colchicine affects axonal transport. We provide the first in-vivo evidence of davunetide's ability to restore axonal transport in mice exposed to colchicine. These data support previous reports that davunetide's neuroprotective effect is mediated through microtubule stabilization. Restoration of axonal transport suggests clinical utility in various neurological conditions characterized by axonal transport impairment. We thank Drs. Michael Gold, Bruce Morimoto and Alistair Stewart, Allon Therapeutics Inc. for excellent suggestions.

O2-05-05 PPAR-GAMMA ACTIVATION WITH AT1 RECEPTOR BLOCKADE PREVENTS BLOOD-BRAIN BARRIER DISRUPTION AND COGNITIVE IMPAIRMENT IN TYPE 2 DIABETIC MELLITUS MICE

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Background: Recently, vascular and metabolic dysfunctions have been highlighted as key risk factors in the pathogenesis of Alzheimer's disease (AD). Type 2 diabetes mellitus (T2DM) is known to be associated with increased risk of AD with clinical studies. We previously reported that T2DM model mice, KKAy, exhibited cognitive impairment age- dependently compared with wild-type mice, and angiotensin II type-1 (AT1) receptor blocker, telmisartan, improved cognitive decline with peroxisome proliferator-activated receptor (PPAR)-g activation; however, the detailed mechanism of T2DM-induced neurodegeneration is not well known. Therefore, we examined the possibility that telmisartan could attenuate blood-brain barrier (BBB) impairment with AT1 receptor blockade and PPAR-g activation, thereby improving T2DM-induced cognitive decline. **Methods:** KKAy were administered telmisartan (1 mg/kg/day by oral injection) and/or GW9662 (0.35 mg/kg/day in drinking water), a PPAR-g antagonist, for 7 weeks from 8 weeks of age. Cognitive function was evaluated by the Morris water maze test at 15 weeks of age.BBB permeability was evaluated by measuring extravasation of Evans Blue dye and extravasation of the fluorescent dye, albumin-Alexa Fluro-488 and IgG-DyLight549. Expression of tight junction (TJ) proteins, zonula occludens-1 and occludin in the brainwere evaluated by immunobloting. Ultrastructural changes of the BBB were assessed by transmission electron microscopy. **Results:** Impairment of cognitive function determined by Morris water maze test was observed in KKAy compared with age-matched C57BL/6J mice. Treatment with telmisartan attenuated this cognitive decline. BBB permeability was increased in both cortex and hippocampus in KKAy mice. Administration of telmisartan attenuated this increase in BBB permeability. Significant decreases in expression of TJ proteins were observed in the brain of KKAy mice, and treatment with telmisartan restored these reduced TJ protein expression. Electron microscopic analysis showed swollen astroglial end-feet in KKAy mice, whereas these changes in BBB ultrastructure were decreased in telmisartan-treated KKAy mice. Interestingly, we observed that co-treatment with GW9662 partially attenuated these effects of telmisartan on cognition and BBB. **Conclusions:** Diabetes enhanced BBB permeability with alterations of TJ proteins, resulting in cognitive impairment. AT1 receptor blockade with PPAR-g activation by telmisartan exerts protective effects on BBB disruption, resulting in improvement of the T2DM-associated cognitive decline.

O2-05-06 MECHANISTIC INVESTIGATION OF NITRATE CHIMERAS FOR ALZHEIMER'S DISEASE

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Background: Alzheimer's Disease is multifactorial and elicits diverse neurological and psychiatric abnormalities, and therefore presents a unique challenge in drug development. The earliest event in Alzheimer's Disease (AD) is synaptic failure, making the disease fundamentally a disorder of impaired cognition and memory. A drug that targets synaptic failure and secondarily prevents neuronal loss would likely prove beneficial to AD patients, and recent efforts showing modification of neuropathology after increased synaptic plasticity suggest these effects would be disease modifying. Nomethiazoles are chimeric compounds that combine the neuroprotective GABA-potentiating activity of the clinically used compound, chlormethiazole (CMZ), and add the ability to activate CREB via NO-mimetic actions. The transcription factor cAMP responsive element-binding protein (CREB) has been shown to be necessary for synaptic plasticity and long-term memory formation, and can be activated through second messenger cascades initiated by NO. In AD, decreased activity of pCREB has been observed in post-mortem AD brains, and molecular network analysis converges on aberrant CREB-mediated gene regulation in the AD hippocampus. **Methods:** Protection from insults in primary neuronal culture, reversal of deficits of long-term potentiation in aged transgenic mice, and long-term in vivo studies with behavioral and biochemical endpoints were used both for efficacy screening and investigation into mechanism of action for all novel compounds. **Results:** In primary neuronal culture models of excitotoxicity and amyloid-induced dysfunction, neuroprotection in some novel compounds correlated to the GABA-potentiating ability of methiazole backbones, while other compounds worked through an unknown mechanism. In electrophysiological investigation of synaptic plasticity in hippocampal slices, reversal of deficits in LTP in 3xTg mice were found to be mediated through an NO/cGMP mechanism. Additionally, in long-term in vivo studies in 3xTg models of Alzheimer's disease, procognitive effect was demonstrated in STPA, a behavioral model of memory, which neatly paralleled increases in levels of pCREB. Finally, these neurorestorative effects in vivo also led to a decrease in levels of Aβ, tau and the neuroinflammatory/apoptotic marker TNF-Îα. **Conclusions:** The above investigation resulted in four optimized novel nomethiazoles slated for pre-IND submission in 2013, with a defined mechanism of action through GABA potentiation and pCREB activation.

ORAL SESSIONS: O2-06 NEUROIMAGING: PREPARING FOR PRESYMPTOMATIC TRIALS—IMAGING OF AT-RISK GROUPS

O2-06-01 DISRUPTED FUNCTIONAL CONNECTIVITY IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE: PRELIMINARY FINDINGS FROM THE DIAN STUDY

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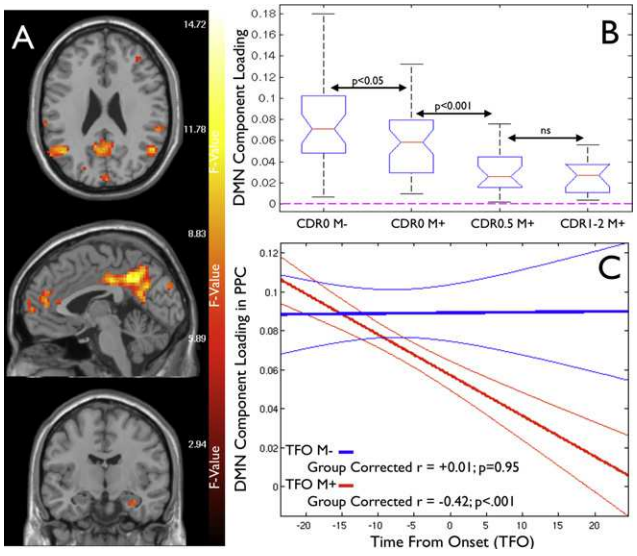
Background: Decreases in the functional connectivity of the default mode network (DMN) have been observed in sporadic, late-onset Alzheimer's Disease (AD) and in amyloid-positive clinically normal

Table 1
Demographic information for DIAN cohort groups.

	CDR0 M-	CDR0 M+	CDR0.5 M+	CDR1-2 M+
N	37	44	24	15
	25 PS1; 5 PS2; 7 APP	35 PS1; 3 PS2; 6 APP	20 PS1; 2 PS2; 2 APP	13 PS1; 0 PS2; 2 APP
Age	38.9 (9.7)	34.6 (8.04)	44.5 (11.7)	49.3 (9.7)
Estimated Time From Age of Onset	-7.7 (12.1)	-12.4 (7.3)	-2.6 (8.6)	2.3 (8.1)

older subjects, suggesting network dysconnection may be an early marker of AD-related synaptic failure. The Dominantly Inherited Alzheimer Network (DIAN) cohort offers a unique opportunity to probe AD related network dysfunction in a much younger cohort, including presymptomatic carriers of presenilin-1 (PS-1), presenilin-2 (PS-2), and amyloid precursor protein (APP) mutations, and to model DMN connectivity as a function of proximity to the observed age of disease onset in these families (time from onset = TFO). **Methods:** A total of 120 subjects, including 83 mutation carriers (PS-1M+ n = 68; PS-2M+ n = 5; APPM+ n = 10) and 37 non-mutation carriers (M-) from the same families, underwent functional MRI during resting state (5.3 min scan). Subjects were then classified into 4 groups based on the Clinical Dementia Rating Scale (CDR) and carrier status (collapsing across mutations; see Table 1 for demographics): CDR0M- (n = 37); CDR0M+ (n = 44); CDR 0.5M+ (n = 24); CDR1-2M+ (n = 15). Functional connectivity MRI (fc-MRI) analyses were conducted with group-independent component analysis using SPM8 and GIFT. **Results:** Whole-brain map ANOVA revealed group differences throughout nodes of the DMN, with the strongest effect in the Precuneus/Posterior Cingulate (PPC; F(3,116) = 14.72, P <0.0001; Fig-A). Post-hoc comparison showed significantly decreased fc-MRI in asymptomatic CDR0M+ compared to CDR0M- in the PPC (P <0.05; Fig-B), right lateral parietal (P <0.01), left lateral temporal (P <0.0001), and medial temporal regions (P <0.001). We observed a negative correlation between DMN connectivity in the PPC and TFO across all mutation carriers (r = -.42; P <0.001), whereas no relationship



A. Whole brain ANOVA across the 4 groups: threshold = P<0.001; F = 5.8. **B**. Box Plots of four groups from the peak voxel in the PPC. **C**. DMN functional connectivity in the PPC (single voxel) by estimated Time from Age of Onset (Unadjusted data shown). Regression model including CDR as covariate revealed significant differences between M- and M+ group sloped (P<0.01).

was observed among non-carriers (r = .01;P = 0.95). The difference in mutation group slopes remained significant when controlling for CDR (difference in slopes P <0.01; Fig-C). **Conclusions:** Impaired connectivity among multiple nodes of the DMN was observed with advancing clinical decline in familial AD, similar to reports in sporadic AD. Presymptomatic mutation carriers demonstrated subtle evidence of DMN dysfunction compared to non-carriers. A strong linear relationship between decreasing DMN integrity and increasing proximity to the expected age of symptom onset suggests that fc-MRI may be useful for tracking disease progression in the preclinical phases of AD.

O2-06-02 FDG METABOLISM IN THE DIAN STUDY OF AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE

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Background: Abnormal brain glucose metabolism has been reported in individuals with genetic risk factors for AD. In order to evaluate the natural history of these changes, participants in the Dominantly Inherited Alzheimer's Network (DIAN) study underwent 18F FDG PET, and we report here an initial assessment of the current baseline FDG-PET DIAN data set. Objective: To evaluate the association of FDG metabolism with age and mutation status in cognitively normal (CDR = 0) and symptomatic (CDR> = 0.5) individuals. **Methods:** FDG data sets from 91 CDR0 (47 carriers/44 non-carriers), 20 CDR0.5 (all carriers) and 13 CDR> = 1 (all carriers) subjects were spatially normalized to an MNI-space template using SPM8, resampled in regions defined by the MNI-based LONI probabilistic atlas, and scaled to cerebellum. Linear regression was used to model the associations of regional average FDG with age, time-to-familial-age-of-onset (TFAO), mutation status and group membership. **Results:** Compared to CDR0 non- carriers and controlling for age, FDG uptake was significantly lower in CDR0.5 subjects globally (P <0.01) and in AD-vulnerable regions