**TRANSLATIONAL THERAPEUTIC DEVELOPMENT OF ALLOPREGNANOLONE TO RESTORE COGNITIVE FUNCTION IN ADULT MALE AND FEMALE TRIPLE TRANSGENIC ALZHEIMER’S MICE**

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**Introduction:** Allopregnanolone (APα) stimulates proliferation of neural progenitor cells derived from rodent hippocampus and human cerebral cortex in vitro (Wang et al., 2005) and in 3-month old triple transgenic Alzheimer’s disease (3xTgAD) male mice in vivo (Wang et al., 2010).

**Aims:** In this study we first analyzed the age-dependent efficacy of APα (SC) on neurogenesis and cognitive function in 6-, 9-, 12-, and 15-month old 3xTgAD mice and compared that to age-matched nonTg male mice. We next tested formulation-dependent efficacy of APα on neurogenesis and cognitive function when APα was administered subcutaneously (SC; 10mg/kg), transdermally (TD; 10mg/kg), or intranasally (IN; 3mg/kg) followed 1hr later by BrdU (100mg/kg).

**Methods:** Both unbiased stereology and FACS were used to quantify BrdU positive cells in the hippocampus. Learning and memory was assessed by trace eyeblink conditioning. Level of Alzheimer pathology was determined by immunocytochemical localization, Western blots, and beta-amyloid ELISA.

**Results:** APα significantly enhanced hippocampal neurogenesis and cognitive performance in 3xTgAD mice in an age-dependent manner. Chronic exposure to APα significantly reduced beta-amyloid accumulation and pTau generation. IN formulation was maximally efficacious at 3-fold less APα compared with SC and TD routes. Preclinical IND-enabling pharmacokinetic, pharmacodynamic and toxicology analyses are in progress.

**Conclusions:** Results of current analyses indicate promising therapeutic efficacy of APα to promote regenerative capacity within the hippocampus, to reverse associative learning and memory deficits and to reduce AD pathology in male brain. Studies are underway to determine efficacy in female AD mouse brain and to develop intranasal formulation of APα.