# 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:

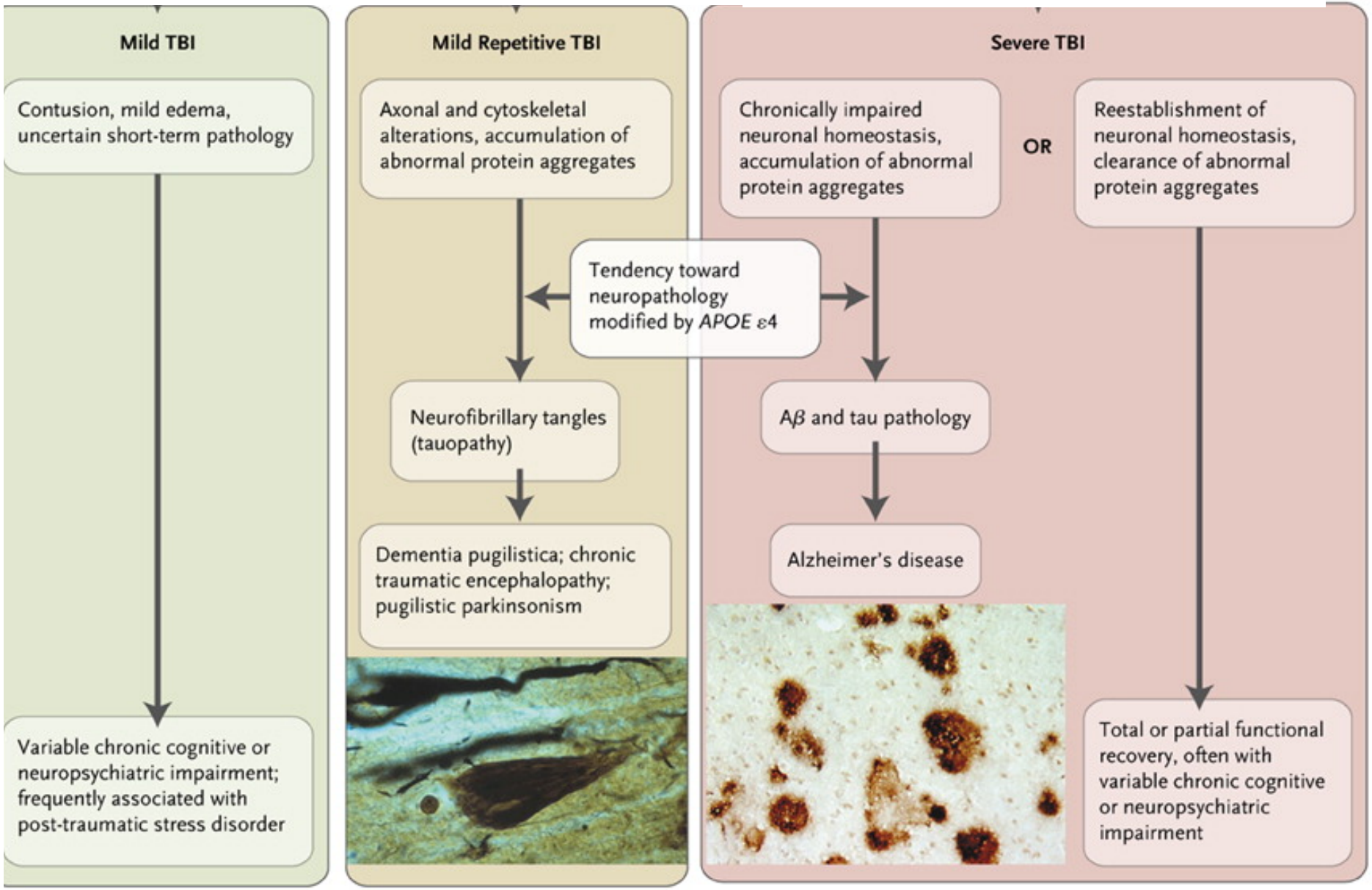
**Clinical and Molecular Biology of Acute and Chronic Traumatic Encephalopathies**

February 28, 2012

# Traumatic Brain Injury — Football, Warfare, and Long-Term Effects

Steven T. DeKosky, M.D., Milos D. Ikonomovic, M.D., and Sam Gandy, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE



# The Alzheimer's-TBI "Nexus"

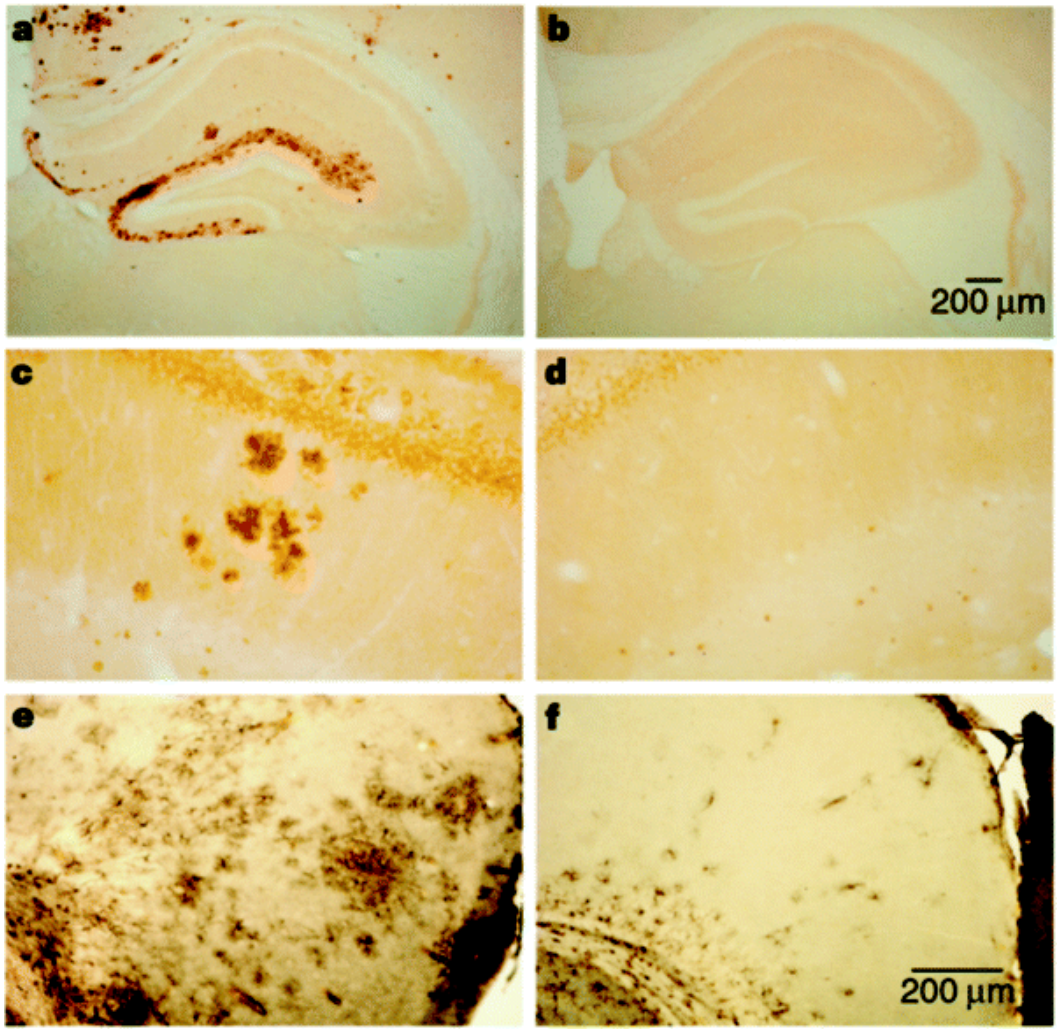
1. How can our understanding of the pathogenesis of Alzheimer's disease inform our understanding of post-traumatic Alzheimer's disease?

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**

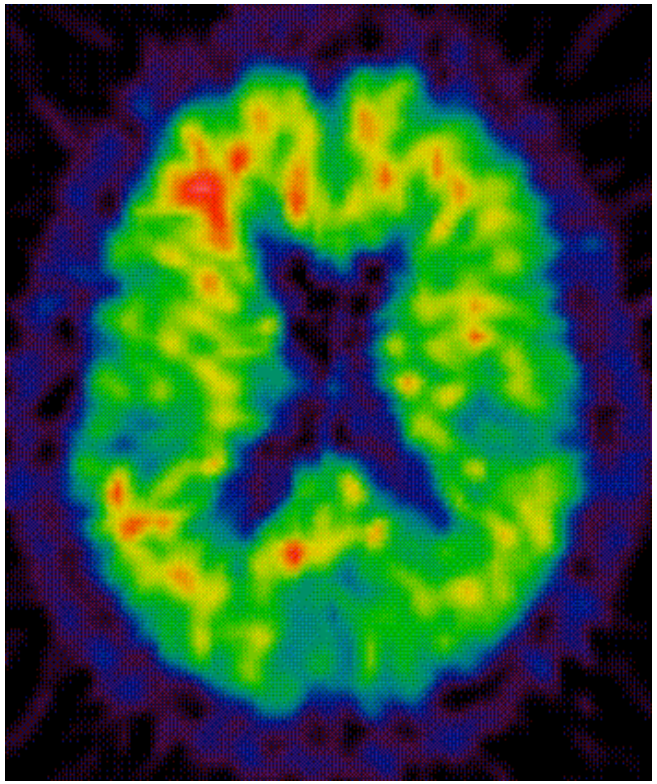
**Alzheimer transgenic mice, following amyloid vaccine**



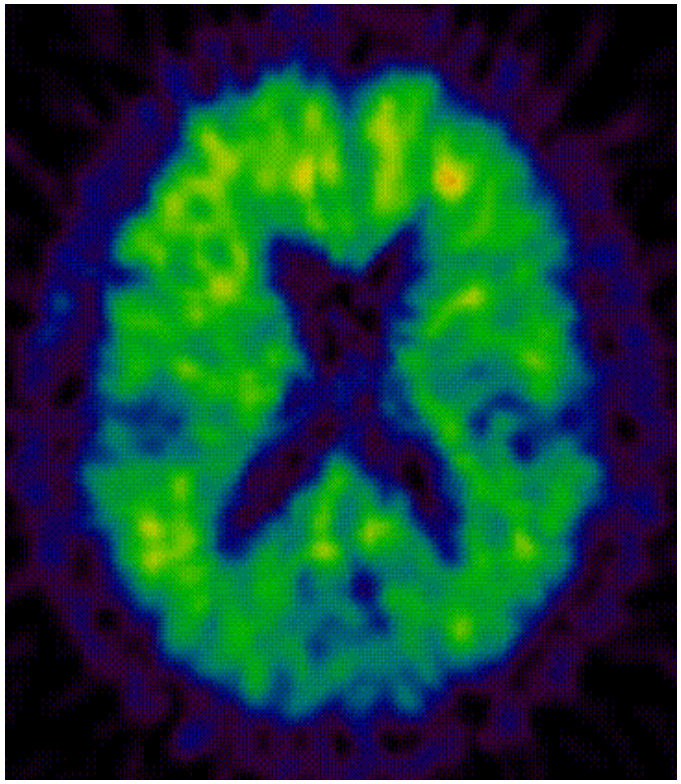
## $^{11}$C-PiB PET assessment of change in fibrillar amyloid-β load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study

*Juha O Rinne, David J Brooks, Martin N Rossor, Nick C Fox, Roger Bullock, William E Klunk, Chester A Mathis, Kaj Blennow, Jerome Barakos, Aren A Okello, Sofia Rodriguez Martinez de Liano, Enchi Liu, Martin Koller, Keith M Gregg, Dale Schenk, Ronald Black, Michael Grundman*

Baseline



78 wks Bapineuzumab Rx

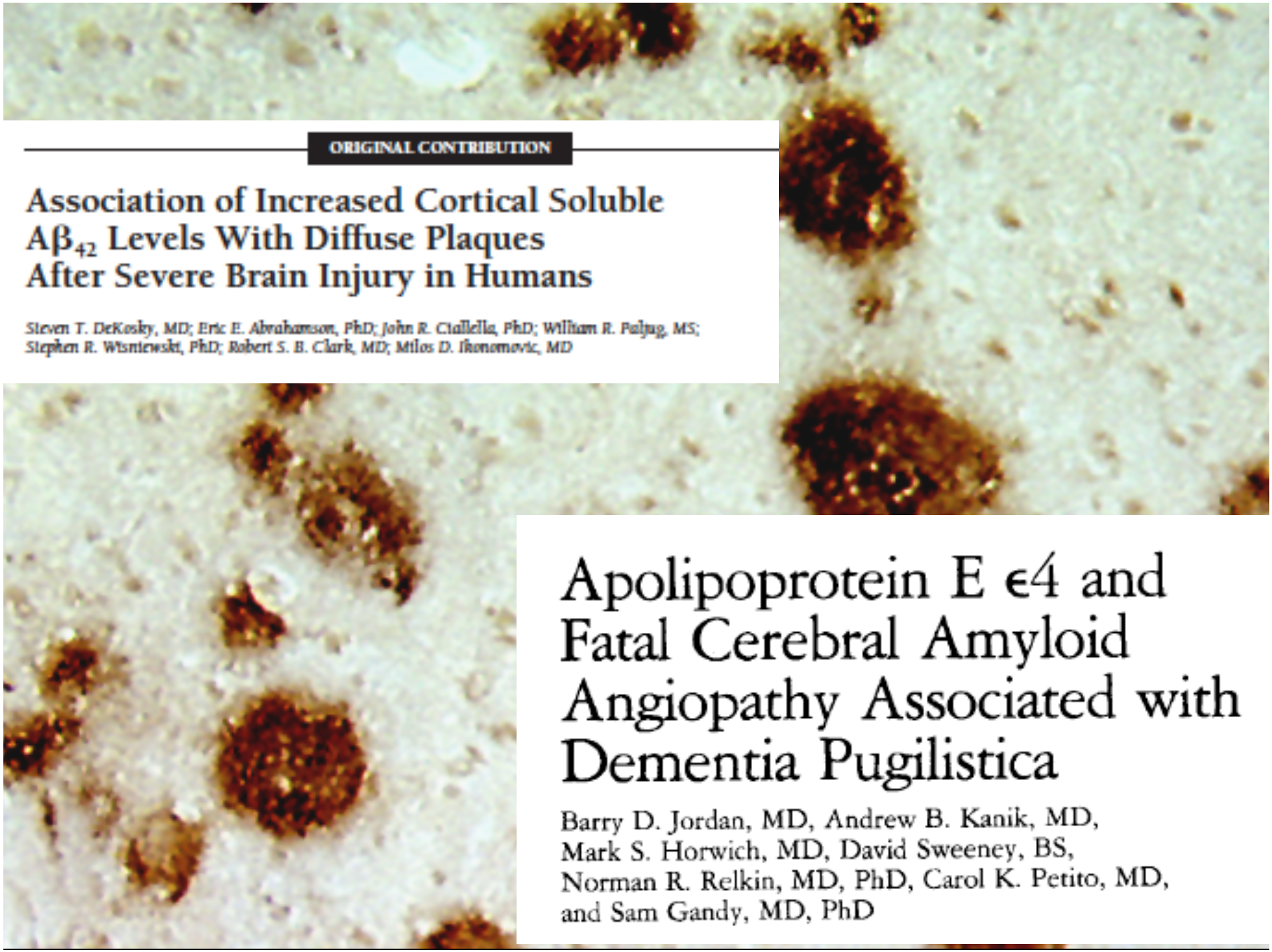


# *Why does plaque lowering not lead to cognitive improvement?*

- 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?

- Aβ oligomers
- Non-Aβ-dependent APP function
- Non-Aβ-dependent PS1 function
- Non-Aβ-dependent apoE isotype-specific function
- Plausible, non-Aβ-initiated pathogenetic pathways (e.g., mitochondria, calcium) that accelerate Aβ accumulation secondarily
- Tau



ORIGINAL CONTRIBUTION

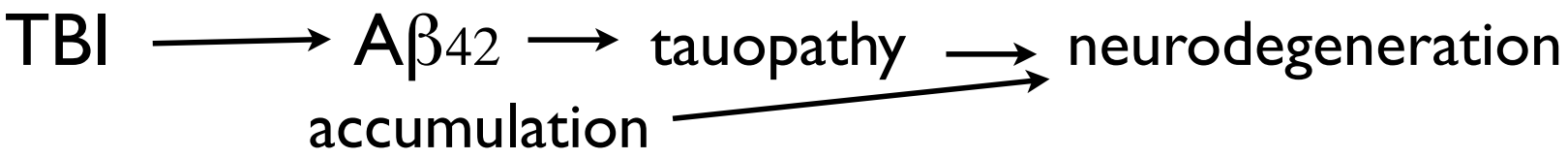
# Association of Increased Cortical Soluble $A\beta_{42}$ Levels With Diffuse Plaques After Severe Brain Injury in Humans

Steven T. DeKosky, MD; Eric E. Abrahamson, PhD; John R. Ciallella, PhD; William R. Paljug, MS; Stephen R. Wisniewski, PhD; Robert S. B. Clark, MD; Milos D. Ikonomovic, MD

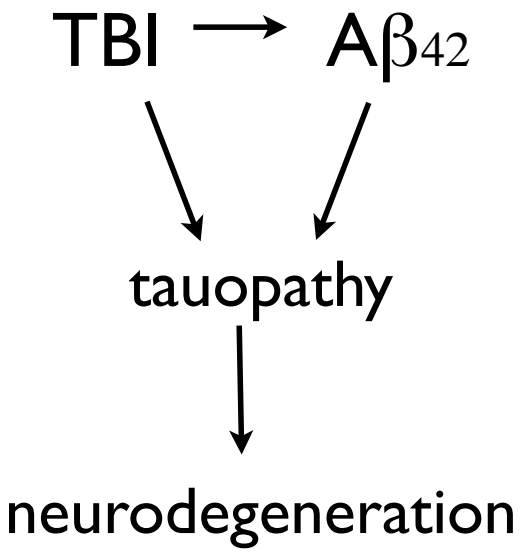
# Apolipoprotein E ϵ4 and Fatal Cerebral Amyloid Angiopathy Associated with Dementia Pugilistica

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*




*Possible pathways from TBI to AD or CTE*



# A-beta regulation by signal transduction

***First messengers***

ACh
Glutamate
IL-1
5-$HT_4$
Estrogen
Testosterone

***Second messengers***

cAMP
$Ca^{2+}$
DAG

***Protein kinases***

PKC
PKA
ERK
ROCK1,2
src
JAK

***Isoprenoid- and Rho-GTPase related signals***

FTI
GGTI
Rho
Rac
Rap

***Electrical depolarization***

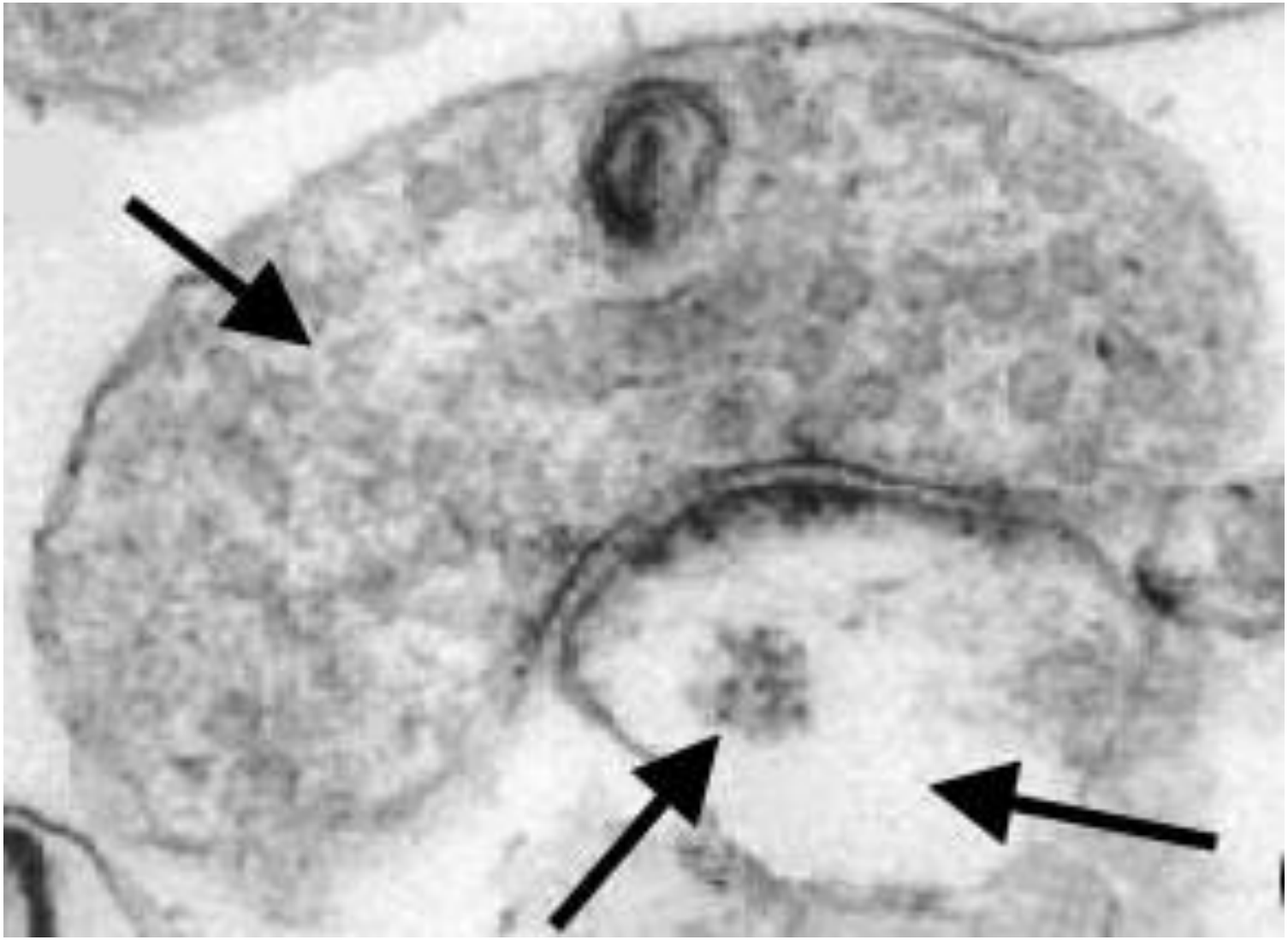
***Protein phosphatases***

PP1
PP2A

POSTER NUMBER: 107

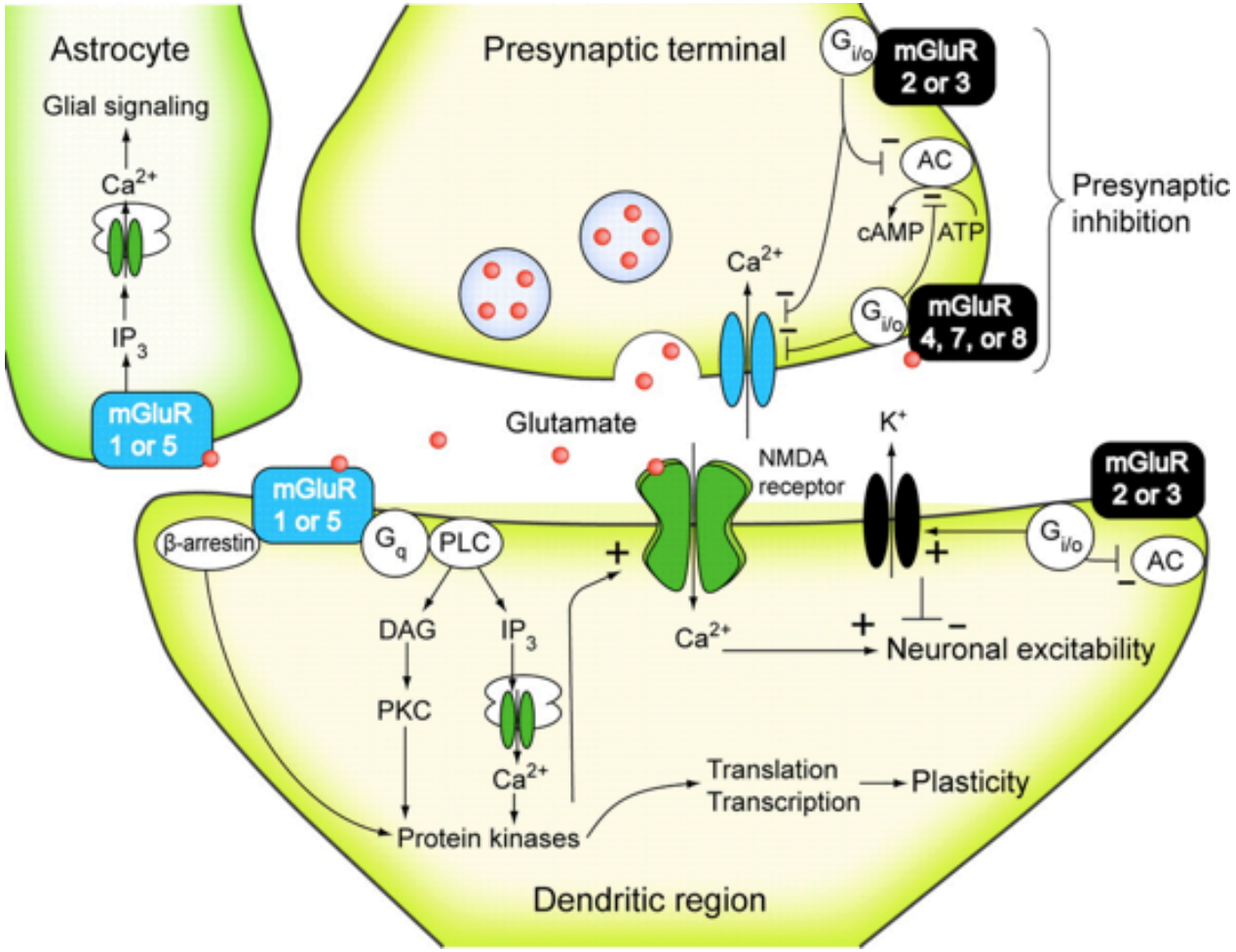
**Group II mGluR antagonist as a potential treatment for neurodegenerative dementia**

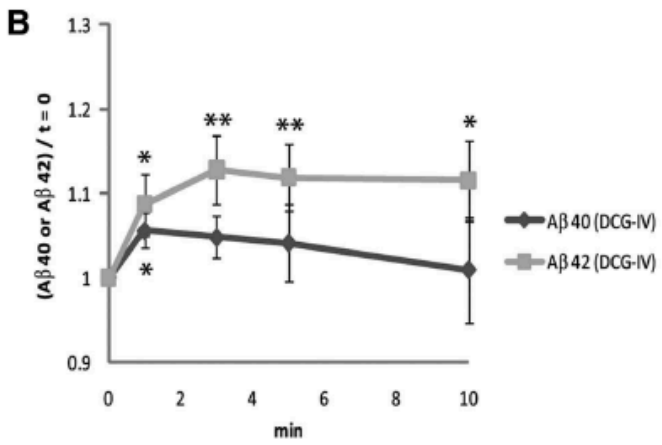
Soong Ho Kim, John W. Steele, Charles Glabe, Carrolee Barlow, Michelle E. Ehrlich, and Sam Gandy



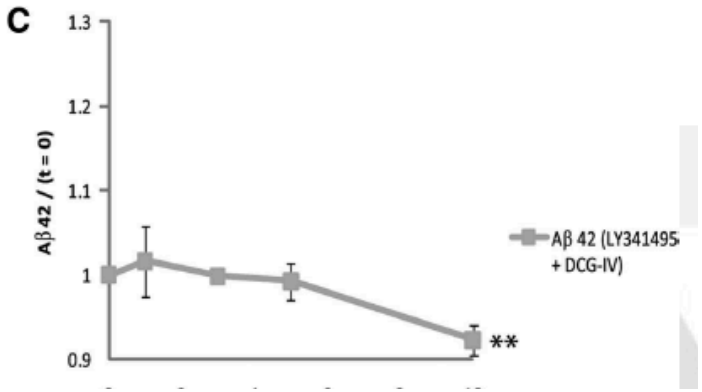
Synaptic accumulation of Aβ42 is proposed to be a major mechanism in cause/progression of AD:

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

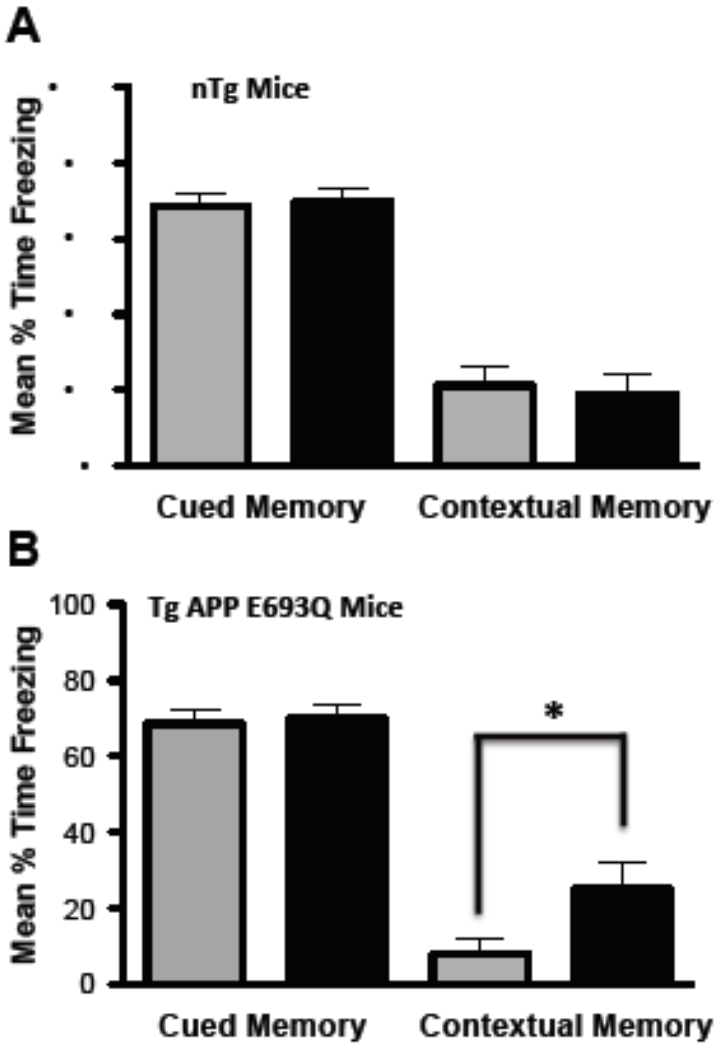
The Journal of Neuroscience, Month ??, 2010 • 30(xx):xxx–xxx • 1

Brief Communications

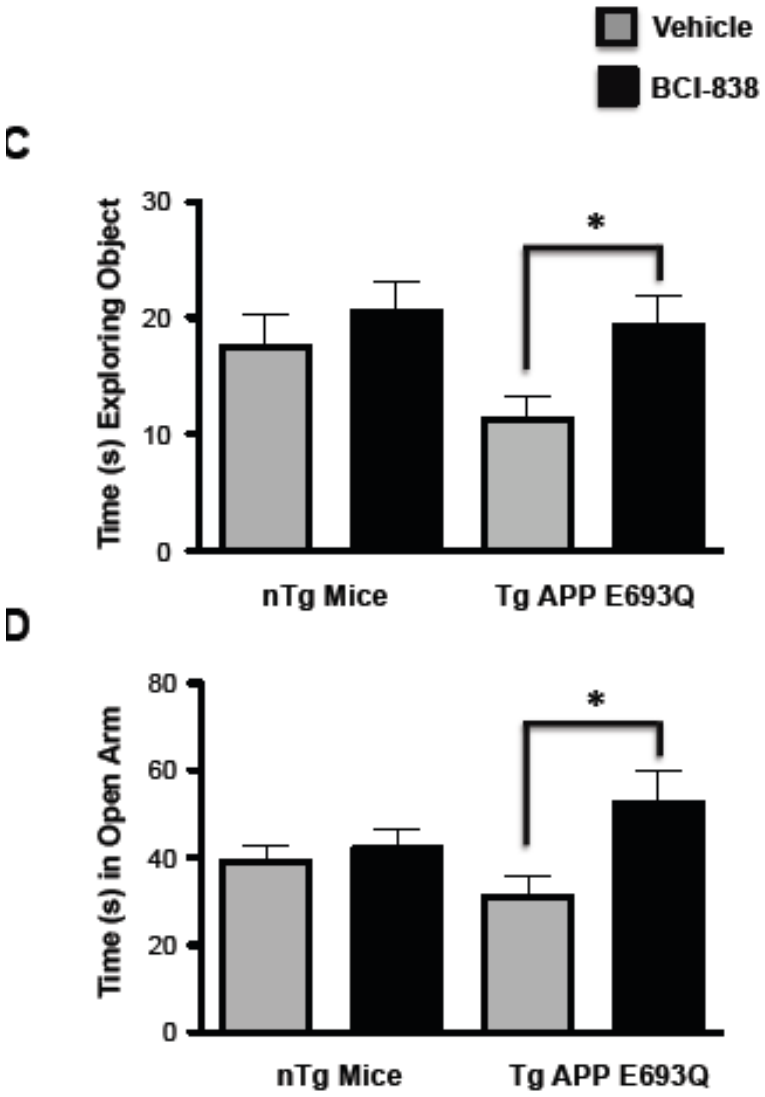
# Group II Metabotropic Glutamate Receptor Stimulation Triggers Production and Release of Alzheimer's Amyloid $\beta_{42}$ from Isolated Intact Nerve Terminals

Soong Ho Kim,[1] Paul E. Fraser,[4] David Westaway,[5] Peter H. St. George-Hyslop,[4,6] Michelle E. Ehrlich,[1,3] and Sam Gandy[1,2,7]

# *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*

| **Cortex** | | Aβ monomer | | Aβ oligomer | |
|---|---|---|---|---|---|
| | | Aβ 40 | Aβ 42 | A11 (prefibrillar) | OC (fibrillar) |
| BCI-838-treated | TBS | *n.c.* | *n.c.* | ↓ *** | *n.c.* |
| | Triton-X-soluble | *n.c.* | *n.c.* | | |
| | Formic acid-soluble | ↓ trend | ↓ trend | | |
| | Total | ↓ trend | ↓ trend | | |

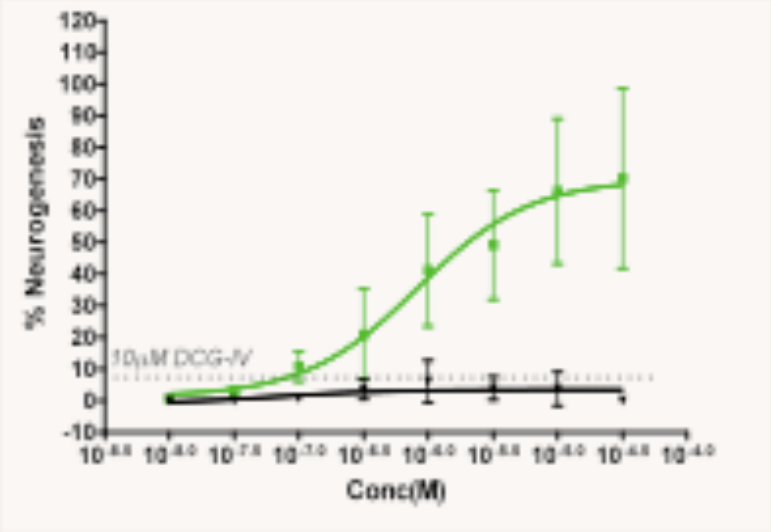
| **Hippocampus** | | Aβ monomer | | Aβ oligomer | |
|---|---|---|---|---|---|
| | | Aβ 40 | Aβ 42 | A11 (prefibrillar) | OC (fibrillar) |
| BCI-838-treated | TBS | ↓ * | ↓ ** | *n.c.* | *n.c.* |
| | Triton-X-soluble | *n.c.* | *n.c.* | | |
| | Formic acid-soluble | ↓ trend | ↓ trend | | |
| | Total | ↓ * | ↓ * | | |

$n = 6 - 7$

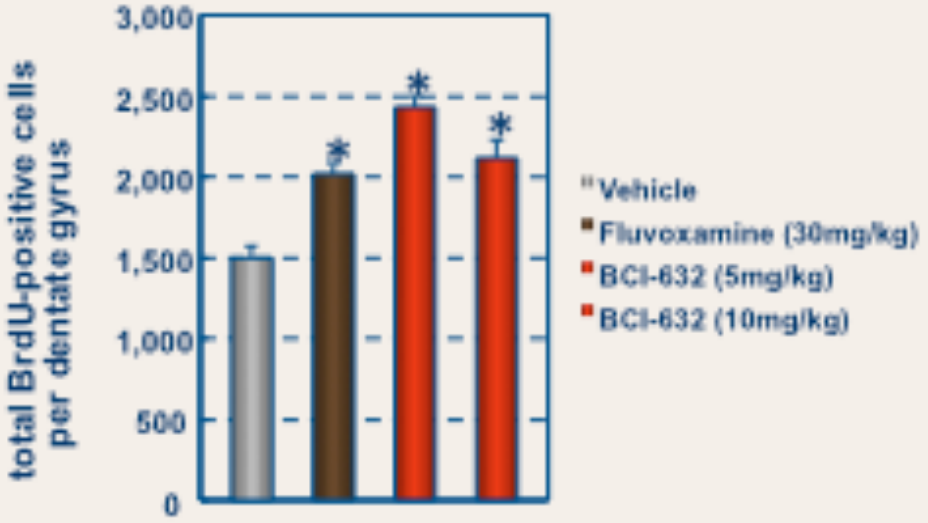
*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

# BCI-632 – A Neurogenic Compound

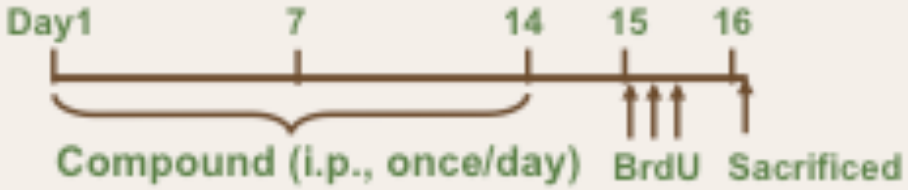
***In vitro***




***In vivo***




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



# Current evidence suggests that pro-neurogenic interventions improve outcome from experimental TBI

Han X, Tong J, Zhang J, Farahvar A, Wang E, Yang J, Samadani U, Smith DH, Huang JH. Imipramine treatment improves cognitive outcome associated with enhanced hippocampal neurogenesis after traumatic brain injury in mice. J Neurotrauma. 2011 Jun;28(6):995-1007.

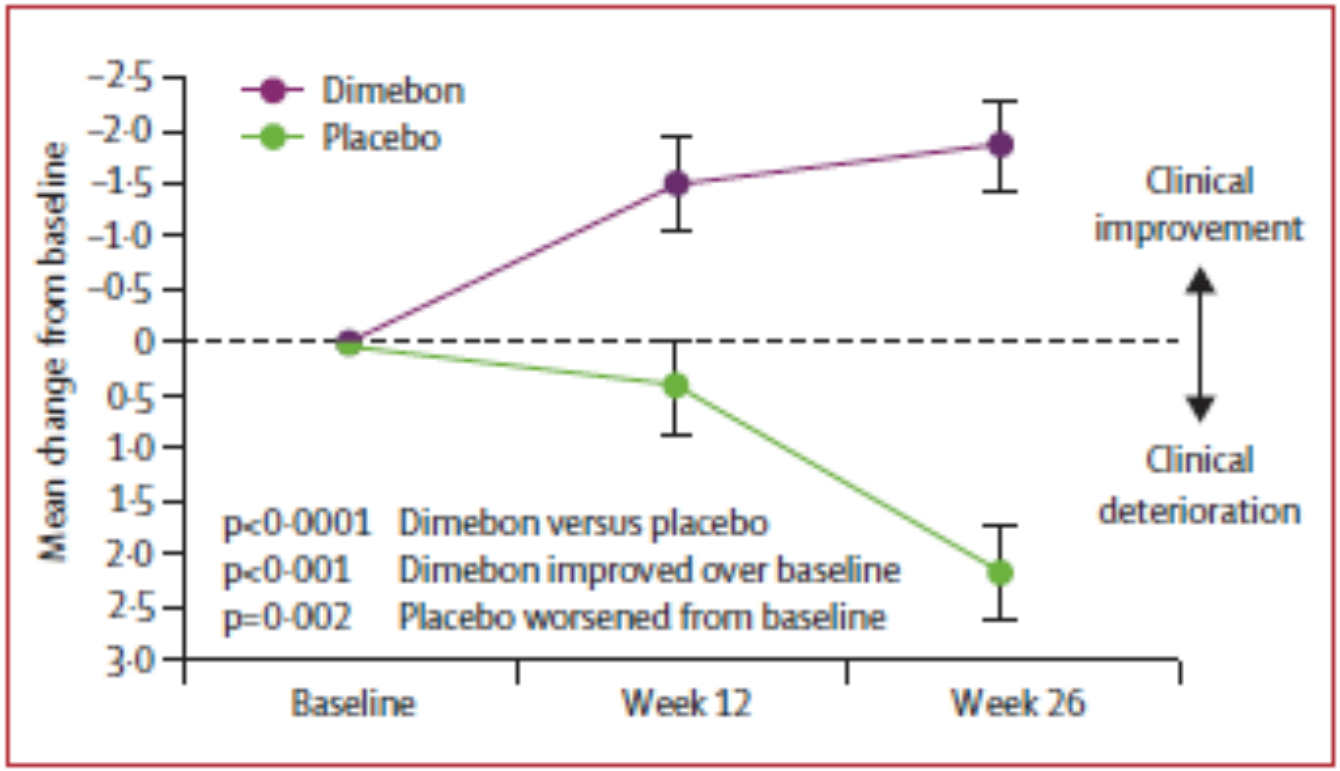
Blaiss CA, Yu TS, Zhang G, Chen J, Dimchev G, Parada LF, Powell CM, Kernie SG. Temporally specified genetic ablation of neurogenesis impairs cognitive recovery after traumatic brain injury. J Neurosci. 2011 Mar 30;31(13):4906-16.

Barha CK, Ishrat T, Epp JR, Galea LA, Stein DG. Progesterone treatment normalizes the levels of cell proliferation and cell death in the dentate gyrus of the hippocampus after traumatic brain injury. Exp Neurol. 2011 Sep;231(1):72-81.

Bregy A, Nixon R, Lotocki G, Alonso OF, Atkins CM, Tsoulfas P, Bramlett HM, Dietrich WD. Posttraumatic hypothermia increases doublecortin expressing neurons in the dentate gyrus after traumatic brain injury in the rat. Exp Neurol. 2012 Feb;233(2):821-8.

# 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**



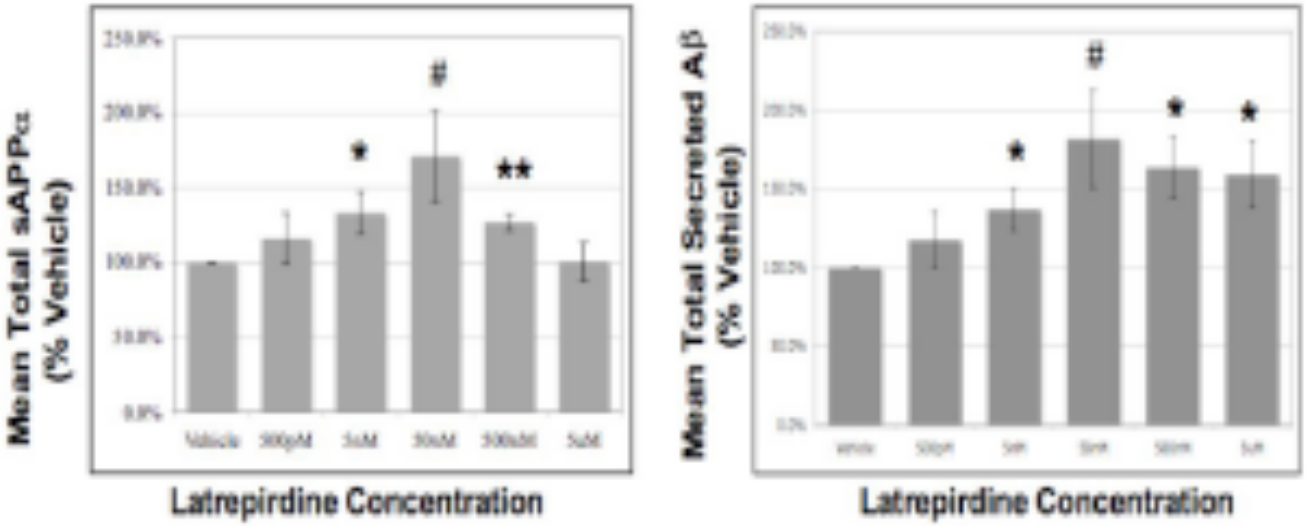
Research article

Highly accessed Open access

# Acute dosing of latrepirdine (Dimebon™), a possible Alzheimer therapeutic, elevates extracellular amyloid-β levels *in vitro* and *in vivo*

John W Steele[1†], Soong H Kim[1†], John R Cirrito[2†], Deborah K Verges[2], Jessica L Restivo[2], David Westaway[3], Paul Fraser[4], Peter SG Hyslop[4,5], Mary Sano[7,6], Ilya Bezprozvanny[8], Michelle E Ehrlich[9], David M Holtzman[2*] and Sam Gandy[1,7*]

**b** Mean band density of secreted APP metabolites from conditioned media following 6h latrepirdine

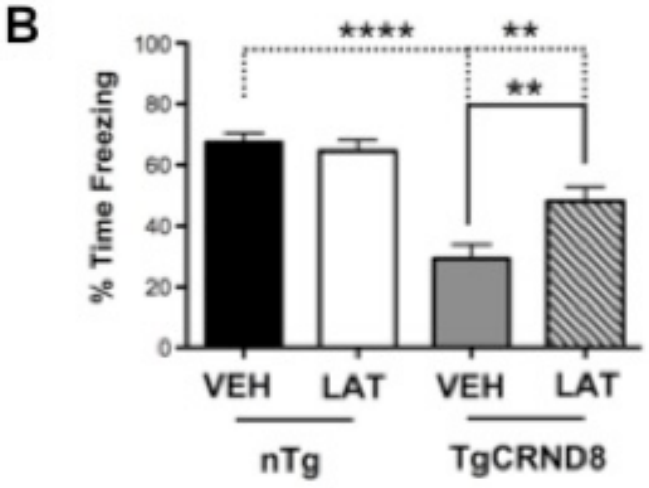


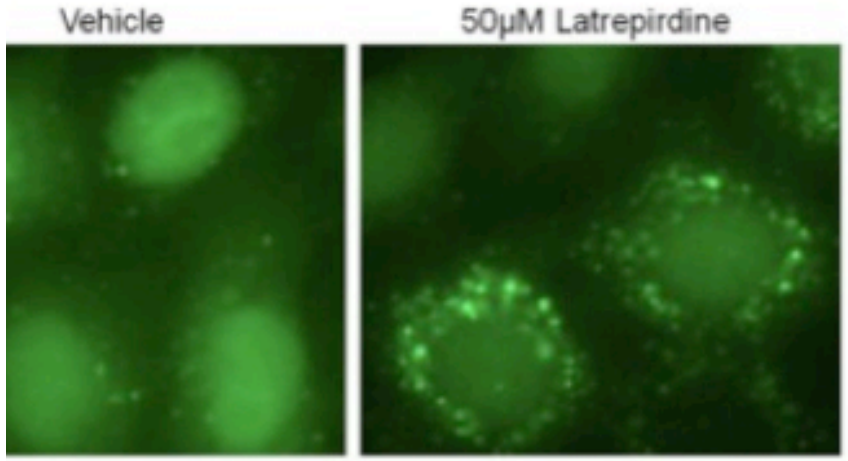

**c** Mean extracellular $A\beta_{x-42}/A\beta_{x-40}$ following 6h latrepirdine

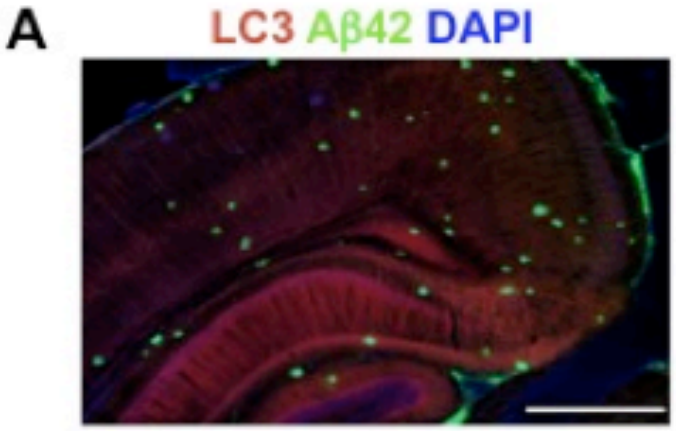
| | Vehicle | 500pM | 5nM | 50nM | 500nM | 5μM |
|---|---|---|---|---|---|---|
| Mean | 0.034 | 0.037 | 0.037 | 0.033 | 0.039 | 0.038 |
| S.E.M | 0.005 | 0.003 | 0.005 | 0.004 | 0.003 | 0.005 |

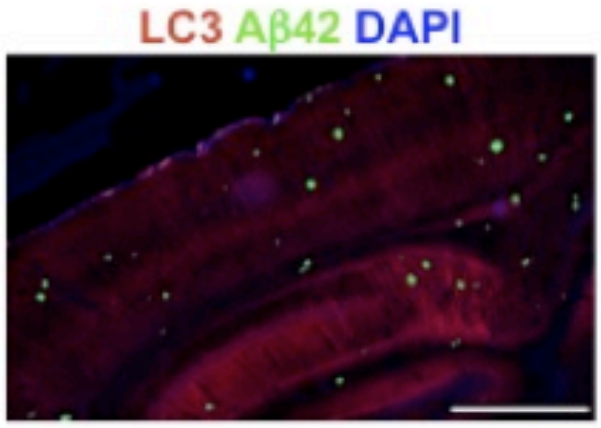
MOLECULAR NEURODEGENERATION

# Dimebon improves memory and arrests progression of molecular neuropathology while activating autophagy in TgCRND8 mice

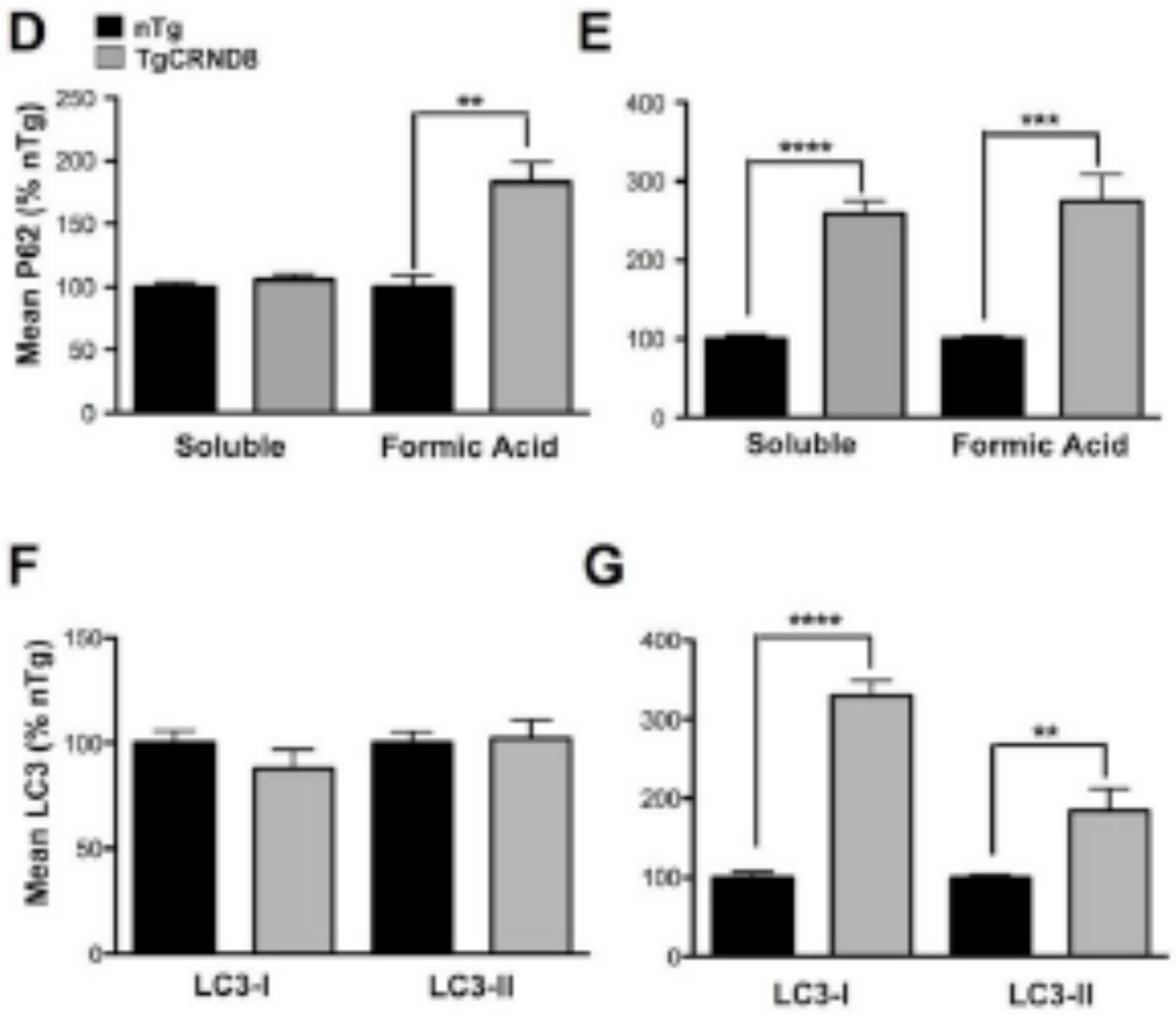


# Dimebon activated autophagy as indicated by changes in p62, LC3-I, LC3-II



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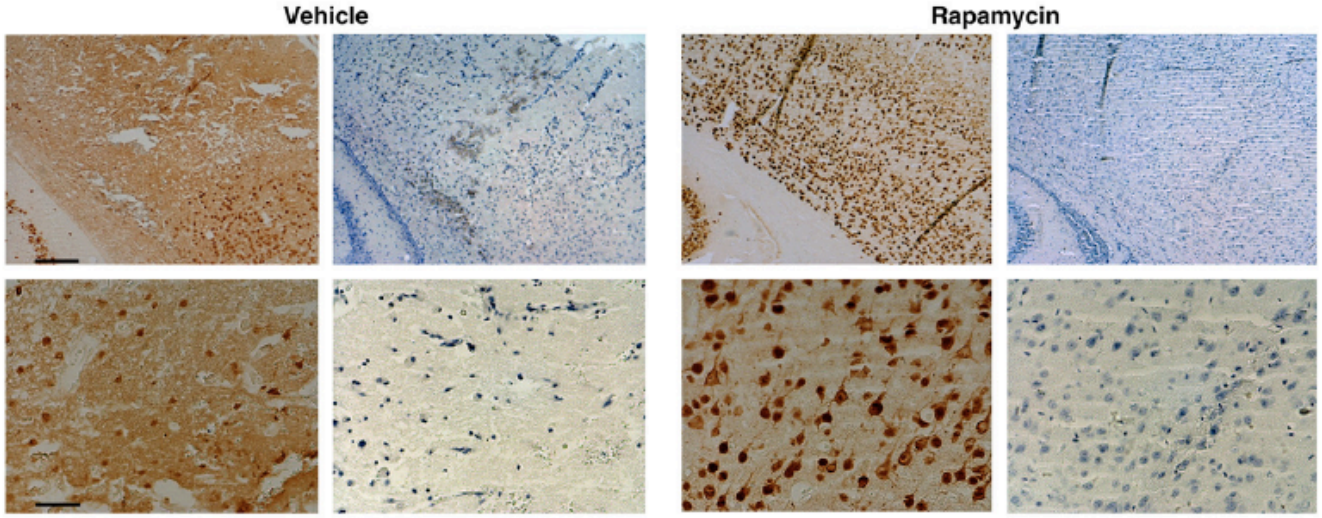
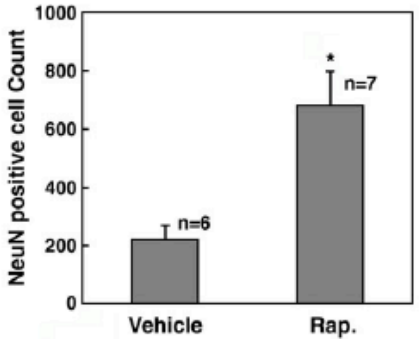
Neurobiology of Disease

www.elsevier.com/locate/ynbdi
Neurobiology of Disease 26 (2007) 86–93

# Rapamycin is a neuroprotective treatment for traumatic brain injury

S. Erlich,[a] A. Alexandrovich,[b] E. Shohami,[b] and R. Pinkas-Kramarski[a,*]



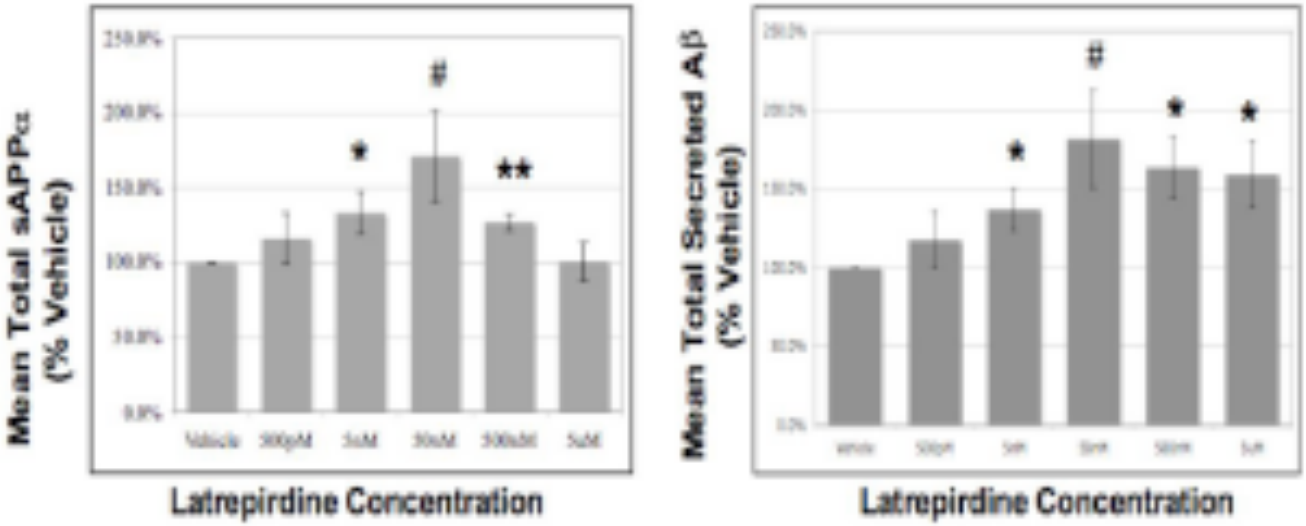
Research article

Highly accessed Open access

# Acute dosing of latrepirdine (Dimebon™), a possible Alzheimer therapeutic, elevates extracellular amyloid-β levels *in vitro* and *in vivo*

John W Steele[1†], Soong H Kim[1†], John R Cirrito[2†], Deborah K Verges[2], Jessica L Restivo[2], David Westaway[3], Paul Fraser[4], Peter SG Hyslop[4,5], Mary Sano[7,6], Ilya Bezprozvanny[8], Michelle E Ehrlich[9], David M Holtzman[2*] and Sam Gandy[1,7*]

**b** Mean band density of secreted APP metabolites from conditioned media following 6h latrepirdine



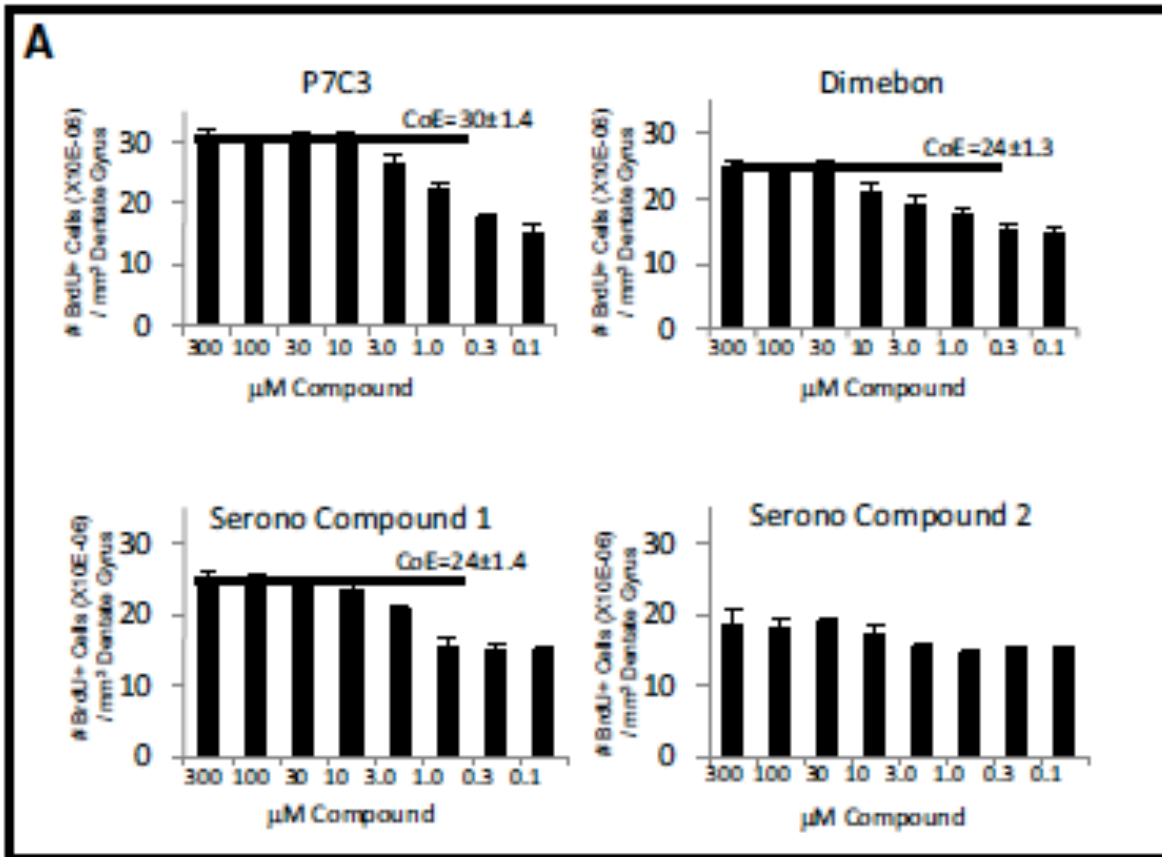

**c** Mean extracellular $A\beta_{x-42}/A\beta_{x-40}$ following 6h latrepirdine

| | Vehicle | 500pM | 5nM | 50nM | 500nM | 5μM |
|---|---|---|---|---|---|---|
| Mean | 0.034 | 0.037 | 0.037 | 0.033 | 0.039 | 0.038 |
| S.E.M | 0.005 | 0.003 | 0.005 | 0.004 | 0.003 | 0.005 |

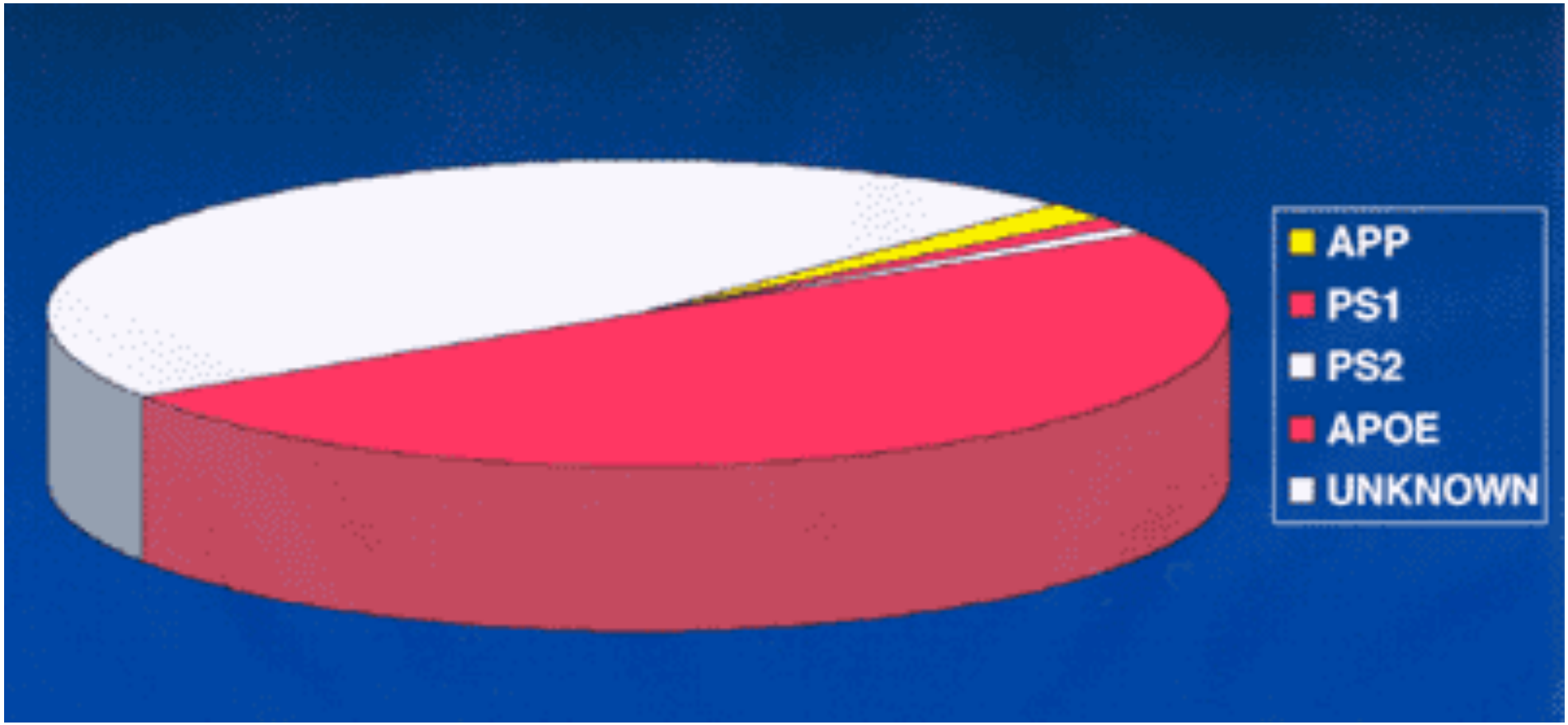
MOLECULAR NEURODEGENERATION

# 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. McKnight[1,*]



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


Mauri M, Sinforiani E, Bono G, Cittadella R, Quattrone A, Boller F, Nappi G. Interaction between Apolipoprotein epsilon 4 and traumatic brain injury in patients with Alzheimer's disease and Mild Cognitive Impairment. Funct Neurol. 2006 Oct-Dec;21(4):223-8.

Luukinen H, Viramo P, Herala M, Kervinen K, Kesäniemi YA, Savola O, Winqvist S, Jokelainen J, Hillbom M. Fall-related brain injuries and the risk of dementia in elderly people: a population-based study. Eur J Neurol. 2005 Feb;12(2):86-92.

Sabo T, Lomnitski L, Nyska A, Beni S, Maronpot RR, Shohami E, Roses AD, Michaelson DM. Susceptibility of transgenic mice expressing human apolipoprotein E to closed head injury: the allele E3 is neuroprotective whereas E4 increases fatalities. Neuroscience. 2000;101:879-84.

Han SH, Chung SY. Marked hippocampal neuronal damage without motor deficits after mild concussive-like brain injury in apoE-deficient mice. Ann N Y Acad Sci. 2000;903:357-65. .

Mayeux R, Ottman R, Maestre G, Ngai C, Tang MX, Ginsberg H, Chun M, Tycko B, Shelanski M. Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. Neurology. 1995 Mar;45(3 Pt 1):555-7.

Neuron, Vol. 15, 219–228, July, 1995, Copyright © 1995 by Cell Press

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

Jan Näslund,* Johan Thyberg,† Lars O. Tjernberg,* Christer Wernstedt,‡ Anders R. Karlström,§ Nenad Bogdanovic,‖ Samuel E. Gandy,# Lars Lannfelt,‖ Lars Terenius,* and Christer Nordstedt*

length (Glenner and Wong, 1984; Masters et al., Roher et al., 1993; Näslund et al., 1994). Aβ is deri proteolytic processing of an integral membrane p the β-amyloid precursor protein (Kang et al., 1987 Aβ peptide is detectable in soluble form in plasm

## 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*

Journal of Neurochemistry
Lippincott-Raven Publishers, Philadelphia


# 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

## Isoform-specific Aβ uptake into cells and in vivo

# *APOE* Genotype Results in Differential Effects on the Peripheral Clearance of Amyloid-$\beta_{42}$ in *APOE* Knock-in and Knock-out Mice

Matthew J. Sharman[a,b,c,d], Michael Morici[c,d], Eugene Hone[c,d], Tamar Berger[c,d], Kevin Taddei[b,c,d], Ian J. Martins[a,b,c,d], Wei Ling F. Lim[c,d], Sajla Singh[b,c], Markus R. Wenk[e,f], Jorge Ghiso[g], Joseph D. Buxbaum[h], Sam Gandy[g] and Ralph N. Martins[a,b,c,d,*]

# POLIPOPROTEIN E PROMOTES THE BINDING AND UPTAKE OF β-AMYLOID INTO CHINESE HAMSTER OVARY CELLS IN AN ISOFORM-SPECIFIC MANNER

S. YANG,* D. H. SMALL,† U. SEYDEL,‡ J. D. SMITH,§ J. HALLMAYER,‖ S. E. GANDY¶ and R. N. MARTINS* **††

ANNOUNCING KEYSTONE SYMPOSIA'S 2012 MEETING ON:

**ApoE, Alzheimer's and Lipoprotein Biology**

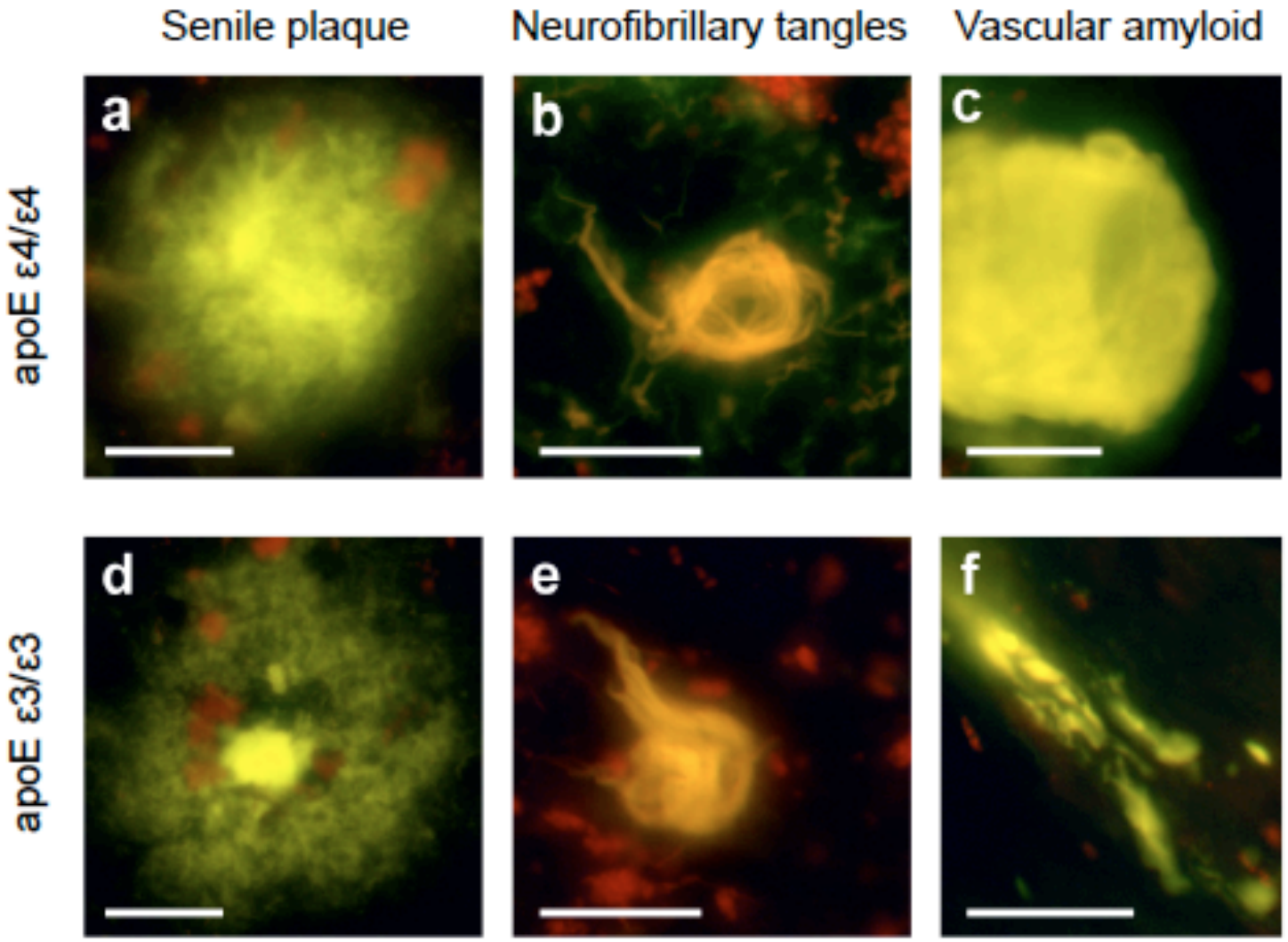
*Joint with* ***Clinical and Molecular Biology of Acute and Chronic Traumatic Encephalopathies***


# Molecular Imaging of ApoE Isoform-related Protein Conformation Changes in human Alzheimer Brain

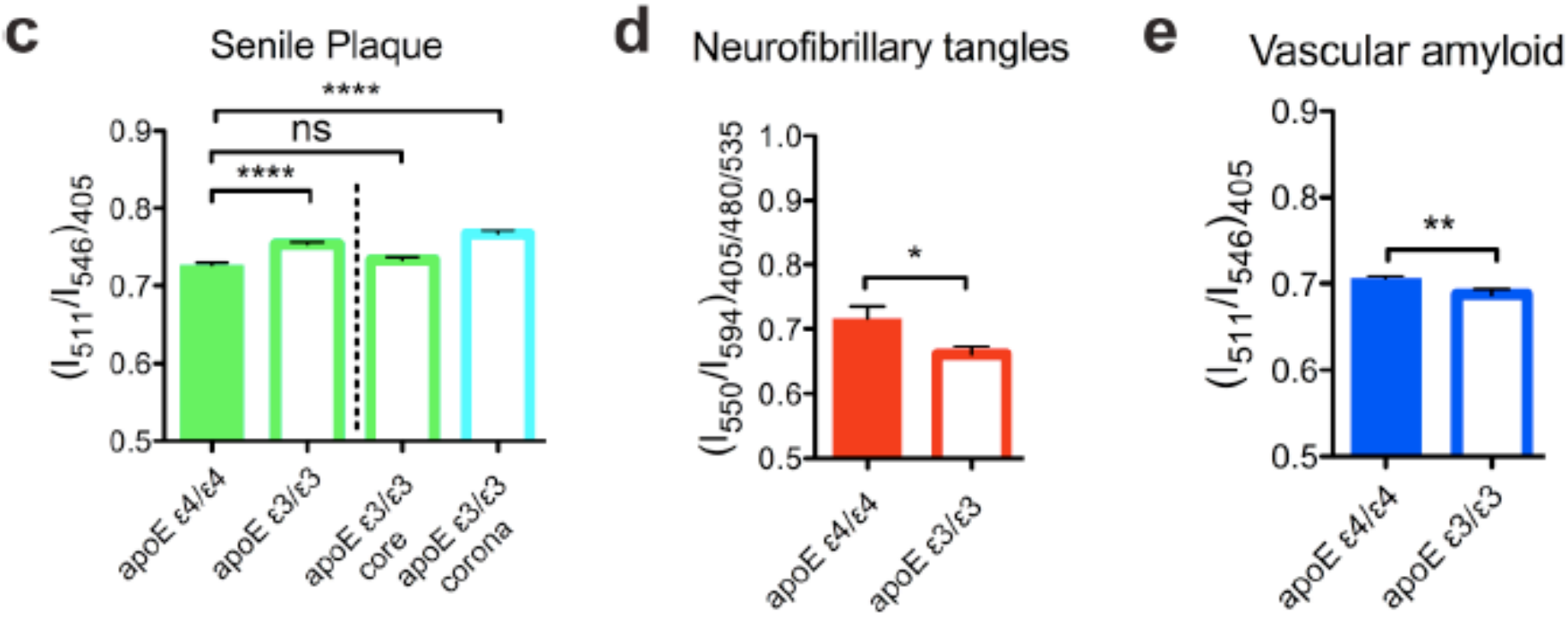
Ina Caesar, K. Peter R. Nilsson, Per Hammarström, Mikael Lindgren, Stefan Prokop, Frank L. Heppner, David M. Holtzman, Patrick R. Hof, Sam Gandy

February 27, 2012

# Aggregate morphology



# ApoE genotype dependent spectral separation



ALZHEIMER'S DISEASE

# Human apoE Isoforms Differentially Regulate Brain Amyloid-β Peptide Clearance

Joseph M. Castellano,[1,2,3]* Jungsu Kim,[1,2,3]* 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. Holtzman[1,2,3,9†]

# 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. Holtzman,[1,2,3,7]

Sciencexpress 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. Zinn,[1] Brad T. Casali,[1] Jessica L. Restivo,[2] Whitney D. Goebel,[2] Michael J. James,[4] Kurt R. Brunden,[4] Donald A. Wilson,[3] Gary E. Landreth[1*]

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

David J. Loane,[2] Patricia M. Washington,[1] Lilit Vardanian,[1] Ana Pocivavsek,[1] Hyang-Sook Hoe,[1] Karen E. Duff,[3] Ibolja Cernak,[4] G. William Rebeck,[1] Alan I. Faden,[2] and Mark P. Burns[1]

# *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 A$\beta_{42}$ 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.