PRECLINICAL DEVELOPMENT OF NEW TETRAHYDROFURANNES DERIVATIVES AS NEUROPROTECTANTS TARGETING THE SIGMA-1 CHAPERONE PROTEIN IN ALZHEIMER’S DISEASE

T. Maurice¹, V. Villard¹,², J. Meunier¹,², E. Keller¹, V. Lahmy¹,², A. Vamvakides³

¹University of Montpellier 2, ²Amylgen, Montpellier, France, ³Anavex Life Sciences, Pallini, Greece

Introduction: The sigma-1 receptor (S1R) is an intracellular protein expressed in the brain and localized on endoplasmic reticulum (ER), mitochondria and plasma membranes. The S1R was identified as a molecular chaperone of the mitochondrion-associated ER membrane modulating IP3 receptor-dependent calcium release, interacting with ER sensors and intracellular kinase-dependent pathways and contributing to lipid rafts formation on the plasma membrane. Moreover, S1R ligands are neuroprotective drugs and such action may potentiate the activity of cholinomimetics.

Aims: We develop mixed muscarinic/S1R ligands and analyze their neuroprotective activity in Alzheimer’s disease (AD) models.

Methods: Most data were obtained using central injection of oligomeric Aβ fragments (oAβ) in the rodent brain, a validated nontransgenic AD model. oAβ induces ER stress, oxidative stress, neuroinflammation, mitochondrial damage, cell loss, memory deficits, increased APP processing and Tau hyperphosphorylation.

Results: ANAVEX1-41 and ANAVEX2-73 prevented cell loss, astrocytic reaction, oxidative stress, induction of proapoptotic caspases, in the hippocampus and cortex, and the learning deficits. Notably, the ligands protected against oAβ-induced ER stress, in coherence with the chaperone role of S1R. Molecular analyses showed that regulations of IP3 receptors and SerCa pumps were involved in Aβ toxicity and ANAVEX effects, suggesting a direct role on calcium homeostasis. Finally, the compounds showed a clear synergistic efficacy between their cholinergic and S1R activities, being active at 10-100 µg/kg doses.

Conclusions: These studies identified new compounds acting as protective agents targeting ER chaperones in AD and pointed out the interest in speeding up S1R drugs at the clinical level.