

## **Context-dependent modulation of brain senescence by senolytics in mouse models of Alzheimer's disease and accelerated ageing**

Our study investigates the role of cellular senescence in brain ageing and Alzheimer's disease and evaluates senolytic therapeutic strategies. We analysed the impact of a senolytic treatment in two complementary mouse models: 5xFAD mice, representing pathological amyloid-driven senescence, and SAMP8 mice, modelling physiological ageing-associated senescence. Five-month-old mice received a chronic intermittent treatment for two months, and cognitive performance was assessed through behavioural tests of anxiety and recognition memory. Senescence-associated  $\beta$ -galactosidase, amyloid burden, lysosomal content, and glial phenotypes were analysed using immunohistochemistry and colorimetric imaging to characterise senescence markers and glial cell heterogeneity, as well as through ELISAs and RNAseq.

The senolytic treatment improved cognitive performance in both models, ameliorating both anxiety phenotypes and memory. In 5xFAD mice, treatment reduced amyloid plaque burden, lysosomal accumulation, and modulated microglial response in specific brain regions. In SAMP8 mice, it altered microglial and oligodendroglial phenotypes, indicating context-dependent effects on neuroinflammation. Our findings highlight senescence heterogeneity and support the therapeutic potential of senolytic strategies to mitigate cognitive decline. The use, in parallel, of two distinct brain senescence paradigms strengthens the translational potential of our findings.

### **Brief summary of the CV**



PhD graduate in Pharmacology from the University of the Basque Country (UPV/EHU, Bilbao, Spain), he completed his doctoral training under the supervision of Dr. Rafael Rodríguez Puertas. Research focused on neurolipids, particularly the endocannabinoid system, in the context of dementia and cognitive impairment, particularly Alzheimer's disease. During this period, he also completed a four-month international research stay at the Institut de Chimie & Biologie des Membranes & des Nano-objets (CBMN, Bordeaux, France), investigating how the membrane lipidome modulates ligand binding properties and activity of cannabinoid receptors. As a postdoctoral researcher, he is working under the supervision of Dr. Ana Guerrero in the Cell Biology Department at the University of Barcelona, affiliated with the Institute of Neurosciences (UBNeuro, María de Maeztu unit of excellence), a leading international centre in neuroscience research. In this setting, he is investigating the contribution of cellular senescence to the pathophysiology of Alzheimer's disease, pursuing neurodegeneration research from a complementary perspective.

As a second-year postdoc, his contributions have resulted in 10 research articles, including 4 first-author papers from his doctoral research and different successful collaborative works, including publications in prestigious and high-impact journals such as *Translational Neurodegeneration* and the *British Journal of Pharmacology*.