A new approach to Common Sporadic Alzheimer’s, Post-Traumatic Alzheimer’s, and CTE:

Roles of Aβ, Tau, ApoE, and Regulatory Signaling in Elucidating Pathogenesis and Experimental Therapeutics

Sam Gandy, M.D., Ph.D.
Mount Sinai Chair in Alzheimer’s Disease Research

Announcing Keystone Symposia’s 2012 Meeting on:
Clinical and Molecular Biology of Acute and Chronic Traumatic Encephalopathies

February 28, 2012
Traumatic Brain Injury — Football, Warfare, and Long-Term Effects

**Mild TBI**
- Contusion, mild edema, uncertain short-term pathology

**Mild Repetitive TBI**
- Axonal and cytoskeletal alterations, accumulation of abnormal protein aggregates
- Neurofibrillary tangles (tauopathy)
- Dementia pugilistica; chronic traumatic encephalopathy; pugilistic parkinsonism

**Severe TBI**
- Chronically impaired neuronal homeostasis, accumulation of abnormal protein aggregates
- OR
  - Reestablishment of neuronal homeostasis, clearance of abnormal protein aggregates
- Aβ and tau pathology
- Alzheimer’s disease

**Variable chronic cognitive or neuropsychiatric impairment; frequently associated with post-traumatic stress disorder**

Trendy toward neuropathology modified by APOE ε4
The Alzheimer’s-TBI “Nexus”

1. How can our understanding of the pathogenesis of Alzheimer’s disease inform our understanding of post-traumatic Alzheimer’s disease?

2. Is there anything special about post-traumatic Alzheimer’s disease that distinguishes this from Alzheimer’s disease without a history of head trauma?

3. How can our current understanding of Alzheimer’s be applied to experimental therapeutics of post-traumatic Alzheimer’s disease?
Alzheimer transgenic mice, no amyloid vaccine

Alzheimer transgenic mice, following amyloid vaccine
$^{11}$C-PiB PET assessment of change in fibrillar amyloid-β load in patients with Alzheimer’s disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study

Why does plaque lowering not lead to cognitive improvement?

- Subjects not treated long enough
- Subjects not treated early enough
- Unknown whether bapineuzumab binds oligomeric Aβ
- Oligomeric Aβ definitely not recognized by PiB
- Bapineuzumab does not “hit the right target”
What could be the “right target” in common AD? Will Rxing one single target ever be sufficient?

- $\alpha\beta$ oligomers
- Non-\(A\beta\)-dependent APP function
- Non-\(A\beta\)-dependent PS1 function
- Non-\(A\beta\)-dependent apoE isotype-specific function
- Plausible, non-\(A\beta\)-initiated pathogenetic pathways (e.g., mitochondria, calcium) that accelerate \(A\beta\) accumulation secondarily
- Tau
Association of Increased Cortical Soluble Aβ₄₂ Levels With Diffuse Plaques After Severe Brain Injury in Humans

Steven T. DeKosky, MD; Eric E. Abrahamson, PhD; John R. Cistulli, PhD; William R. Paljug, MS; Stephen R. Wasmieslski, PhD; Robert S. B. Clark, MD; Milos D. Ikonenovic, MD

Apolipoprotein E ε4 and Fatal Cerebral Amyloid Angiopathy Associated with Dementia Pugilistica

Barry D. Jordan, MD, Andrew B. Kanik, MD, Mark S. Horwich, MD, David Sweeney, BS, Norman R. Relkin, MD, PhD, Carol K. Petito, MD, and Sam Gandy, MD, PhD
Conventional Alzheimer pathway

TBI $\rightarrow$ A$\beta_{42}$ $\rightarrow$ tauopathy $\rightarrow$ neurodegeneration

accumulation

Possible pathways from TBI to AD or CTE

TBI $\rightarrow$ A$\beta_{42}$

\[
\begin{align*}
\text{tauopathy} \\
\text{neurodegeneration}
\end{align*}
\]
<table>
<thead>
<tr>
<th><strong>First messengers</strong></th>
<th><strong>Second messengers</strong></th>
<th><strong>Protein kinases</strong></th>
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**A-beta regulation by signal transduction**

**Isoprenoid- and Rho-GTPase related signals**
- FTI
- GGTI
- Rho
- Rac
- Rap

**Protein phosphatases**
- PP1
- PP2A

**Electrical depolarization**
Group II mGluR antagonist as a potential treatment for neurodegenerative dementia

Soong Ho Kim, John W. Steele, Charles Glabe, Carrolee Barlow, Michelle E. Ehrlich, and Sam Gandy
Synaptic accumulation of Aβ42 is proposed to be a major mechanism in the cause/progression of AD:

Is mGluR signaling involved in regulating Aβ42 metabolism at the synapse?
DCG-IV stimulates generation of Aβ42 but not Aβ40

Pretreatment with mGluR2/3 antagonist blocks DCG-IV stimulated generation of Aβ42

Brief Communications

Group II Metabotropic Glutamate Receptor Stimulation Triggers Production and Release of Alzheimer’s Amyloid β42 from Isolated Intact Nerve Terminals

Soong Ho Kim, Paul E. Fraser, David Westaway, Peter H. St. George-Hyslop, Michelle E. Ehrlich, and Sam Gandy
mGluR2/3 antagonist corrects Aβ-induced contextual memory deficits
mGluR2/3 antagonist improves NOR, decreases anxiety in APP transgenic mice
mGluR2/3 antagonist lowers levels of various Aβ conformers in hippocampus and cortex

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<th>Aβ oligomer</th>
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<td>fibrillar</td>
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<td>Total</td>
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n = 6 - 7

*, p < 0.05; **, p < 0.01; ***, p < 0.001
BCI-632 – A Neurogenic Compound

**In vitro**

- Human neuronal stem cells treated for 7 days in culture stained for TuJ1

**In vivo**

- Graph showing total BrdU-positive cells per dentate gyrus

- **Vehicle**
- Fluvoxamine (30mg/kg)
- BCI-632 (5mg/kg)
- BCI-632 (10mg/kg)

- Day 1, 7, 14, 15, 16
- Compound (i.p., once/day) BrdU Sacrificed
Current evidence suggests that pro-neurogenic interventions improve outcome from experimental TBI


Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer’s disease: a randomised, double-blind, placebo-controlled study

Rachelle S Doody, Svetlana I Gavrilova, Mary Sano, Ronald G Thomas, Paul S Aisen, Sergey O Bachurin, Lynn Seely, David Hung, on behalf of the dimebon investigators*
Acute dosing of latrepirdine (Dimebon™), a possible Alzheimer therapeutic, elevates extracellular amyloid-β levels in vitro and in vivo

John W Steele¹, Soong H Kim¹, John R Cirrito², Deborah K Verges², Jessica L Restivo², David Westaway³, Paul Fraser⁴, Peter SG Hyslop⁴, Mary Sano², Ilya Bezprozvanny⁸, Michelle E Ehrlich⁵, David M Holtzman², and Sam Candy¹,²,*
Dimebon improves memory and arrests progression of molecular neuropathology while activating autophagy in TgCRND8 mice.
Dimebon activated autophagy as indicated by changes in p62, LC3-I, LC3-II.
Rapamycin is a neuroprotective treatment for traumatic brain injury

S. Erlich, A. Alexandrovich, E. Shohami, and R. Pinkas-Kramarski

![Image of histochemistry images showing comparison between Vehicle and Rapamycin treatments.](image)

![Graph showing Neuron positive cell count comparison between Vehicle and Rapamycin treatments.](image)
Acute dosing of latrepirdine (Dimebon™), a possible Alzheimer therapeutic, elevates extracellular amyloid-β levels in vitro and in vivo

John W Steele1, Soong H Kim1, John R Cirrito2, Deborah K Verges2, Jessica L Restivo2, David Westaway3, Paul Fraser4, Peter SG Hyslop4,5, Mary Sano2,6, Ilya Bezprozvanny8, Michelle E Ehrlich8, David M Holtzman2,* and Sam Cady1,7,*
Discovery of a Proneurogenic, Neuroprotective Chemical

Andrew A. Pieper,¹,²,* Shanhai Xie,¹ Emanuela Capota,² Sandi Jo Estill,¹ Jeannie Zhong,² Jeffrey M. Long,¹ Ginger L. Becker,² Paula Huntington,² Shauna E. Goldman,² Ching-Han Shen,¹ Maria Capota,² Jeremiah K. Britt,² Tiina Kotti,¹ Kerstin Ure,³ Daniel J. Brat,⁴ Noelle S. Williams,¹ Karen S. MacMillan,¹ Jacinth Naidoo,¹ Lisa Melito,¹ Jenny Hsieh,³ Jef De Brabander,¹ Joseph M. Ready,¹ and Steven L. McKnight¹,*

A

![Graphs showing the effect of compounds on cell viability and neuroprotection](image-url)
Deterministic mutations are rare causes of Alzheimer’s. Another pro-amyloidogenic gene, *APOE* ε4, increases risk but does not guarantee Alzheimer’s.
**APOE epsilon 4 carriers are especially prone to develop Alzheimer’s after head injury (single severe) type**


Isoform-specific apoE:Aβ complexes

Original Articles

Alzheimer Amyloid-β Peptide Forms Denaturant-Resistant Complex with Type ε3 but Not Type ε4 Isoform of Native Apolipoprotein E

Zhongmin Zhou,* Jonathan D. Smith,‡ Paul Greengard,‡ and Sam Gandy*

Charaterization of Stable Complexes Involving Apolipoprotein E and the Amyloid β Peptide in Alzheimer's Disease Brain

Jan Näslund,*, Johan Thyberg,† Lars O. Tjemberg,*, Christe Wernerståedt,‡ Anders R. Karlström,‡ Renad Bogdanovic,‖ Samuel E. Gandy,*, Lars Lannfelt,‖ Lars Terenius,*, and Christer Nordstedt†

Isoform-specific Aβ uptake into cells and in vivo

Characterization of the Binding of Amyloid-β Peptide to Cell Culture-Derived Native Apolipoprotein E2, E3, and E4 Isoforms and to Isoforms from Human Plasma

Dun-Sheng Yang, *Jonathan D. Smith, †Zhongmin Zhou, ‡Samuel E. Gandy, and Ralph N. Martins

APOE Genotype Results in Differential Effects on the Peripheral Clearance of Amyloid-β42 in APOE Knock-in and Knock-out Mice

Matthew J. Shamam,a,b,c,d, Michael Mocici,a,d, Eugene Horn,a,d, Tamar Berger,a,d, Kevin Taddeia,b,c,d, Ian J. Martins,a,b,c,d, Wei Ling F. Liua,b,c,d, Sajja Sangu,b,c,d, Markus R. Wnek,a,d, Jorge Glasb,b,c,d, Joseph D. Burbaum,a, Sam Gandy,a and Ralph N. Martinsa,b,c,d,
Molecular Imaging of ApoE Isoform-related Protein Conformation Changes in human Alzheimer Brain

Ina Caesar, K. Peter R. Nilsson, Per Hammarström, Mikael Lindgren, Stefan Prokop, Frank L. Heppner, David M. Holtzman, Patrick R. Hof, Sam Gandy

February 27, 2012
Aggregate morphology

Senile plaque

Neurofibrillary tangles

Vascular amyloid

apoE ε4/ε4

apoE ε3/ε3

(a) Senile plaque
(b) Neurofibrillary tangles
(c) Vascular amyloid

(d) Senile plaque
(e) Neurofibrillary tangles
(f) Vascular amyloid
ApoE genotype dependent spectral separation

c
Senile Plaque

(d)
Neurofibrillary tangles

(e)
Vascular amyloid


(apoE ε4/ε4, apoE ε3/ε3)

(apoE ε4/ε4, apoE ε3/ε3)
ALZHEIMER’S DISEASE

Human apoE Isoforms Differentially Regulate Brain Amyloid-β Peptide Clearance

Joseph M. Castellano,1,2,3a Jungsu Kim,1,2,3a Floy R. Stewart,1,2,3 Hong Jiang,1,2,3
Ronald B. DeMattos,4 Bruce W. Patterson,5 Anne M. Fagan,1,2,3 John C. Morris,1,3
Kwasi G. Mawuenyega,1,2,3 Carlos Cruchaga,2,3,6 Alison M. Goate,1,2,3,6 Kelly R. Bales,7
Steven M. Paul,8 Randall J. Bateman,1,2,3 David M. Holtzman1,2,3,9†

Apolipoprotein E4 Influences Amyloid Deposition But Not Cell Loss after Traumatic Brain Injury in a Mouse Model of Alzheimer’s Disease

Richard E. Hartman,1,2,3 Helmut Laurer,4 Luca Longhi,4 Kelly R. Bales,5 Steven M. Paul,5,6
Tracy K. McIntosh,4 and David M. Holtzman1,2,3,9†

ScienceExpress

Report

ApoE-Directed Therapeutics Rapidly Clear β-Amyloid and Reverse Deficits in AD Mouse Models

Paige E. Cramer,1 John R. Cirrito,2 Daniel W. Wesson,1,3 C. Y. Daniel Lee,1 J. Colleen Karlo,1 Adriana E. Zimm,1 Brad T.
Casali,1 Jessica L. Restivo,2 Whitney D. Goebel,3 Michael J. James,4 Kurt R. Brunden,4 Donald A. Wilson,3 Gary E. Landreth17

Modulation of ABCA1 by an LXR Agonist Reduces Beta-Amyloid Levels and Improves Outcome after Traumatic Brain Injury

David J. Loane,5 Patricia M. Washington,1 Lilit Yardenian,2 Ana Pociavsek,1 Hyang-Sook Hoe,1
Karen E. Duff,3 Ibolja Cernak,4 G. William Rebeck,1 Alan I. Faden,2 and Mark P. Burns1
Summary

1. mGluR2/3 antagonists and pro-neurogenic/pro-autophagic compounds may be useful in preventing or treating late neurodegenerative sequelae of TBI.

2. An important issue for clarification is whether APOE epsilon 4 requires aggregatable human Aβ42 to exert its effects on tauopathy (e.g., should we test bapineuzumab infusion during acute post TBI phase?)

3. Surprisingly, APOE epsilon 4 alters structure and/or conformation of both plaques and tangles in LCO studies.