FRANCE - URUGUAY : TREIZIEME APPEL A PROJETS ECOS Sud - UDELAR (2024)

Tableau des projets sélectionnés AAP ECOS Sud – UDELAR 2024

Code Projet	Titre du projet	Abstract	Responsable et établissement français	Responsable et établissement uruguayen
U24B01	Functional studies of human TFP and SQOR proteins, identified as targets of the PtpA virulent factor of Mycobacterium tuberculosis.	Mycobacterium tuberculosis (Mtb) is the etiological agent of tuberculosis (TB) an infectious disease responsible on average for 1.5 million human deaths every year. Although there is chemotherapy for its treatment, the disease has not yet been eradicated due to many factors such as late diagnosis and treatment, the appearance of multi-resistant strains and co-occurrence with other diseases. An important prerequisite to developing new clinically relevant drugs is the understanding, at the molecular level, of host-bacteria interactions responsible for pathogenesis. Mtb can subvert the host immune response, surviving and replicating within host macrophages assisted by several virulence factors. During infection, the mycobacterial phosphatase PtpA is introduced in the cytosol where interacts with numerous eukaryotic proteins, modulating several cell signaling pathways such as phagosome maturation, innate immune response, apoptosis, and host metabolism, favoring the persistence of the bacteria within infected cells. The Uruguayan group from this proposal identified two of these eukaryotic partners of PtpA: the mitochondria human trifunctional enzyme (hTFPα) and the mitochondria human sulfide quinone oxidoreductase (hSQOR). In the mitochondria, TFP plays a central role in the β-oxidation of long-chain fatty acids catalyzing three of the four stages of this pathway; and hSQOR catalyzes the oxidation of hydrogen sulfide (H2S) a small molecule with modulating properties. Interestingly, it has been described that hTFPα and hSQOR are no longer detected in mitochondria during macrophage infection with the virulent Mtb H37Rv strain. The absence of these proteins into the mitochondria could have important metabolic consequences for the macrophage and the bacteria, as an increased availability of fatty acids in the cytosol, which are known to be used as Mtb nutrients. In this context, it seems relevant to determine the role of the mycobacterial phosphatase PtpA on the hTFP and hSQOR activities. In the present project, we propose to analyze in cellulo if PtpA interacts with hTFP and/or hSQOR. We will evaluate if the potential interactions correlate with changes in the phosphorylation state or localization of these proteins, or with a modulation of the metabolic pathways in which they are involved. In addition, using the recombinant hTFP and hSQOR proteins and mutants defined in this work, we will study the role of Tyr-phosphorylation in the activity of these proteins. We consider that the expertise of each member of the French and Uruguayan team will be fundamental to the success of this proposal, which will allow the creation of a new line of research on a little-studied topic of great relevance at a basic level and human health.	**SELLES Benjamin** Laboratoire IMoPA, UMR 7365 CNRS-Université de Lorraine, Biopôle, campus Biologie-Santé, 9 Avenue de la Forêt de Haye, BP 20199 54505 Vandoeuvrelès- Nancy Cédex benjamin.selles@univ-lorraine.fr	**VILLARINO RUFENER Andrea** Sección Bioquímica, Facultad de Ciencias, Universidad de la República, Iguá 4225, CP 11400. avillarino@fcien.edu.uy
U24B02	Réparation de la moelle épinière : Exploiter le potentiel des cellules souches épendymales	Spinal cord injuries (SCIs) cause devastating paralysis due to disrupted nerve pathways. Ideally, treatment would involve replacing lost nerve cells, promoting nerve fiber regrowth, and restoring insulation for efficient nerve impulses. While some animals can self-repair after SCI, mammals like humans cannot. However, a promising approach lies within the spinal cord itself: ependymal stem cells. Ependymal cells line the spinal cord central canal and react to injury by multiplying and migrating towards the damaged area. Their stem cell properties have been unequivocally showcased in vitro, showcasing the remarkable capacity to generate both	**Jean-Philippe HUGNOT** IGF, UM, CNRS UMR5203, Inserm U1191, Brain plasticity,	**Raul RUSSO** Instituto de Investigaciones Biológicas Clemente Estable, UDELAR. rrusso@iibce.edu.uy

		neurons and glial cells. Moreover, our recent findings have conclusively established that these properties persist throughout the entirety of human life. Unfortunately in vivo, these cells mainly form scar tissue, hindering spinal cord repair. This project focuses on unlocking their regenerative potential. Connexins (Cx) are proteins that enable communication between cells. Our past and ongoing research has shown that Connexins play a vital role in activating ependymal stem cells after injury in mice. This project will investigate the Connexins expression (Cx26 and Cx43) in human spinal cord ependymal stem cells and compare it to mice. In addition, we are currently generating long term cultures of human ependymal cells and the role of Connexin in the proliferation and differentiation will be explored in these cells. Project Aims: Human Spinal Cord Cx Characterization: We will examine Cx26 and Cx43 expression in human ependymal cells at different stages (juvenile, adult, aged) alongside stem cell markers, using human spinal sections Characterization of Cx Expression in Human Ependymal Cell Lines We will conduct an analysis on recently established human spinal cord stem cell lines to determine their expression of connexin proteins. We''ll also investigate if these lines have subpopulations based on connexin expression, similar to what's seen in mice spinal cord stem cells. Aim 3: Role of Cx26 in Activation of Mouse Spinal Cord Stem Cells We will use genetic engineering in mice to eliminate Cx26 and analyze the resulting gene expression profile, comparing it to the human ependymal cell profile and activated profile previously established by Dr Hugnot's lab Methods: We will use a unique biobank of 17 human spinal cords collected from organ donors and newly-established ependymal cell lines. Animal experiments will adhere to ethical guidelines. Tissue sections will be analyzed by histochemistry to visualize Cxs and stem cell markers. Mouse and Human Ependymal cells will be isolated for genetic analysis of role of Cx in proliferation and differentiation International Collaboration: French and Uruguayan researchers will collaborate on this project. A Uruguayan PhD student will visit France to learn human tissue analysis techniques and human ependymal culture, while a French student will visit Uruguay to participate in experiments using genetically modified mice. Expected Outcome: This project aims to understand Cx signaling in human and mouse ependymal stem cells after SCI. By identifying key differences between humans and mice, we hope to lay the groundwork for future therapies to promote self-repair and improve functional recovery after SCI in humans.	stem cells and Glial Tumors. jean-philippe.hugnot@umontpellier.fr	
U24E01	Dynamics of gluons at low energies and its relation to confinement and the generation of mass in nuclear matter	The project aims to provide an innovative approach to fundamental questions around the strong nuclear interaction, such as the confinement of quarks within nucleons, the origin of the mass of these nucleons, or the properties of nuclear matter under extreme conditions of temperature or density. All these questions should in principle find an answer within the framework of Quantum Chromodynamics (QCD), the fundamental theory governing the strong interaction. Due to the magnitude of the latter, there are few methods that allow these basic phenomena to be described based on first principles and with good control over the error. For about fifteen years, however, certain results from numerical simulations of QCD in the so-called Landau gauge have changed our understanding of the strong interaction at low energies and have allowed the development of semi-perturbative methods, with good control of the error, to the price of introducing a single phenomenological parameter, an effective mass for the gluon, which can be fixed by comparison with the results of lattice simulations. An important part of the activity of the Franco-Uruguayan team during these years has been devoted to calibrating the approach and making sure that it allows one to reproduce a number of already known results of QCD or of related theories such as Yang-Mills theories or QCD in the presence of heavy quarks. Our collaboration has reached sufficient maturity to address the fundamental questions mentioned above, some of which have not yet found a fully definitive answer within the most sophisticated QCD methods.	**REINOSA MINCHERO Urko** CPHT - Ecole polytechnique. urko.reinosa@polytechnique.edu	**PELAEZ Marcela** Instituto de Física Teórica - Universidad de la República. mpelaez@fing.edu.uy

U24S01	Influence de la sénescence sur le transfert des mitochondries dans le microenvironnement tumoral	Cellular senescence is a state characterized by the inhibition of proliferation and a specific secretory phenotype. Factors secreted by senescent cells contribute to the development of age-associated pathologies, including cancer, and to the side effects of chemotherapy with genotoxic agents. Conventional protein secretion involves transport in vesicles from the endoplasmic reticulum to the Golgi apparatus, and then to the plasma membrane. Additionally, there are also unconventional intercellular communication mechanisms such as extracellular vesicles and tunneling nanotubes. Recently, it has been observed that these unconventional pathways can be used for the transfer of mitochondria between cells. Despite the relevance of the senescent secretory phenotype, there is still little information about what happens with these unconventional pathways during senescence. Preliminary results from our groups show that senescent cells are formed in the context of cancer chemotherapy. Moreover, they reveal that senescent melanoma cells and senescent medullary stromal mesenchymal cells show a significant increase in energy metabolism and changes in the length of mitochondria and the mitochondrial network. Studies from the Uruguayan group show that inhibiting the expression of mitochondrial fusion proteins mitofusins 1 and 2 in melanoma cells inhibits the secretion of multiple factors and affects the recruitment of immune system cells and tumor development. Meanwhile, studies from the French group indicate that the transfer of mitochondria from medullary stromal mesenchymal cells to T lymphocytes in the tumor microenvironment in acute myeloid leukemia (AML) inhibits the proliferative capacity of these latter cells, leading to a pro-tumoral state. Furthermore, they show that the cellular senescence of mesenchymal cells inhibits the transfer of mitochondria to T lymphocytes. The project aims to assess the impact of cellular senescence on the mitochondrial transfer processes among cells present in the tumor microenvironment, particularly cancerous and mesenchymal cells. It also attempts to contribute to the elucidation of the molecular events involved in mitochondrial transfer, by studying the role of energy metabolism and mitochondrial dynamics. These studies will be conducted on two biomedical interest models developed by the involved groups: senescence induced by chemotherapy in melanoma cells and in mesenchymal cells. Mesenchymal cells from the bone marrow of patients with AML will also be used. This will be possible thanks to the complementary skills of the partners ranging from exploring metabolism and precise quantification of the mitochondrial network (Uruguay) to studying mitochondrial transfer and its impact on immune cells (France). The results obtained will help determine whether senescence affects mitochondrial transfer, and if changes in energy metabolism and mitochondrial dynamics play a role in the transfer of mitochondria between senescent and non-senescent cells.	**DE ISLA Natalia** Université de Lorraine, IMoPA UMR CNRS 7563, 9, avenue de la forêt de Haye - BP 20199, 54505 Vandoeuvre-lès-Nancy natalia.de-isla@univ-lorraine.fr	**Celia QUIJANO** Universidad de la Republica - Facultad de Medicina, Departamento de Bioquímica y Centro de Investigaciones Biomédicas. celia.quijano@gmail.com ; celiq@fmed.edu.uy