Brain and Spine Institute (ICM) Imagine Institute - Paris, France

Recent studies at the Brain and Spine Institute, Imagine Institute have focused on a drug (Masitinib) used for Mastocytosis, a disease associated with mast cell accumulation. Some Mastocytosis patients experience cognitive dysfunctions that mimic symptoms of Alzheimer's disease. A study has demonstrated that Masitinib improved symptoms of Mastocytosis — including those associated with neurological and psychiatric symptoms. In addition, a clinical study demonstrated that Masitinib slows down cognitive decline in Alzheimer's patients.

Project:

This project focuses on the role of mast cells and enzymes they produce in the development of Alzheimer's disease. A better understanding of the mechanisms of action underlying Masitinib's effect might allow us to define a strategy to improve Alzheimer disease. We investigated:

1. Whether the structure of Amyloid proteins is altered and if the toxic proteins are decreased after Masitinib treatment.
2. Whether Masitinib may improve synapse loss possibly by reducing Tau phosphorylation.
3. Whether a recent theory, suggesting that Alzheimer's might be due to "seeding spreading lesions" like prions diseases, is involved. Mast cells may help to propagate these lesions, and if true one can hypothesize that Masitinib may be beneficial by decreasing lesions dissemination.

Preliminary results:

A daily dose of Masitinib (75mg/kg) versus placebo was orally administered during two months in male mice modeling Alzheimer's disease as well as their control wild-type littermates. Cognition was assessed using a paradigm measuring learning and memory using a Morris water maze. Brain pathology was characterized by histological and biochemical measurements. Complementary analyses were performed using mice with a genetically induced depletion in mast cells.

While mice displayed cognitive deficits in the water maze, chronic treatment with Masitinib restored normal learning performances. Masitinib treatment had neither significant effect on Aß plaque loads nor on markers of neuroinflammation. However, Masitinib treatment reduced the number of cerebral mast cells and lead to recovery of synaptic integrity in the mice. Genetic depletion of mast cells in mice similarly rescued synaptic impairments, suggesting that the pro-cognitive effects of Masitinib were associated with mast cell reduction.

These results underline a preclinical efficacy of Masitinib in cognitively-impaired transgenic mice modeling Alzheimer's disease. The mechanism of action of Masitinib does not rely on anti-amyloid or anti-inflammatory effects but appears to be associated with a synapto-protective action in relation with mast cells inhibition.