Commentary

Treating the Lesions, Not the Disease

Xiongwei Zhu,* Jesus Avila,[†] George Perry,^{*,‡} and Mark A. Smith*

From the Department of Pathology, Case Western Reserve University, Cleveland, Ohio; the Centro de Biología Molecular,[†] Facultad de Ciencias, Universidad Autónoma de Madrid, Madrid, Spain; and the College of Sciences,[‡] University of Texas at San Antonio, San Antonio, Texas*

In this issue of *The American Journal of Pathology*, Caccamo and colleagues¹ demonstrate that treatment of the triple transgenic mouse model of Alzheimer's disease (AD) with lithium, a weak inhibitor of glycogen synthase kinase (GSK), attenuates tau pathology but not amyloid- β nor working memory. This work follows closely on the heels of another therapeutic strategy in these mice, where reductions of soluble amyloid- β and tau, but not soluble amyloid- β alone, attenuated cognitive decline.² Taken together, these articles likely provide important insights into potential treatment strategies for AD.

The most conspicuous microscopic changes in the brains of individuals with AD are senile plaques composed of amyloid- β and neurofibrillary tangles composed of tau protein. Although arguments have been made that the diagnostic requirement³ of clinical dementia coupled with neuropathological senile plaques and neurofibrillary tangles is a somewhat artificial construct that forces a correlation between disease and pathology,⁴ the majority of investigators remain convinced that either amyloid- β or tau causes AD. In this regard, for the most part, amyloid- β has been clearly ahead in terms of the popular vote.⁵ Amyloid- β is toxic *in vitro*,⁶ and mutations in the amyloid- β protein precursor^{7,8} are associated with familial forms of the disease. These findings coalesced into the Amyloid Hypothesis⁹ that, to this day, remains the leading hypothesis for disease pathogenesis.¹⁰ However, the development of transgenic mice with supra-physiological loads of amyloid- β , but little evidence of neurodegeneration,^{11–13} led many to question whether amyloid- β was sufficient to cause AD.¹⁴ This lull in the amyloid- β field was coincident with a major tau-related finding—namely, that mutations in tau were associated with familial forms of neurodegeneration,¹⁵ albeit FTDP-17 and not AD. Currently, therefore, which lesion to therapeutically target, amyloid- β or tau, has been keenly debated with the fragmented view of the disease leading,

naturally, to a fragmented approach to treating the disease.

At present, therapeutic approaches are mainly divided along “party” lines,⁵ either looking at reducing amyloid- β or blocking tau phosphorylation. Regarding the latter, upstream kinases that phosphorylate tau have received the most attention, in particular GSK. GSK-3 β can phosphorylate tau both *in vivo* and *in vitro* and is found at increased levels in the AD brain, as well as in normal neurons and those containing neurofibrillary tangles.^{16,17} The appearance of GSK-3 β is associated with amyloid- β , presenilins, and the acetylcholine pathway, making it a seemingly attractive target with which to attack multiple pathways involved in the disease. However, it is worth noting, especially in a chronic disease such as AD, where cause and consequence are omnipresent, that GSK-3 β has been attributed to other factors involved in the disease, such as oxidative stress^{18,19} and oxidative stress-induced neuronal cell pathology.²⁰

Transgenic models overexpressing amyloid- β but lacking neuronal degeneration^{11–13} were followed by the development of transgenic models with abnormal tau phosphorylation in the brain.²¹ The logical and consequent step was the triple transgenic model,²² which develops both amyloid- β plaques and tau aggregation, closely mimicking the human condition. This mouse therefore offered the promise to be useful not only for testing potential therapeutic targets but also in settling the argument about whether amyloid- β or tau is the primary pathogenic protein.

Lithium is an effective, albeit weak, inhibitor of GSK and has been used therapeutically for a variety of disorders.²³ Relevant to AD, lithium acts, presumably via GSK inhibition, to modulate tau phosphorylation and has previously been shown to prevent hippocampal tau pathology in a transgenic mouse model overexpressing GSK-3 β and in the FTDP-17 mutant tau model when administered early in the disease.²⁴ Of relevance to the current work by Caccamo,¹ lithium administration at later

Accepted for publication February 23, 2007.

This commentary relates to Caccamo et al, *Am J Pathol* 2007, 170: 1669–1675, published in this issue.

Address reprint requests to Mark Smith, Ph.D., Department of Pathology, Case Western Reserve University, 2103 Cornell Rd., Cleveland, OH 44106. E-mail: mark.smith@case.edu.

stages, although reducing tau phosphorylation, was not able to reverse tau aggregation.²³ Likewise, using a molecular approach, transgene shutdown in Tet/GSK-3 mice results in both normalized GSK activity and reduced levels of phosphorylated tau, which consequently prevents neuronal death and cognitive decline.²⁵ These findings, along with others,²⁴ recently led the Alzheimer Cooperative Disease Study Center to enter lithium into clinical trials for the treatment of AD. Although the results from using lithium in triple transgenic mice¹ might forecast pessimism for the outcome in human patients, there are a number of important aspects that provide food for thought, and it is therefore premature to write off lithium in AD patients based on lack of efficacy in a mouse model.

First, although close to 50 different therapeutic strategies have proven effective in treating single amyloid precursor protein transgenic mice, none have proven effective in human clinical trials thus far. Although this does not mean that none will prove effective, it does indicate that these transgenic mouse models are not predictive of which treatments will work. Whether the triple transgenic animal is a more reliable barometer for therapeutics remains to be seen.

Second, in triple transgenic mice, it seems that both amyloid- β and tau are important, and individually targeting one, but not the other, is insufficient to attenuate cognitive decline.^{1,2} On the other hand, targeting both pathologies² is effective. However, is it valid to translate such findings to the human condition? Simply stated, the fact that forced overexpression of tau and amyloid- β in vulnerable regions of the brain leads to cognitive dysfunction and that reversing these leads to improved cognitive function is as artificial a system as one can think of—ie, preventing the insult prevents the phenotype. Although this works wonderfully in animal models, where we know the (transgenic) insult, this lesion-centric approach will only translate effectively into human AD if the lesions are the cause of the disease. However, if the lesions are a consequence of the disease, we should not expect similarly spectacular results.^{26,27}

Third, in conjunction with the findings of Engel et al,²⁵ Caccamo's work¹ presented in this issue reiterates the fact that early intervention is key. The current work uses lithium administered to the triple transgenic mice aged at 15 months, after pathological structures have been well developed. Although tau phosphorylation is reduced, cognition deficits were not attenuated.

In summary, the triple transgenic model may prove to be a very useful tool in understanding the development of AD. Biochemically, the abnormal proteins mimic those found in the human brain. Morphologically, the amyloid- β plaques develop similarly to AD, and the phosphorylated tau accumulates in the brain regions and cell types as in the human counterpart.²² Cognitive deficits can be reliably measured. Moreover, like their human counterparts, prevention may be far easier to attain than treatment. However, knowing whether AD is caused by amyloid- β and/or tau is critical in translating any findings into humans. If amyloid- β and/or tau are downstream markers of disease, we learn naught.

References

- Caccamo A, Oddo S, Tran LX, LaFerla FM: Lithium reduces tau phosphorylation but not Abeta or working memory deficits in a transgenic model with both plaques and tangles. *Am J Pathol* 2007, 170:1669–1675
- Oddo S, Caccamo A, Tran L, Lambert MP, Glabe CG, Klein WL, LaFerla FM: Temporal profile of amyloid-beta (Abeta) oligomerization in an in vivo model of Alzheimer disease. A link between Abeta and tau pathology. *J Biol Chem* 2006, 281:1599–1604
- Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, Vogel FS, Hughes JP, van Belle G, Berg L: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* 1991, 41:479–486
- Castellani RJ, Lee HG, Zhu X, Nunomura A, Perry G, Smith MA: Neuropathology of Alzheimer disease: pathognomonic but not pathogenic. *Acta Neuropathol (Berl)* 2006, 111:503–509
- Perry G, Raina AK, Cohen ML, Smith MA: When hypotheses dominate. *The Scientist* 2004, 18:6
- Mattson MP, Tomaselli KJ, Rydel RE: Calcium-destabilizing and neurodegenerative effects of aggregated beta-amyloid peptide are attenuated by basic FGF. *Brain Res* 1993, 621:35–49
- Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, Chi H, Lin C, Holman K, Tsuda T, Mar L, Sorbi S, Nacmias B, Piacentini S, Amaducci L, Chumakov I, Cohen D, Lannfelt L, Fraser PE, Rommens JM, St George-Hyslop PH: Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. *Nature* 1995, 376:775–778
- Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, Mant R, Newton P, Rooke K, Roques P, Talbot C, Pericak-Vance M, Roses A, Williamson R, Rossor M, Owen M, Hardy J: Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 1991, 349:704–706
- Hardy JA, Higgins GA: Alzheimer's disease: the amyloid cascade hypothesis. *Science* 1992, 256:184–185
- Hardy J, Selkoe DJ: The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 2002, 297:353–356
- Takeuchi A, Irizarry MC, Duff K, Saido TC, Hsiao Ashe K, Hasegawa M, Mann DM, Hyman BT, Iwatsubo T: Age-related amyloid beta deposition in transgenic mice overexpressing both Alzheimer mutant presenilin 1 and amyloid beta precursor protein Swedish mutant is not associated with global neuronal loss. *Am J Pathol* 2000, 157:331–339
- Irizarry MC, McNamara M, Fedorchak K, Hsiao K, Hyman BT: APPSw transgenic mice develop age-related A beta deposits and neuropil abnormalities, but no neuronal loss in CA1. *J Neuropathol Exp Neurol* 1997, 56:965–973
- Irizarry MC, Soriano F, McNamara M, Page KJ, Schenk D, Games D, Hyman BT: Abeta deposition is associated with neuropil changes, but not with overt neuronal loss in the human amyloid precursor protein V717F (PDAPP) transgenic mouse. *J Neurosci* 1997, 17:7053–7059
- Joseph J, Shukitt-Hale B, Denisova NA, Martin A, Perry G, Smith MA: Copernicus revisited: amyloid beta in Alzheimer's disease. *Neurobiol Aging* 2001, 22:131–146
- D'Souza I, Poorkaj P, Hong M, Nochlin D, Lee VM, Bird TD, Schellenberg GD: Missense and silent tau gene mutations cause frontotemporal dementia with parkinsonism-chromosome 17 type, by affecting multiple alternative RNA splicing regulatory elements. *Proc Natl Acad Sci USA* 1999, 96:5598–5603
- Yamaguchi H, Ishiguro K, Uchida T, Takashima A, Lemere CA, Imahori K: Preferential labeling of Alzheimer neurofibrillary tangles with antisera for tau protein kinase (TPK) I/glycogen synthase kinase-3 beta and cyclin-dependent kinase 5, a component of TPK II. *Acta Neuropathol (Berl)* 1996, 92:232–241
- Leroy K, Yilmaz Z, Brion JP: Increased level of active GSK-3beta in Alzheimer's disease and accumulation in argyrophilic grains and in neurones at different stages of neurofibrillary degeneration. *Neuropathol Appl Neurobiol* 2007, 33:43–55
- Nunomura A, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, Jones PK, Ghanbari H, Wataya T, Shimohama S, Chiba S, Atwood CS, Petersen

- RB, Smith MA: Oxidative damage is the earliest event in Alzheimer disease. *J Neuropathol Exp Neurol* 2001, 60:759–767
19. Nunomura A, Perry G, Pappolla MA, Wade R, Hirai K, Chiba S, Smith MA: RNA oxidation is a prominent feature of vulnerable neurons in Alzheimer's disease. *J Neurosci* 1999, 19:1959–1964
20. Lee KY, Koh SH, Noh MY, Park KW, Lee YJ, Kim SH: Glycogen synthase kinase-3beta activity plays very important roles in determining the fate of oxidative stress-inflicted neuronal cells. *Brain Res* 2007, 1129:89–99
21. Götz J, Chen F, Barmettler R, Nitsch RM: Tau filament formation in transgenic mice expressing P301L tau. *J Biol Chem* 2001, 276:529–534
22. Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kaye R, Metherate R, Mattson MP, Akbari Y, LaFerla FM: Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. *Neuron* 2003, 39:409–421
23. Wada A, Yokoo H, Yanagita T, Kobayashi H: Lithium: potential therapeutics against acute brain injuries and chronic neurodegenerative diseases. *J Pharmacol Sci* 2005, 99:307–321
24. Engel T, Goni-Oliver P, Lucas JJ, Avila J, Hernandez F: Chronic lithium administration to FTDP-17 tau and GSK-3beta overexpressing mice prevents tau hyperphosphorylation and neurofibrillary tangle formation, but pre-formed neurofibrillary tangles do not revert. *J Neurochem* 2006, 99:1445–1455
25. Engel T, Hernandez F, Avila J, Lucas JJ: Full reversal of Alzheimer's disease-like phenotype in a mouse model with conditional overexpression of glycogen synthase kinase-3. *J Neurosci* 2006, 26:5083–5090
26. Perry G, Nunomura A, Raina AK, Smith MA: Amyloid-beta junkies. *Lancet* 2000, 355:757
27. Smith MA, Atwood CS, Joseph JA, Perry G: Predicting the failure of amyloid-beta vaccine. *Lancet* 2002, 359:1864–1865