Carlos Dotti Laboratory: past accomplishments and future plans.

Past achievements (2018-2022)
Our interest lies in establishing the mechanisms responsible for the balance between synaptic plasticity and neuronal survival during aging and what conditions -and how- break this balance, leading to pathological cognitive disorders. In relation to achievements of the immediate past, I believe that the most remarkable aspect that we have contributed to has been the demonstration that age affects the lipid composition of the neuronal plasma membrane, leading, due to the allosteric function of lipids, to different receptors undergoing a process of tonic activation, resulting in their desensitization. We demonstrated that the desensitization occurs both for receptors of trophic factors, BDNF, Insulin, and also for the excitatory neurotransmitter glutamate. We also showed that although desensitization to these ligands has a "loss-of-function" effect on synaptic plasticity, both in biochemical, gene expression and functional terms, it produces a survival "gain-of-function" effect, making us propose that the loss of function that we experience with age is the payment that our neurons make to stay alive. In addition to the study of the balance between plasticity and survival in the normal old, we have advanced in the knowledge of the mechanisms that cause the balance to be broken and pathological cognitive changes to occur. We have investigated this using a model of type 2 diabetes mellitus (T2DM) and showed that for T2DM to produce significant AD-like cognitive changes, it is necessary for the affected individual to carry a subclinical neurological pathology (*Carús-Cadavieco, Berenguer et al., 2022*).

PhD Thesis defended (2018-2022)
Silvia de Vidania Ballester: 30-04-2019
Álvaro Casadomé Perales: 18-11-2022

Institutional responsibilities and other relevant merits (2018-2022)
Chair of the Physiological and Pathological Programme

Future plans (for the next 5 years 2023-2027)
For the future we have a series of questions that we believe are important to answer:
i) how does the shift from plasticity to survival occur at the molecular level ?,
ii) what relevance do defects in this shift have in the appearance of degenerative diseases? (i.e. could certain cases of neurodegenerative diseases be the consequence of a loss of survival function rather than a gain of toxicity)
iii) how relevant are the survival/plasticity shift mouse data to the human situation?
The different questions will require studies of a different nature. Thus, for the first, we plan to carry out biochemical and transcriptomic/epigenomics experiments in in vivo and ex-vivo/in vitro models.
For the second we are focusing on the model of type 2 diabetes mellitus and induction of cognitive disorders.
For the third objective we will establish models of human brain organoids and human neuron/mouse brain chimeras.