**Phenotyping Age-Dependent Changes in the 5xFAD Alzheimer’s Disease Model Mice**

**Charles R. Yang, Ruibin Feng, Ling Yang, Shujuan Jiang, Na Liu, Li Yan, Yi Liu, Lizhao Wang, Cecilia S.Yang, and KeWei Wang**

ChemPartner Co Ltd., Shanghai, and 1Peking University School of Pharmaceutical Sciences, China

**Program #: LB556**

**Abstract (11970)**

5xFAD transgenic (Tg) mouse express 5 human familial Alzheimer’s Disease (AD) gene mutations --- Amyloid Precursor Protein mutations from the Swedish, Florida and London families, along with 2 mutations in presenilin-1. Their early onset brain pathology, accelerated Ab42 amyloid deposition, age-dependent neurodegeneration and cognitive decline, make these mice an attractive translatable AD model.

We used behavioral, biochemical and electrophysiological analyses to track age-dependent changes in 5xFAD mice, compared with their age-matched wild-type mice. With sensitive Nestin::Cre, 2-month old 5xFAD mice showed a significant increase of Aβ42, Aβ40 in the core striatal area. Their hippocampal ELISA Ab42 and Ab40 levels increased progressively from 2.34 months. Under confocal microscopy, the secondary and tertiary dendritic spines counts in Golgi-stained 5xFAD transgenic pyramidal neurons showed a significant loss. Hippocampal spine electrophysiology using the multielectrode MED64 system is used to assess synaptic plasticity, i.e. long-term potentiation. Using the t-TBS, duration-namely platform, we observed that there was a significant dark phase hypoactivity and no directional circling during the light phase activity. Using the DSI telemetry system, we discovered that there was a significant dark phase hypoactivity and no directional circling during the light phase activity.

**INTRODUCTION**

The 5xFAD transgenic mice express 5 human familial Alzheimer’s Disease (AD) gene mutations --- Amyloid Precursor Protein mutations from the Swedish, Florida and London families, along with 2 mutations in presenilin-1. Their early onset brain pathology, accelerated Ab42 amyloid deposition, age-dependent neurodegeneration and cognitive decline, make these mice an attractive translatable AD model.

**METHODS**

1) Biomarkers Ab42 and Ab40 were measured by ELISA and Western Blot.
2) Dendritic Spines after Golgi stained (FD Neurotechnologies) were analyzed under confocal microscopy and spine density of secondary and tertiary dendritic branches were quantified using ImageProPlus software.
3) Hippocampal C/A1 LTP was induced and recorded using MED64 multielectrode planar chip placed under perfused hippocampus slices that were specially prepared using N-methyl-D-glucamine NREM EEG recording solution (15min).
4) Sleepwake EEG recordings were made using DSI telemetry system and EEG data measured using SleepSign software.
5) Behavioral data (locomotion, circling, rearing, climbing, grooming) were recorded using the Laboras vibration-sensitive platforms.
6) Nesting behavior were recorded by video and scored and analyzed offline.

**RESULTS**

**1. Hippocampal Ab42 and Ab40 Changes with Age in 5xFAD Mice**

(Hippocampal Ab42 and Ab40 levels were below 5 ng/mL in wild-type mice from 2-6 months of age)

**Female 5xFAD mice showed a significantly greater accumulation of Ab40, but not Ab42, at a younger age than in the males.**

**2. Dendritic Spine Density in Prefrontal and Hippocampal Neurons**

Significant reduction of spine density on the secondary and tertiary dendritic branches of: A) apical dendrites of medial prefrontal Layer II/III pyramidal neurons, B) hippocampal CA pyramidal neurons and Dentate Gyrus granule cells in 5xFAD mice both at 4-month and 9-month old.

**3. Hippocampal LTP – in 10 month old 5xFAD vs WT Mice**

In 10 month old 5xFAD mice, the post-TBS synaptic response Schaffer Collateral CA1 decayed with time while the WT showed a full sustained LTP.

**4. Wake/Sleep EEG Analyses in 9 months old 5xFAD Mice**

In 9 month old 5xFAD mice, there was increased wakefulness and corresponding reduction of REM and NREM sleep during the dark (active) phase.

**5. Nest Building, Locomotor & Circling Behaviors in 5xFAD Mice**

Nesting behavior, an analogue of ‘daily living activities’, was significantly disrupted in 11 month old 5xFAD mice. At dark phase, there was also a significant increase in spontaneous locomotor activities and bi-directional circling behavior.

**Summary and Conclusion**

The onset of age-dependent changes in the biomarkers and phenotypes in 5 X FAD mice enable us to initiate drug testing at specific ages that pairs with specific meaningful readouts for detection of pharmacological effects.