Our lab is devoted to the study of ethiopathogenic mechanisms involved in brain aging and associated pathologies such as Alzheimer’s type dementia (ATD) and prion diseases. We therefore develop projects using both in vitro and in vivo approaches. Different mammal models are investigated: mice, rats, and primates (grey mouse lemur or microcebe, Microcebus murinus).

Our first aim is dedicated to the understanding of structural and physico-chemical modifications of proteins leading to the formation of fibrillar aggregates. For that purpose, we focus on two proteins: lithostathine and the prion protein (PrP). Both of them tend to precipitate as fibrils in ATD or prion diseases. We study the mechanisms leading to the formation of fibrils or oligomeric, i.e. pre-fibrillar, structures using biophysical approaches. We initiate a program for identifying ligands able to disaggregate these fibrils. Compounds are screened by in silico docking of a virtual library, and then tested for their ability to prevent fibril formation. With regard to PrP, we check whether these ligands can inhibit or delay the formation of PrPres infectivity (the pathological form of the normal prion PrPc) in vitro with cellular models, and in vivo with mice.

Our second objective is to study the transmissibility of prion agents in microcebes and in mice in relation to physico-chemical treatments of PrP (high pressure, chemical agents, in vitro formation of fibrils, etc…). In addition, we develop gene therapy studies in mice with "PrP dominant negatives".

Our third objective is to explore the modifications of brain gene expression in microcebes during aging or in the presence of ATD lesions via a transcriptomic approach. Our purpose is to evidence new genetic pathways involved in healthy aging or in AD that could provide future therapeutic issues. Finally, we aim at determining whether new therapeutic strategies linked to the potentiation of endogenous neuroprotection systems could be proposed. The neurotrophic factor BDNF, interacting with specific receptors TrkB in the brain, and the intraneuronal neuromodulatory sigma1 protein, are promising candidates. We therefore analyze their modification and pharmacological interest in non-transgenic models of ATD. We develop selective in vivo ligands able to induce short-term neuromodulatory effects and long-term neuroprotective effects.

This project is an integrated project from the molecule to the animal. It should help in the identification of molecular and physicochemical mechanisms involved in dementia. In addition, it should allow the development of therapeutic approaches for these devastating diseases.
**Keys publications**


Silhol M, Bonnichon V., Rage F and Tapia-Arancibia L. Age-related changes in Brain-derived neurotrophic factor and tyrosine kinase receptor isoforms in the hippocampus and hypothalamus in male rats. Neuroscience, 2005, 132: 613-624.


**Key words**

Protein Folding, Biophysics, Primate (Microcebus Murinus), Physiopathology