

hippocampal synaptic plasticity and memory and causes progressive neurodegeneration throughout the aging cerebral cortex. Collectively, our findings reveal that FAD mutations can cause complete loss of Presenilin-1 function in vivo, suggesting that clinical PSEN mutations produce FAD through a loss-of-function mechanism. Our results imply that therapeutic strategies aimed at restoring, rather than inhibiting, Presenilin function in the brain may hold promise for effective treatment of AD.

M211. Using Toxoplasma Gondii to Find New Neuroinflammatory Targets for Treating Alzheimer's Disease

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A hyperinflammatory CNS immune response is now recognized to play an important role in the pathophysiology of Alzheimer's disease (AD), suggesting that dampening the immune response may slow the progression of AD. Consistent with this idea, a recent study using the Tg2576 AD mouse model showed that chronic infection with *Toxoplasma gondii*, a ubiquitous and CNS-persistent parasite, led to improved cognition and decreased β -amyloid ($A\beta$) deposition in the setting of elevated levels of the immunosuppressive cytokines Transforming Growth Factor β (TGF β) and interleukin 10. To extend this work, we infected a different AD mouse model (J20) with three different strains of *Toxoplasma* that provoke different CNS inflammatory responses. Using this approach, we are able to show that the reduction in $A\beta$ plaque burden requires a persistent CNS infection and is only associated with one of the *Toxoplasma* strains even though both CNS-persistent strains elicited elevated TGF β levels. On-going work focuses on understanding the strain-specific effects of *Toxoplasma* on CNS pathways implicated in AD, with the goal of identifying the host and parasite factors that lead one strain to be neuroprotective and while the other is not.

M212. Neuroinflammation as a Therapeutic Target in Neurodegenerative Disorders

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Whole molecule erythropoietin induces potent neuroprotection in several CNS disorders. We developed a novel small EPO-derived peptide -JM4- that retains the full neuroprotective capability of the whole molecule without erythropoietic side effects. JM4 acts as a potent immune/inflammatory modulator against both innate and adaptive elements of the immune response and was tested on two well-established chronic neurodegenerative disease models – the P301S tauopathy and the 5XFAD amyloid mouse model.

Chronic therapy was initiated at one month of age (10 μ g subcutaneously x5 days/week). JM4 treated tau animals showed a remarkably longer disease free period as well as longer survival when compared to sham-treated diseased littermates ($p < 0.004$, Kaplan-Meier curve). JM4 treatment of tau mice strikingly reduced upregulation of MHC II expres-

sion in microglia, greatly decreased phosphorylated tau burden, and decreased ventricular enlargement and neuronal cell death. JM4 therapy in the amyloid model showed beneficial effects on Barnes maze deficits and this was accompanied by a striking decrease in beta-amyloid deposition.

JM4 delays progression in mouse models of chronic neurodegenerative disease and indicates neuroinflammation may represent an important therapeutic target in the treatment of Alzheimer's dementia and other neurodegenerative conditions.

M216. Quantitative FDG-PET, Paraclinical and Pathological Correlates in Definite Creutzfeldt-Jakob Disease

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Background: FDG-PET has been proposed to provide evidence of altered cerebral metabolism in CJD. Descriptions of FDG-PET in CJD have been limited by qualitative descriptions or availability of tissue correlates. Here we describe quantitative FDG-PET findings in definite CJD.

Methods: Retrospective review of clinical data, initial MRI, initial FDG-PET and pathological samples from autopsy confirmed CJD patients. Z-scores and 3D stereotactic surface projection maps of brain metabolism on FDG-PET were generated by comparison with age-matched controls.

Results: Eight patients with definite CJD were identified (6 female; 7 sporadic, 1 familial) with median 9.5 weeks of symptoms prior to FDG-PET and median 5.5 days between FDG-PET and MRI. FDG-PET demonstrated areas of hypometabolism of varying degree and extent, correlating with clinical findings and generally concordant with MRI. In two patients with normal initial MRI, areas of FDG-PET hypometabolism were noted. Pathology samples collected from areas with corresponding severe FDG-PET hypometabolism revealed marked spongiosis, astrogliosis and neuronal loss.

Conclusions: Areas of FDG-PET hypometabolism were observed to correlate with clinical findings in patients with definite CJD and in some cases with the pathological changes characteristic of the disease.

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M217. Hemoglobin A1c is Related to Brain Infarcts But Not AD Neuropathology

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Objective: To examine the relationship of hemoglobin A1c to common neuropathological causes of dementia.

Methods: 400 subjects (mean age-at-death=89.8, SD=6.4; 73% female) agreed to autopsy as part of Rush longitudinal cohort studies of aging. HbA1c was measured a mean 2.8 years before death. Postmortem neuropathological data were collected on chronic gross and micro-infarcts, and