

Control Number: 09-HT-2700-ALZ

S4-04 - Hot Topics 2

Presentation #: S4-04-06; Speaking Time: 7/15/2009, 11:45 - 12:00 PM

## **Dimebon®, A Clinically Promising Drug For Alzheimer Disease, Regulates Amyloid-Beta Metabolism In Cultured Cells, In Isolated Nerve Terminals, And In The Interstitial Fluid Of The Living Rodent Brain**

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Disclosure Block: **S. Gandy**, Forest; Wyeth, Elan, Amicus, Diagenic, Epix.

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**Background:** Recent evidence indicates that the retired Russian antihistamine Dimebon® (dimebolin) improves cognitive function in aged rodents and in humans suffering from mild to moderate Alzheimer disease (AD). A recent screen against a set of biochemical targets indicated that Dimebon® inhibits alpha-adrenergic receptors (alpha-1A, alpha-1B, alpha-1D, alpha-2A), histamine H1 and H2 receptors, and serotonin 5-HT<sub>2c</sub>, 5-HT<sub>5A</sub>, and 5-HT<sub>6</sub> receptors with high affinity (Wu et al., Molec Neurodeg, 2008, 3: 15doi:10.1186/1750-1326-3-15). Dimebon® has also been shown to modulate Ca<sup>2+</sup> flux, apoptosis, and mitochondrial stability.

**Objective:** Given the clinical benefit, and given the known modulation of A-beta metabolism by neurotransmitters and by mitochondrial function, we assessed the ability of Dimebon® to modulate levels of APP metabolites including A-beta in a series of in vitro and in vivo experimental systems.

**Methods:** Under control conditions or following Dimebon® treatment, we measured A-beta levels in either: (1) the conditioned media of SweAPP-overexpressing cultured N2a mouse neuroblastoma cells; (2) the releasate from isolated nerve terminals from TgCRND8 mice overexpressing Swe/Indiana APP, or (3) the interstitial fluid (ISF) of the brains of freely moving Tg2576 SweAPP-overexpressing transgenic mice.

**Conclusion:** Acute treatment with Dimebon® increased A-beta levels in the releasate from TgCRND8 nerve terminals and in the ISF of freely moving Tg2576 transgenic mice. In media conditioned by SweAPP N2a cells overnight in the presence of drug, Dimebon® either had no effect on A-beta or lowered A-beta. Since questions have been raised regarding the nature of Dimebon® preparations, we performed these studies using Dimebon® from two independent vendors; both gave similar results. Elevation of A-beta release from isolated nerve terminals and elevation of ISF A-beta levels are unexpected phenomena to associate with a clinically beneficial AD drug. Further study is required to elucidate the molecular mechanism underlying the acute regulation of A-beta metabolism by Dimebon®. Chronic Dimebon® exposure also merits study. Dimebon® may be a useful chemical probe for advancing our understanding of the role of A-beta in AD and for identifying unexplored druggable mechanisms in the molecular pathogenesis of AD. (Supported by Cure Alzheimer's Fund and National Institute on Aging.)

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S4-04 - Hot Topics 2  
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## **Immunotherapy Targeting Pathologically Phosphorylated Tau In A Tauopathy Mouse Model**

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Disclosure Block: H. Rosenmann, None.

**Background:** It has now become clear that amyloid immunization, while displaying clearance of amyloid, not only caused neuroinflammation, but did not improve cognitive impairment (and did not reduce the neurofibrillary-tangles (NFTs)). As NFTs are the best correlate with dementia, targeting the NFT pathology seems to be a preferential goal. As an aggregated protein, tau in the NFTs - seems to be a candidate for immunotherapy. Yet, the encephalitogenicity of full-length tau recently reported by us (Arch Neurol, 2006) demands to selectively target pathological tau and address both, efficacy and safety.

**Objective:** Here we set up to specifically target pathologically phosphorylated (P)-tau conformers by immunizing NFT-mice with NFT-related P-tau peptides, using an immunization protocol aimed to predispose a proinflammatory milieu in CNS, similarly to what we used when the neurotoxicity of tau protein was detected (i.e., the use of complete-Freund's-adjuvant (CFA) with pertussis-toxin (PT)).

**Methods:** We immunized NFT-mice with a mixture of three tau-peptides phosphorylated at five residues characteristic of NFT-pathology with CFA and PT. Clinical, immunological and pathological evaluations were performed.

**Results:** Anti-P-tau Abs were detected in sera of tau-immunized mice. However, no neurological deficits were noted following P-tau-immunotherapy for at least 8 months. Reduced NFT-burden (~40%;  $p < 0.001$ ) was noticed in the brains and spinal cords of immunized animals relative to controls, as indicated by Gallyas-staining and with AT8- and AT180-immunohistochemistry. This was accompanied with an increase (~20%;  $p = 0.01$ ) in microglial burden as indicated by lectin staining.

**Conclusion:** Our results show: 1. A decreased NFT-burden following P-tau-immunotherapy. This is in accord with Asuni et al. (2007) who used a similar approach of immunizing mice against NFTs, yet with a different P-tau immunogene and immunization protocol (without CFA+PT). 2. Presence of anti-P-tau Abs in the sera of immunized mice with no evidence of clinical deficits, indicating that these specific P-peptide-immunogens used by us are not encephalitogenic, in contrast to the encephalitogenicity of full-length tau, demonstrated by us previously. This anti-NFT effect induced by immunotherapy targeting pathologically phosphorylated tau, together with the lack of encephalitogenicity of these P-peptide-immunogens, points to the therapeutic anti-NFT potential of P-tau-immunotherapy.

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## **Clinical Practices Regarding Mild Cognitive Impairment (MCI) Among Neurology Service Providers**

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Disclosure Block: J. Karlawish, None.

**Background:** MCI is a research categorization that is entering clinical practice, but little is known about how it is being used.

**Objective:** To assess how neurologists are diagnosing and treating patients with mild cognitive symptoms and how they view MCI as a clinical diagnosis.

**Methods:** Members of the Geriatric and Behavioral Neurology sections of the American Academy of Neurology (AAN) were surveyed by the AAN Survey Department via mail and Internet.

**Results:** Four hundred twenty providers (response rate = 48%) completed the survey. 88% reported at least monthly encounters with patients experiencing mild cognitive symptoms. Most respondents recognize MCI as a clinical diagnosis (90%) and use its diagnostic code for billing purposes (70%). When seeing this population, most respondents report routinely making recommendations for monitoring and follow-up (88%), counseling patients on physical (78%) and mental exercise (75%), and communicating about risk of dementia (63%). Relatively few respondents routinely provide information on support services (27%) or a written summary of findings (15%). Most (70%) prescribe cholinesterase inhibitors at least sometimes for this population, with memantine (39%) and “other” agents (e.g., vitamin E, ginkgo) prescribed less frequently. Respondents endorsed several benefits of making a clinical diagnosis of MCI: 1) labeling the problem is helpful (91%); 2) involving the patient in planning for the future (87%); 3) motivating the patient’s risk reduction activities (85%); 4) helping the family with financial planning (72%); and 5) prescribing medications useful for treating MCI (65%). Some respondents noted potential drawbacks of MCI as a clinical diagnosis, including 1) it is too difficult to diagnose accurately or reliably (23%); 2) it is usually better described as early AD (21%); and 3) a diagnosis can cause unnecessary worry (20%).

**Conclusion:** Patients with MCI are commonly seen by neurologists and prescribed various medications to address their symptoms. The MCI concept is generally viewed as a useful diagnostic category in clinical practice. Clinicians vary significantly in the education and support they provide or recommend for MCI patients, suggesting a need for practice guidelines in this area. Future research is needed to illuminate decision-making around MCI treatment. (*Funding source: Alzheimer's Association*)