Job ID: 115809 https://www.fens.org/careers/job-market/job/115809
Job ID: 139046 https://euraxess.ec.europa.eu/jobs/139046

Project#1 - Investigating common pathogenic mechanisms of rare genetic hereditary spastic paraplegia

We seek motivated applicants for a pre-doctoral / post-doctoral fellowship aimed at investigating molecular mechanisms of rare genetic forms of hereditary spastic paraplegia. The project combines in vitro, in silico and clinical approaches aimed at better understanding the pathogenesis of these still incurable pathologies. For the in vitro approach, the successful applicant will have a background in cellular / molecular neurobiology, with some experience in culturing primary neurons and astroglia and human fibroblasts. For more information and to send your application, please contact Dr. Fabrizia Cesca at fcesca@units.it **by September 30th, 2023**. Please note that **the starting date is flexible**. Below a detailed abstract of the Research Project.

Hereditary Spastic Paraplegia (HSP) is linked to mutations in several genetic loci with a broad variety of clinical manifestations; despite this complexity, most HSP genes converge into a relatively small group of cellular pathways. We study two early onset, childhood forms of HSP due to mutations in the Kinase D-interacting substrate of 220 kDa (KIDINS220) gene that codes for Kidins220, a membrane protein implicated in the neurotrophic pathways controlling neural cell survival and maturation, and in the Alsin Rho Guanine Nucleotide Exchange Factor (ALS2) gene, coding for Alsin, an endosome-associated Rac1 and Rab5 activator. Kidins220 and Alsin share a number of pathways, as they are both involved in brain-derived neurotrophic factor (BDNF) signaling, AMPA receptor trafficking, mitochondrial functionality and actin cytoskeleton dynamics.

In this project, we aim at finding common pathways that are altered in rare genetic HSPs and explore their druggability as treatment option for a restricted number of patients. Our approach will be based on: (i) neurobiology experiments on primary neural cell models; (ii) patient-derived induced pluripotent stem cells differentiated into neural cells; (iii) a dedicated in silico approach. The in vitro research will address how Kidins220 and Alsin mutations affect the above-mentioned pathways. The in silico approach will inform about pathogenic mechanisms and, through virtual drug screening, about therapeutic molecules that will be cross-tested in cell-based assays. Finally, the collaboration with clinicians who are presently following KIDINS220 and ALSIN children will provide the clinical framework for our analysis. The project is intrinsically multidisciplinary, as the teams involved cover complementary aspects of the proposed research: Dr. Cesca (UniTS) for the neurobiology and neurophysiology experiments, Dr. Ermondi (UniTO) for the in silico approach, and Dr. Santorelli (IRCCS Fondazione Stella Maris, Pisa) for the clinical information of KIDINS220 and ALSIN patients.

The clinical data about KIDINS220- and ALSIN-HSP is limited and no information is available to newly diagnosed patients about their conditions or possible treatments. However, we are aware of an increasing number of patients through web-based groups and family associations, who are in contact with the Applicants and already express their will to participate to the study. Indeed, the strict collaboration between families and researchers is one of the strengths of this proposal, and one of our aims is to create a network of scientists, clinicians and family foundations working together to raise awareness about these rare conditions both within the scientific community and within the wider society. Importantly, we believe that the information collected through our study could be extended to other rare genetic HSPs impinging on the same pathways, to identify personalized treatments to improve the lives of patients and their families.

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Project#2 - A chemo-optogenetic nanosensor for the control of drug-resistant epilepsy (pH4Health)

We seek motivated applicants for a pre-doctoral / post-doctoral fellowship aimed at developing a novel chemo-optogenetic tool for drug-refractory epilepsy. The project will optimize ad-hoc probes that will sense extracellular acidic pH shifts associated with epileptic activity and optogenetically silence excitatory neurons to inhibit seizure generation. For the in vitro approach, the successful applicant will have a background in cellular / molecular neurobiology and molecular cloning, with some experience in culturing primary neurons and astroglia. For more information and to send your application, please contact Dr. Fabrizia Cesca at fcesca@units.it **by September 30th, 2023**. Please note that **the starting date is flexible**. Below a detailed abstract of the Research Project.

Epilepsy is a neurological disorder characterized by repeated seizures. Several therapeutic approaches are available but, unfortunately, around 30% of patients do not respond to medical therapies. In the last decade, optogenetics has emerged as a tool to both explore neuronal networks dynamics and to treat neurological conditions such as epilepsy. The optogenetic strategy is based on the expression, in precise brain areas, of light-sensitive proteins called opsins that are able to change the membrane potential upon wavelength-specific illumination, usually achieved using invasive optical fibers. Despite the many advantages of this technique, it still faces practical and translational challenges because of the difficulties of illuminating multiple and deep areas of the brain. In this scenario, the search of alternative light sources is an unmet need.

Luciferases are enzymes able to emit light upon addiction of their substrate coelenterazine and can be used to deliver endogenously generated light to opsins and modulate their action non-invasively. In this project, we aim to develop a closed-loop chemo-optogenetic nanomachine called pHIL (pH-sensitive inhibitory luminopsin) that senses the extracellular acidic pH shifts associated with epileptic activity and optogenetically silences excitatory neurons to inhibit seizure generation. In fact, seizure activity leads to an extracellular pH shifts toward acidosis, which in turn aggravates hyperexcitability by stimulating depolarizing acid-sensing ion channels. A triple chimeric probe pHIL has been designed in which a bioluminescent variant of Renilla luciferase (RLuc8) is coupled to a fluorescent pH sensor (EGFP mutant, called E2GFP) and the inhibitory opsin eNpHR3.0. In the proposed strategy, under acidic pH evoked by hyperexcitation, the fluorescence emission of E2GFP excited by endogenous RLuc8 UV-light will increase, in turn activating eNpHR3.0 to actuate a hyperpolarizing outward current that delays/silence epileptic activity. A first pHIL1.0 chimera has already been engineered and expressed in cell lines and primary hippocampal neurons. On the basis of promising preliminary data, we will: (i) optimize the chimera for optimal energy transfer between its building blocks; (ii) study the activation of the inhibitory opsin by the acidic pH in cell lines and primary neurons; (iii) express pHIL in the hippocampus and study pHIL responses to epileptic-like activity in cortico-hippocampal slices; (iv) test the efficacy of pHIL in vivo on drug-evoked tonic-clonic seizures and in experimental models of genetic epilepsy. We propose pHIL as a cell-autonomous close-loop nanomachine to counteract neuronal hyperexcitability and restore neural network homeostasis in drug-resistant epilepsy.