Project title: Establishing an Innovative methodology for Exosome Isolation in Alzheimer's Disease Research

Summary: Alzheimer's disease (AD) is a neurodegenerative disease and the first cause of human dementia. Unfortunately, the finding of an effective treatment to slow down the cognitive decline in AD patients remains elusive. In the last years, a revolutionary method has emerged that allows to study the alterations occurring in the brain of alive AD patients through a blood sample. This method consists of the isolation and characterization of blood-derived small vesicles, named **exosomes**, originated in almost all kind of cells including neurons, and secreted to the circulatory system. Neuronal exosomes are isolated from other exosomes originated in non-neuronal tissues by means of an antibody against the neuron-specific protein **L1CAM**. However, in the last years, it was found that L1CAM is also expressed in non-neural tissues and certain types of cancer, casting doubts on the purity of the exosomes isolated by this method. Thus, it is crucial to find out new exosomal proteins that show a stronger and a more specific neuronal expression, for the isolation and study of neuronal exosomes derived from the blood of AD patients, in order to advance in our understanding of this devastating disorder.

The present proposal aims to compare the efficiency of three different methods for the isolation of exosomes based on three different antibodies against neuronal proteins: an antibody against L1CAM (standard protocol), an antibody against the neuronal membrane glycoprotein M6alpha (GPM6A) and an antibody against the brain-specific receptor GRIN2A. These three methods will be compared in terms of their capacity to isolate exosomes from the media of a **neuroblastoma cell line expressing a protein related to AD (SH-SY5Y-APP)**. Then exosomes will be analyzed and **characterized by NTA**, by **flow cytometry**, **western blot** and **ELISA**. The presence of proteins related to AD in the isolated exosomes will be assessed.

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Supervisor: Dr. Martí Lecina, Dr. Francesc Guix
Laboratory: GEMAT, Department of Bioengineering
Contact email: marti.lecina@iqs.url.edu; Francesc.guix@iqs.url.edu