

## **D-chiro-inositol prevents memory deficits in the 3xTg mouse model of Alzheimer's disease in a sex-dependent manner.**

*Beatriz Pacheco-Sánchez<sup>1,2,3</sup>, Juan Antonio Navarro<sup>1,2,4</sup>, Rubén Tovar<sup>4</sup>, Fernando Rodríguez de Fonseca<sup>1,2\*</sup>, Patricia Rivera<sup>1,2\*</sup>*

*1 Instituto de investigación Biomédica de Málaga-IBIMA, 29010 Málaga, Spain*

*2 UGC Salud Mental, Hospital Regional Universitario de Málaga, 29010 Málaga, Spain*

*3 Universidad de Málaga, Andalucía Tech, Facultad de Ciencias, Campus de Teatinos s/n, 29071 Málaga, Spain*

*4 Universidad de Málaga, Andalucía Tech, Facultad de Medicina, Campus de Teatinos s/n, 29071 Málaga, Spain*

Alzheimer's disease (AD) is recognized as an age-related neurodegenerative disorder, characterized by the aggregation and deposition of amyloid- $\beta$  ( $A\beta$ ) in plaques and neurofibrillary tangles (NFTs) composed of aggregates of hyperphosphorylated tau, a microtubule-associated protein. Sporadic AD, the most prevalent form of the disease, has been proposed to be associated with alterations on insulin signaling. Insulin regulates a series of cognitive processes, such as learning and memory formation and emerging data demonstrate pivotal roles for brain insulin resistance and insulin deficiency as mediators of neurodegeneration, particularly in AD.

The present study describes the effect of oral dietary administration of D-Chiro-inositol (DCI), an inositol used against insulin resistance, on the occurrence of the cognitive impairment of 3xTg-AD mice. This so called "triple-transgenic mice" model mimics many critical aspects of AD neuropathology. To this end, we analysed the effects of daily oral administration DCI 200 mg/Kg/day in male and female 3xTg and WT mice of 9 and 3 months of age. In addition to the evaluation of memory on the Novel Object Recognition, both the locomotion and time in the centre zone of an open field (OF), and the locomotion and anxiety-like behaviour in the elevated plus maze (EPM) test, were monitored.

Our results showed that the exploration time of the new object was remarkably higher in the male 3xTg-DCI group when compared to those obtained from the 3xTg-vehicle and WT-vehicle groups at a middle and older age (3 and 9 months). When the center exploration time was analyzed in OPF test, three-way ANOVA showed an effect of the genotype in middle-aged animals. In the EPM test, only 9 months old 3xTg-DCI females were more prone to explore the open-arm, suggesting DCI decreases anxiety levels related to AD. In conclusion, our study suggest that DCI prevents and improves in a sex-dependent manner, the cognitive impairment associated to AD.