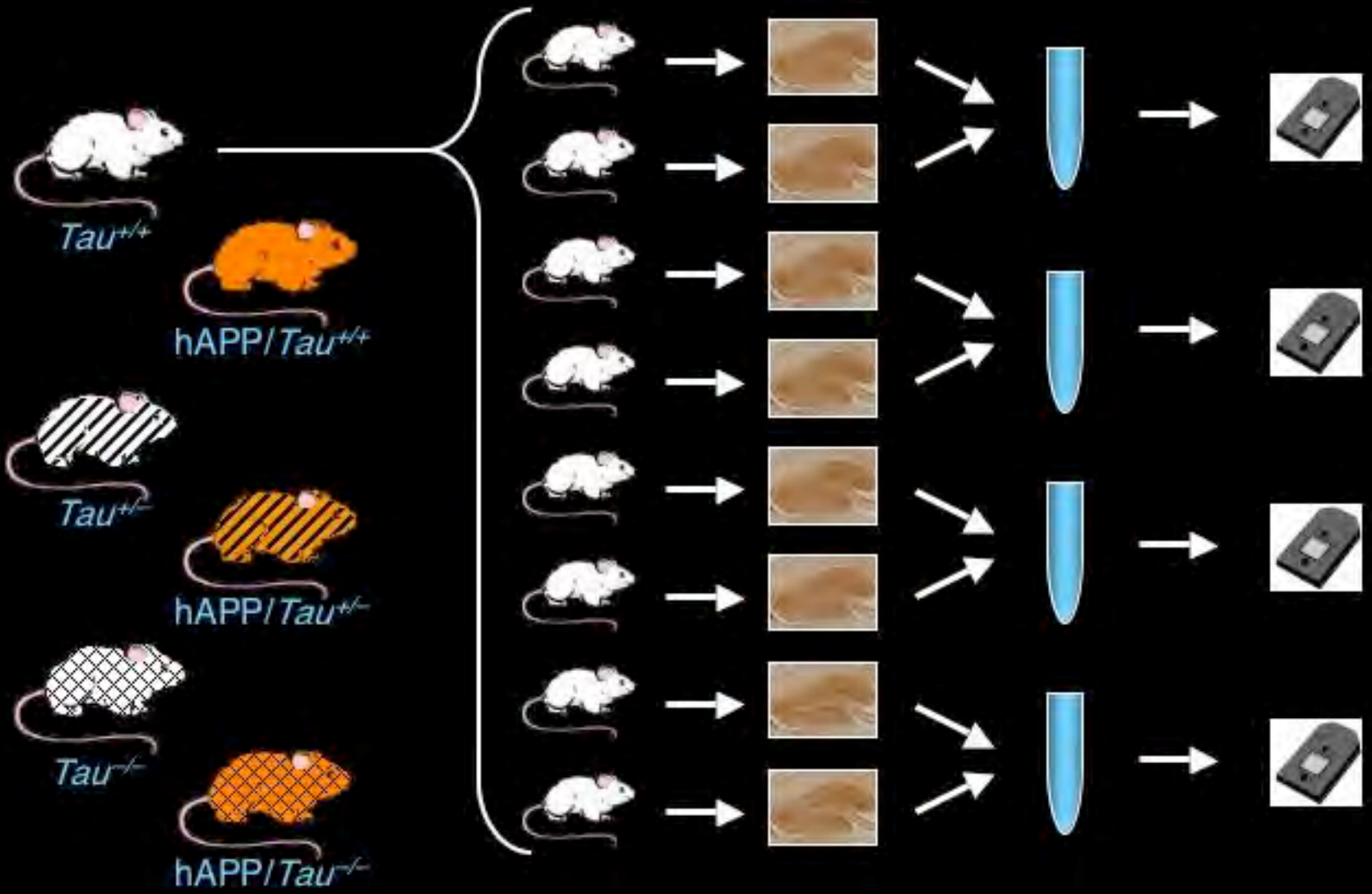
Potential Roles of Tau in the Pathogenesis of Neurodegenerative Disease



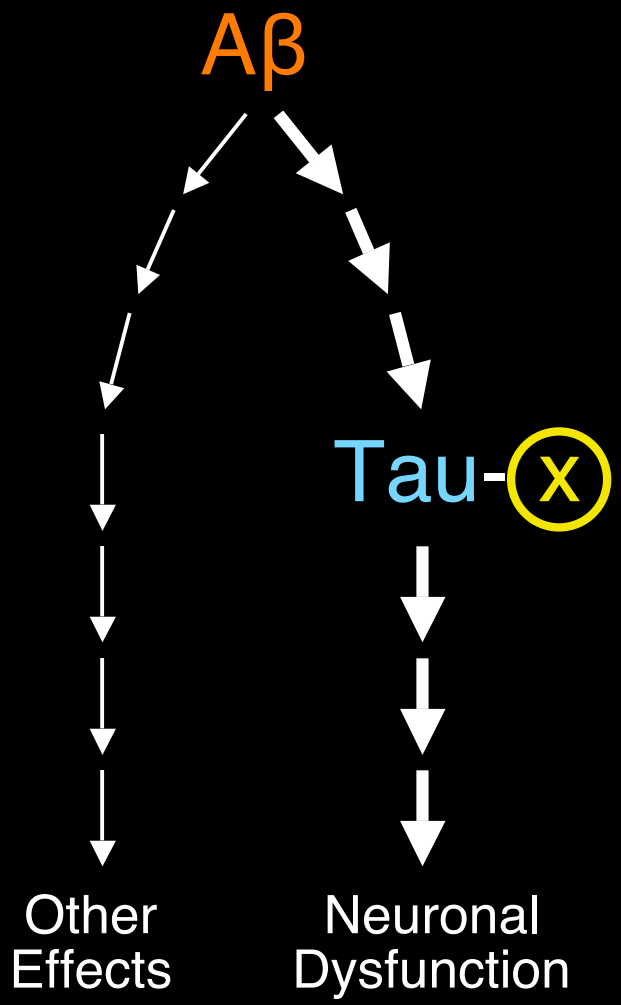
Tau Is a Microtubule-associated Protein (MAP) that May Regulate Axonal Transport

Courtesy of Eva-Maria Mandelkow

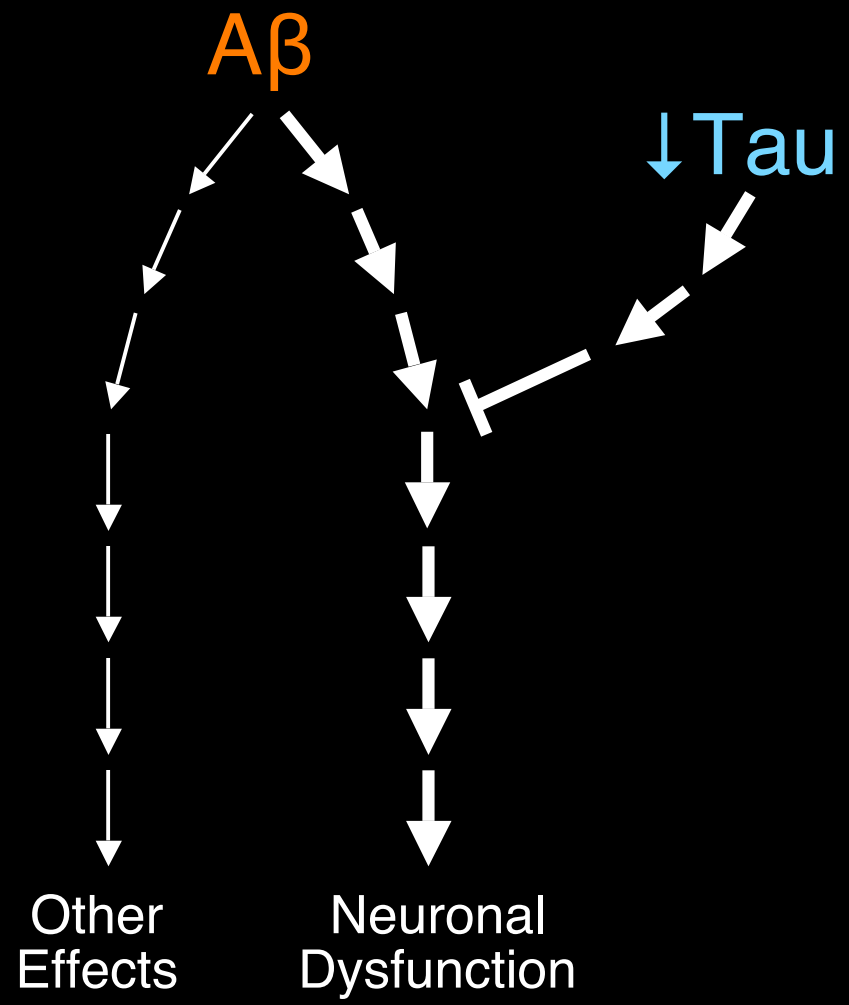
Microarray Experimental Design



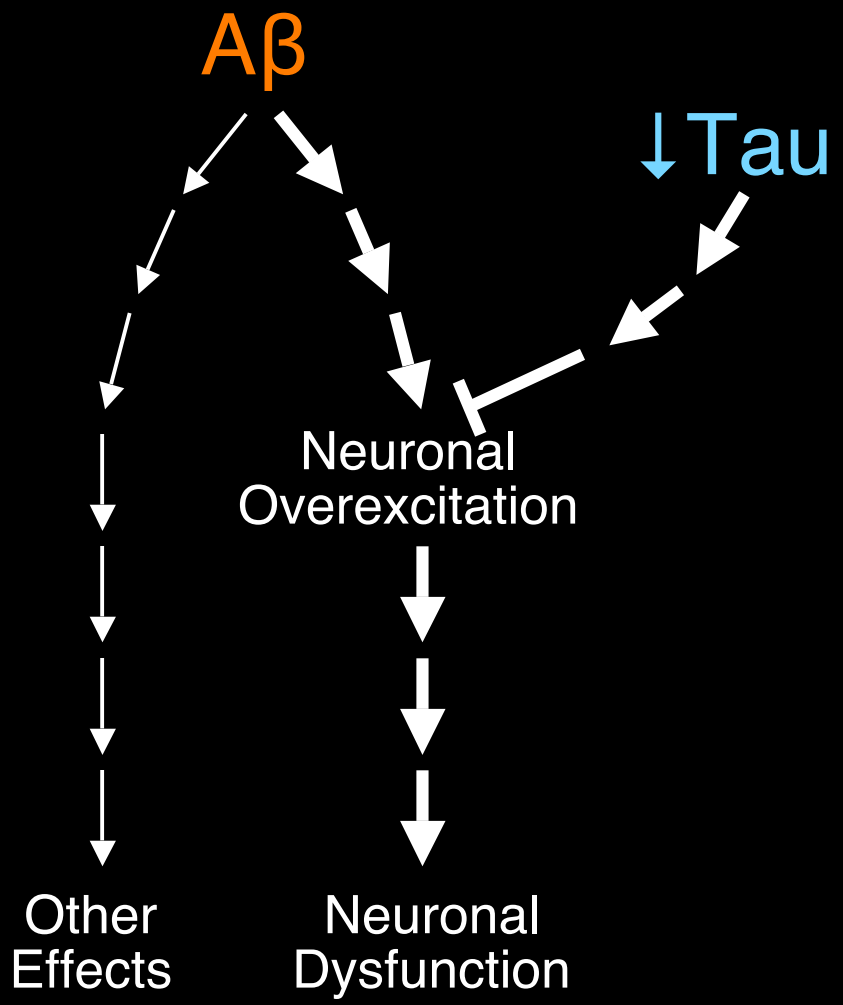
Working Hypothesis



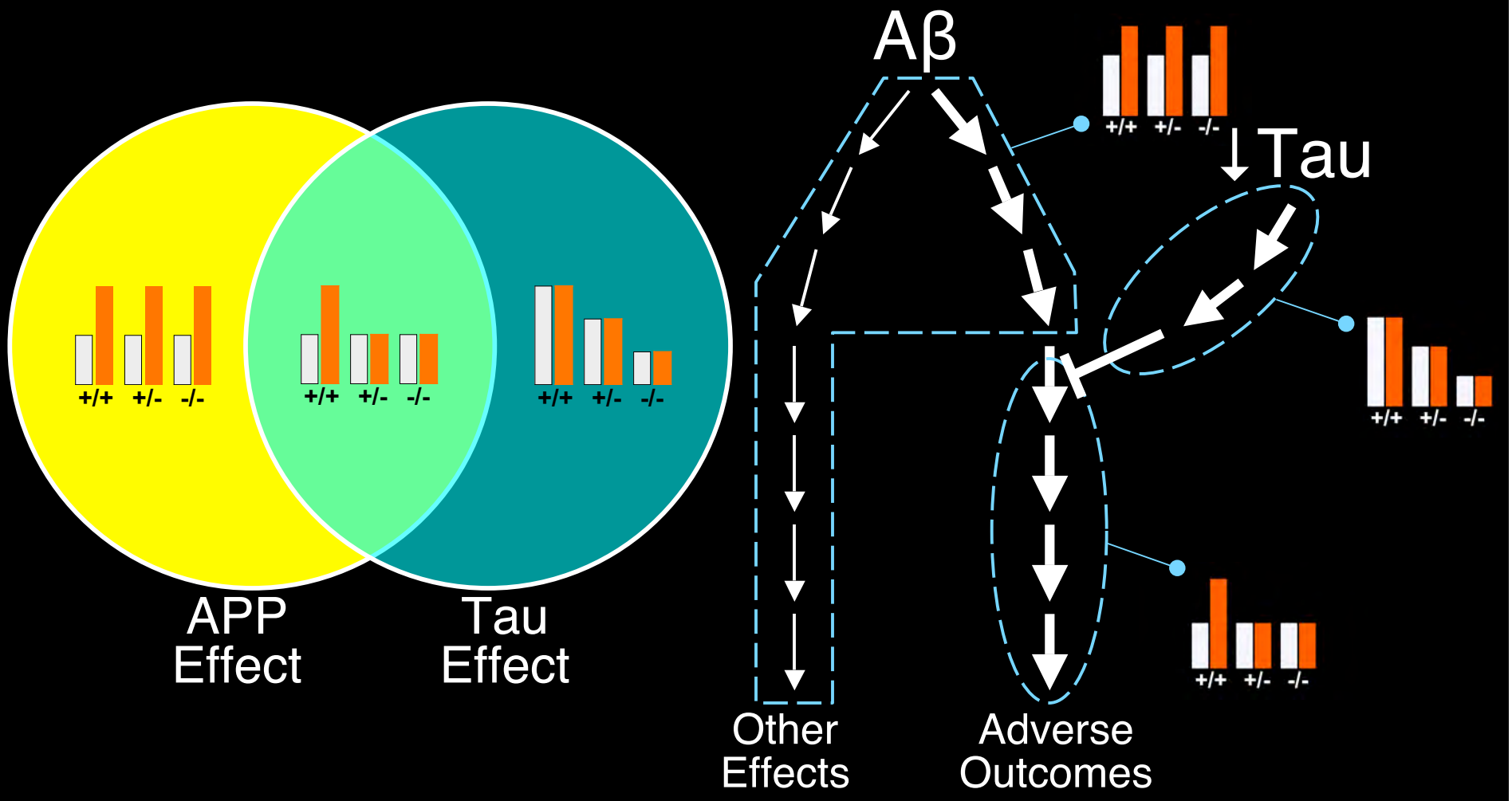
Working Hypothesis



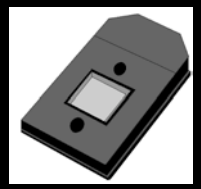
Working Hypothesis



Microarray Analysis: Questions

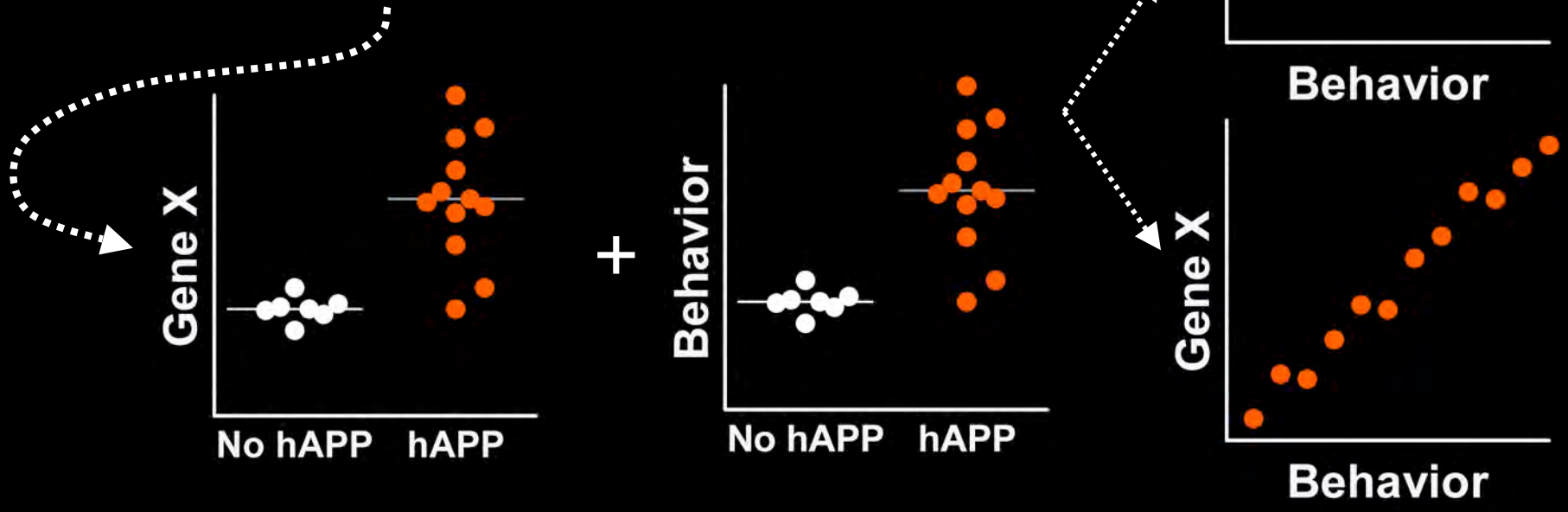


Gene Expression–Behavior Correlation as a Tool for Microarray Analysis



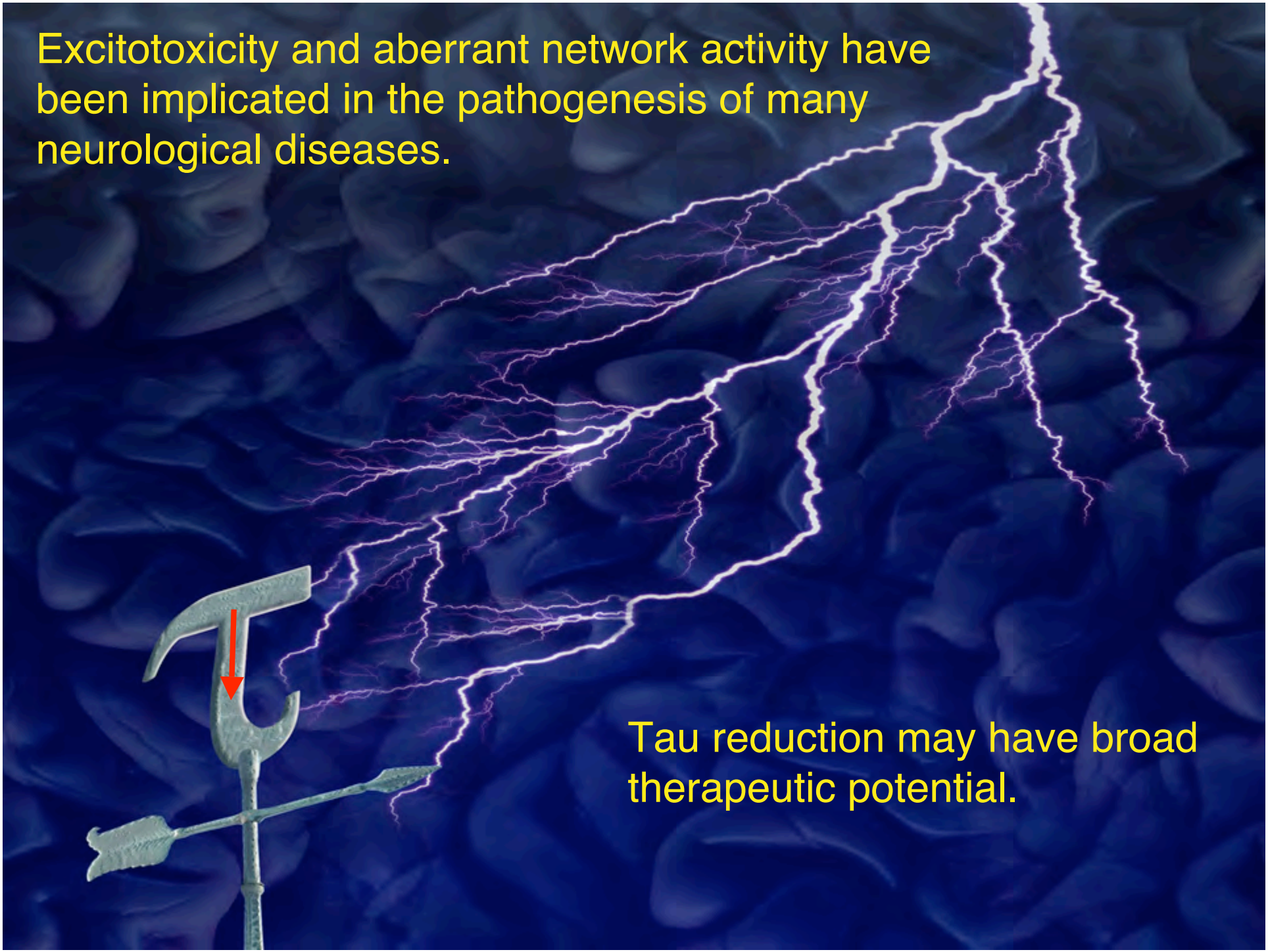
Expression

Behavior



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

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Jeffrey Noebels
Jong Yoo

Duke:
Hana Dawson
Michael Vitek

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