LAB BACKGROUND

Our laboratory at the Centro Biología Molecular Severo Ochoa (http://www.cbm.uam.es/dledesma) is interested in understanding the role of lipids in the physiology and pathology of brain cells. We focus on the analysis of sphingolipids and cholesterol using mice in which proteins related to the metabolism and transport of these lipids have been genetically altered. These mice mimic fatal lysosomal storage disorders, such as Niemann pick types A and C, which lead to neurodegeneration, cognitive and psychiatric problems. In addition, we are currently implementing the use of human pluripotent cells (iPSCs) with lipid alterations. Research in the group has unveiled relevant roles of sphingomyelin and cholesterol in synaptic plasticity, autophagy, calcium homeostasis, or the establishment of axonal polarity in neurons, as well as in microglia activation and oligodendrocyte differentiation. We preclinically assess pharmacological and genetic therapies to prevent/revert the consequences of lipid alterations. The translational side of our research allows the generation of patents, the collaboration with pharma companies, the contact with patient associations and the participation in clinical trials.

SELECTED PUBLICATIONS (in the last 5 years)

Gaudioso A, Jiang X, Casas J, Schuchman EH, Ledesma MD. Sphingomyelin 16:0 is a therapeutic target for neuronal death in acid sphingomyelinase deficiency. **Cell Death Dis.** (2023) 14:248.

A. Gaudioso, T.P. Silva TP, M.D. Ledesma. Models to study basic and applied aspects of lysosomal storage disorders. **Adv Drug Deliv Rev** (2022) 190:114532.

A.Bartoll, A. Toledano-Zaragoza, J. Casas, M. Guzmán, E.H. Schuchman, M.D. Ledesma**.** Inhibition of fatty acid amide hydrolase prevents pathology in neurovisceral acid sphingomyelinase deficiency by rescuing defective endocannabinoid signaling. **EMBO Mol Med**. (2020) 12: e11776.

D.N. Mitroi, G. Pereyra-Gómez, B. Soto-Huelin, F. Senovilla, T. Kobayashi, J.A. Esteban, M.D. Ledesma. NPC1 enables cholesterol mobilization during long-term potentiation that can be restored in Niemann-Pick disease type C by CYP46A1 activation. **EMBO Rep.** (2019) 20: e48143.

L.Samaranch, A. Pérez-Cañamás, B. Soto-Huelin, V. Sudhakar, J. Jourado-Arjona, P. Hadaczek, J. Ávila, J.R. Bringas, J. Casas, H. Chen, X.He, E.H. Schuchman, S.H. Cheng, J. Forsayeth, K.S. Bankiewicz, M.D. Ledesma. Adeno-associated viral vector serotype 9-based gene therapy for Niemann Pick disease type A. **Science Translational Medicine** (2019) 11: eaat3738.

E. Gabandé-Rodríguez, A. Pérez-Cañamás, B. Soto-Huelin, D.N. Mitroi, S. Sánchez-Redondo, E. Martínez-Sáez, C. Venero, H. Peinado, M.D. Ledesma. Lipid-induced lysosomal damage after demyelination corrupts microglia protective function in lysosomal storage disorders. (2019) **EMBO J.** 38: e99553.

TRAINING PROGRAM

The training program planned for the PIF fellow will include joining the PhD program on Molecular Biosciences of the Autonomous University of Madrid. PhD students are always supervised in our laboratory by senior researchers (including weekly meetings with the PI) and participate (as attendants and speakers) in the laboratory meetings and department seminars. They also assist to the seminar series of invited scientists organized each year at the CBM. The students benefit from the multidisciplinary nature of the institute, which has different programs covering fields such as gene expression, development, virology and microbiology, immunology, cell biology and neurobiology with a specific unit dedicated to Molecular Neuropathology. The project proposed will allow the student to get familiar with a broad range of disciplines and techniques including lipid and protein biochemistry, cell and molecular biology, primary cultures of mouse neurons and oligodendrocytes and human iPSC differentiation, confocal and electron microscopy, electrophysiology and mouse behaviour. The collaboration with different laboratories will allow short stays to learn specific methodology. Moreover, the PhD student will assist to the annual meetings of NPD family associations (at least in Spain and US) to which the PI is regularly invited to present results. This will allow him/her to get in contact with patients,

clinicians and pharma. The student will also present his/her work in scientific meetings such as those of the Spanish Societies for Neuroscience (SENC) and the Federation of European Neuroscience Societies (FENS).