INPhINIT

"la Caixa" Fellowship Programme

IBEC

Institute for Bioengineering of Catalonia

EXCELENCIA SEVERO OCHOA

Many people form part of history.
Only a few manage to change it.

IBEC participates in "la Caixa" Fellowship Programme with a set of stimulating PhD projects and excellent research groups to host the fellows

Nanoprobes and nanoswitches group

Group leader: Pau Gorostiza

NANOPROSTHETICS: Molecular prosthetics for vision restoration based on targeted covalent photoswitches

Light-regulated drugs allow remotely photoswitching biological activity and enable plausible therapies based on small molecules. However, only freely diffusible photochromic ligands have been shown to work directly in endogenous receptors, and methods for covalent attachment depend upon genetic manipulation. We have developed a chemical strategy to covalently conjugate and photoswitch the activity of endogenous proteins, and we have demonstrated its application to GluK1 kainate receptors. The approach is based on photoswitchable ligands containing a short-lived highly reactive anchoring group that is targeted at the protein of interest by ligand affinity. These targeted covalent photoswitches (TCPs) constitute a new class of light-regulated drugs and act as molecular nanoprostheses that photocontrol the activity of GluK1-expressing neurons, and restore photoresponses in degenerated retina. In this proposal we will exploit the modularity of TCPs by optimizing their pharmacology (target receptors), reactivity and optical properties. These adjustments will be aimed at obtaining efficient compounds to manipulate neuronal activity for fundamental and therapeutic purposes. In the first case, simultaneous photocontrol of synaptic receptors and fluorescence imaging of neuronal activity in tadpoles (calcium and voltage imaging) will allow studying synaptic plasticity from the single dendritic spine level up to the whole brain. Regarding therapeutic applications, the compounds developed in this proposal will be used to impart light sensitivity to remaining inner retinal neurons in animal models of degenerated retina. As small molecules, TCPs can be subject to optimization in well-established pharmacological and safety assays, and can be tested in non-genetic model organisms of the disease. Thus they have the potential to become preclinical candidate drugs to be transferred to the pharmaceutical industry. The development, optimization and applications of TCPs in several animal models offers outstanding opportunities as a fundamental tool to photomanipulate synaptic plasticity in vivo, as well as a small-molecule therapeutic approach to vision restoration.

Job position description

The training plan for the candidate covers the three years of the research period of the doctoral program. The title of the project of thesis will be: "Nanoprosthetics for vision restoration", and the supervisor will be Prof. Gorostiza. The research activities of the PhD will start with an advanced training in photochemical characterization, cell biology and ion imaging in cell lines, cultured neurons and brain slices. In parallel, he/she will be trained on electrophysiology (patch clamp). After this initial training phase, he/she will focus his/her efforts in the characterization of the TCP library. Then, during the last two years of the thesis he/she will be involved in doing the in vivo experiments in tadpoles. If successful, it is expected that these results give rise to a number of first-author publications, including the possibility of participating in high impact publications. The requested PhD candidate should preferentially have a background in chemistry, biochemistry, biology, biotechnology or equivalent. The candidate will enrol in the Doctoral Program on Nanoscience and Nanotechnologies from the University of Barcelona, which has the distinction of excellence. The group has proven its capacity for training predoctoral and postdoctoral fellows and offers them the possibility of being trained in a multidisciplinary environment in the framework of international projects. Moreover, the profile of the members of the group include physicists, pharmacologists, biologists, chemists and biotechnologists working together in projects ranging from chemical biology to synaptic physiology and molecular therapies. Thus, the different research expertise of the members of the group (from PostDoc to the technician level) has guaranteed the maximum research synergy, while providing adequate training to the younger investigators within the group. Moreover, the group has also internal activities (student seminars, paper discussion sessions) aimed at improving communication skills both oral and written for the PhD student. Thus, the research group, the research institute and the project offers excellent opportunities for the training of students. Dr. Gorostiza's commitment with PhD training is reflected by being scientific in charge of several Marie Curie Fellowship grants within the 7th Framework Programme (FP7-PEOPLE-IIF-2008 (235255), FP7-PEOPLE-2010-IRG (277182), H2020-MSCA-IF-2014 (660259)). Within the last 5 years period, more than 25 visiting scholars (i.e. master and bachelor students) have been performing mobility stages (between 1 and 3 months at least) at the laboratory.