# BRAIN AND SPINE INSTITUTE (ICM) IMAGINE INSTITUTE - PARIS, FRANCE

A grant was given to The Brain and Spine Imaging Institute to carry out research by Benoit Delatour, Marc Dhenain, Patrice Dubreuil, and Olivier Hermine to investigate whether changing the structure of amyloid proteins (the proteins that can form into plaques, thought to be a major cause of Alzheimer's disease) causes protein aggregates to be decreased. In this hypothesis, Masitinib was tested for its ability to block the formation of these plaques.

Masitinib is a drug-like compound which inhibits a type of signaling protein called a kinase. Kinases are important regulators of cellular communication. Initially, Masitinib has been shown to specifically block the activity of three such kinases: c-Kit, Lyn and Fyn. These are important for a type of cells called mast cells. Signaling of mast cells play a crucial role for the immune system and the brain. Masitinib has also been shown to target another kinase called MCSFR-1 that plays a critical role in microglia modulation. Microglia is a type of cell that has a scavenger function in the brain and is believed to be highly relevant for Alzheimer's. In summary, Masitinib could act on four different targets that involve dysfunctional mechanisms: modulation of microglia, protection of synapses, inhibition of Tau protein, and control of mast cell activity.

In one experiment (the Morris Water Maze test), we use a mouse model of Alzheimer's disease and compare it to normal mice. The test measures the ability of mice to memorize the location of a small submerged platform in a pool of milky water. After several attempts, normal mice quickly memorize the location of the platform, while mice with Alzheimer's are significantly slower. Masitinib significantly improved the cognitive ability of the Alzheimer's mice. Similarly, Masitinib could protect against synaptic loss (the active zones between neurons which are crucial for neuronal communication) by reducing mast cell activity.

In a novel clinical trial, three varying doses of Masitinib were tested on Alzheimer's patients: 3 mg/kg/day, 4.5 mg/kg/day and titration from 4.5 to 6 mg/kg/day. Early on, the study arm involving the lower dose was stopped. The study enrolled 718 patients from 118 sites in 21 countries. The latest results reported correspond to 24 weeks of treatment. Significant effects were observed in the areas of cognitive function, daily activity, as well as some numerical advantages (not statistically significant) of Masitinib on other tests. From those encouraging studies, it is possible to conclude that 4.5 mg/kg/day represents the effective dose for AD.