In each of the three study cohorts, patients were randomized to CHF5074 (n = 24) or placebo (n = 8). An independent Data & Safety Monitoring Board (DSMB) reviewed blinded safety and tolerability data of each cohort before recommending advancement to the subsequent treatment cohort. Patients were monitored for vital signs, cardiac activity, neuropsychological performance and safety laboratory parameters. Plasma samples were collected throughout the study for measuring drug concentrations. CSF was optionally collected at the end of the treatment period to measure drug levels and potential biomarkers of pharmacodynamic activity (sCD40L, A b 42, tau, phospho-tau, TNF- a).

Results: The 200-mg/day and 400-mg/day cohorts have completed treatment. The 600-mg/day cohort is ongoing. There were no serious treatment-related adverse events. Two patients in the 200-mg/day cohort and 7 in the 400-mg/day cohort did not complete the 12-week treatment. Two patients in the 400-mg/day group dropped out for drug-related adverse events (diarrhea and headache). The DSMB judged that CHF5074 is well tolerated by MCI patients after a 12-week treatment. Two patients in the 400-mg/day dose regimen well tolerated and allowed initiation of the 600 mg/day dose. Preliminary drug level analysis indicated a similar pharmacokinetic profile in MCI patients as compared to healthy volunteers from previous studies with CHF5074 being slowly eliminated from plasma (terminal half-life of about 30 hours). Conclusions: This study indicated that CHF5074 is well tolerated by MCI patients after a 12-week treatment at doses up to at least 400 mg/day. The pharmacokinetics of CHF5074 in MCI patients appears to be similar to that in healthy subjects.

**PI-270 MODIFIED HOSPITAL ELDER LIFE PROGRAM IMPROVES LONG-TERM COGNITIVE OUTCOMES**

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**Background:** Postoperative delirium is common in older patients and can lead to poor outcomes. It is unclear whether delirium prevention strategies such as the modified Hospital Elder Life Program (HELP) affect long-term cognitive outcomes. Methods: A pre-and postintervention clinical trial. Consecutive patients (N = 179) were enrolled if they had undergone common elective abdominal surgical procedures such as gastrectomy, cholecystectomy, and Whipple surgery. A modified HELP intervention, consisting of early mobilization, nutritional assistance, and cognitive stimulation activities implemented by a trained nurse, was introduced on a surgical ward in May 2008. Patients enrolled before May 2008 received usual care and served as controls (n = 77). Those enrolled after the modified HELP intervention comprised the experimental group (n = 102). Changes in cognitive function measured at admission, discharge, and 3 months afterward were the primary endpoints. Results: Patients in the HELP group did not present delirium while 16.7% of patients in control met the criteria of delirium by hospital discharge. At 3 months afterward, improvement in global cognitive status (measured by the mini-mental state examination) and depressive symptoms (measured by the geriatric depression scale) persisted. Conclusions: This in-hospital modified HELP intervention not only effectively reduced older surgical patients’ delirium rates by hospital discharge but also improve the 3 months cognitive outcomes afterward.

**PI-271 INDUCING AUTOPHAGY BY RAPAMYCIN BEFORE, BUT NOT AFTER, THE FORMATION OF PLAQUES AND TANGLES AMELIORATES COGNITIVE DEFICITS**

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**Background:** Autophagy, one of the major intracellular proteolytic systems, plays a key role in several age-dependent neurodegenerative disorders characterized by protein accumulation, including Alzheimer’s disease (AD). Indeed, the well-documented decrease in autophagy function with age may contribute to the accumulation of proteins in the brain. Furthermore, previous studies have shown that inducing autophagy ameliorates early cognitive deficits associated with the build-up of soluble amyloid-β (Aβ). However, the effects of inducing autophagy on plaques and tangles are yet to be determined. While soluble Aβ and tau represent toxic species in AD pathogenesis, there is well documented evidence that plaques and tangles also are detrimental to normal brain function. Thus, it is critical to assess the effects of inducing autophagy in an animal model with established plaques and tangles. Methods: We use the 3xTg-AD, a well-established animal model of AD that develops plaques and tangles, to determine the effects of pharmacologically inducing autophagy on plaques, tangles and cognitive decline. Results: Here we show that rapamycin, when given prophylactically to 2-month-old 3xTg-AD mice throughout their life, induces autophagy and significantly reduces plaques, tangles and cognitive deficits. In contrast, inducing autophagy in 15-month-old 3xTg-AD mice, which have established plaques and tangles, has no effects on AD-like pathology and cognitive deficits. Conclusions: Our results indicate that autophagy induction via rapamycin may represent a valid therapeutic strategy in AD when administered early in the disease progression.

**PI-272 A REGULATORY IMMUNE RESPONSE AFTER DNA VACCINATION AGAINST Aβ42**

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**Background:** All immunotherapy for Alzheimer’s Disease (AD) harbors the danger of an inflammatory autoimmune response, and a clinical trial in which AD patients received Aβ42 peptide immunizations was stopped when participants developed encephalitis due to an inflammatory Th1 response targeting Aβ in brain. We have used DNA Aβ42 trimer immunizations in mice and found a Th2-type antibody response indicative of a non-inflammatory immune response and the disappearance of Aβ42 specific T cells. This low level of T cell proliferation in DNA Aβ42 trimer immunized mice might be due to regulatory T cells (Tregs). Methods: CD4+CD25+ cells (Tregs) were depleted by injection of a CD25 antibody (clone PC61) in half of the mice, which received DNA Aβ42 trimer immunizations. Humoral and cellular immune responses were compared by ELISA, ELISPOT, and CFSE proliferation. Results: Depletion of CD25 positive cells did lead to increased antibody titers: 1:700 in CD25 depleted mice compared to 1:350 in DNA Aβ42 trimer immunized mice after 4 immunizations. In both groups, the IgG1 antibody isotype indicated a Th2 response. After one immunization we found increased CD4 proliferation index in the CD25 depleted mice: 1.7 ± 0.19 compared to 1.1 ± 0.06 in DNA vaccinated mice (P = 0.0433). After four immunizations the T cell response in the DNA immunized mice disappeared while in CD25 depleted mice an increased but rather unspecific proliferation was found. Parallel ELISPOT analyses showed no IFNγ, IL-17, or IL-5 secretion in the DNA immunized mice but increased levels for the regulatory cytokines IL-10 and TGFβ1 after Aβ42 peptide re-stimulation (P = 0.01 and 0.004, respectively). IL-10 was likely produced by T cells as the re-stimulation assays showed increased IL-10 levels for T cell peptides Aβ22-27, 9-27, 10-26, 12-28, but not Aβ1-15 which is a B cell peptide. Conclusions: Depletion of CD25 positive T cells increased the specific antibody response in our model. Data obtained thus far are consistent with the disappearing effector T cell response in DNA Aβ42 trimer immunized mice (no proliferation, no IFNγ secretion) and the proposed regulatory T cell response (IL-10 secretion after DNA Aβ42 immunization) demonstrating safety for this immunization approach as potential AD therapy.

**PI-273 CHANGES IN SLEEP/WAKE PARAMETERS IN MALE PD-APP TRANSGENIC MICE**

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**Background:** Alzheimer’s disease (AD) is the most common form of dementia diagnosed in the elderly with sleep disturbances being common in