DADES DELS SUPERVISORS i GRUP DE RECERCA	
NOM DEL(s) SUPERVISOR(s)*: Rosa M Soler/Ana Garcerá	
DEPARTAMENT*: Medicina Experimental	
ADREÇA: Biomedicina 1 b4.1 Rovira Roure, 80	
GRUP DE RECERCA*: Unitat de Senyalització Neuronal	
E-mail del supervisor(s)*: rosa.soler@udl.cat	Telèfon: 973702264

*Dades Obligatòries.

MASTER'S THESIS PROPOSAL
TITLE*: Spinal Muscular Atrophy: molecular mechanisms and new therapeutic strategies
SUMMARY: Analysis of intracellular signaling pathways in Spinal Muscular Atrophy disease models Tasks: - Primary cultures of isolated mouse spinal cord motoneurons - In vitro differentiation of human iPSCs to motoneurons - Cell line cultures - Animal models of Spinal Muscular Atrophy disease - Western blot experiments: analysis of protein level in cell extracts from in vitro experiments or mouse tissues - Immunofluorescence experiments: analysis of protein localization and fluorescence intensity in cultured cells or mouse tissues slices - Cell survival and neurite degeneration experiments of cultured human and mouse motoneurons
Additional information: A PhD position may be offered after TFM

DADES DELS SUPERVISORS i GRUP DE RECERCA	
NOM DEL(s) SUPERVISOR(s)*: Concepción Mora Giral	
DEPARTAMENT*: MEX	
ADREÇA: Lab. Immunologia 2-13. Edifici Biomedicina 2. Av. Rovira Roure 80.25198 Lleida	
GRUP DE RECERCA*: Grup Immunologia i Immunopatologia	
E-mail del supervisor(s)*: conchi.mora@udl.cat	Telèfon: 973702958

*Dades Obligatòries.

MASTER'S THESIS PROPOSAL

TITLE*: **Role of cyclin D3 in the regulation of mitochondrial oxidative stress in pancreatic beta cells. Studies in autoimmune diabetes**

The main goal of the current project is to demonstrate that cyclin D3 exerts a key anti-apoptotic action in pancreatic beta cells through the regulation of mitochondrial function.

We have recently discovered a novel, cell cycle-independent, role for cyclin D3 in promoting beta-cell survival and fitness. It was observed that cyclin D3 interacts with a protein involved in mitochondrial function (C2). In the current proposal, we aim to confirm that cyclin D3 is involved in controlling at least this cell physiological function: mitochondrial redox balance.

Initially, in T1D, islet inflammation is triggered by a pro-inflammatory autoimmune assault which would promote impaired glucose metabolism, mitochondrial dysfunction, and loss of integrity, and, as a consequence, beta cell death by both, the intrinsic apoptotic pathway (cytochrome c/apoptosome) and extrinsic one (Fas death receptor). This cell cycle-independent role of cyclin D3 would be conducted in a complex manner by orchestrating the activity of C3, in response to challenging stimuli such as high glucose and/or pro-inflammatory cytokines. In collaboration with Dr. José Serrano, University of Lleida, we will assess mitochondrial function using the Seahorse technology (by Aglient).

Our working hypothesis in this project is: the anti-apoptotic role of cyclin D3 in beta cells is accomplished at least by maintaining the redox and energetic balance in the cell through the regulation of the mitochondrial respiratory activity. The regulation of the mitochondrial respiratory activity is achieved by the interaction of cyclin D3 with the mitochondrial protein C2, involved in the respiratory chain.

Specific Research Objectives:

1. Specific Aim 1 (SA1): To study the effect that either the cyclin D3 deficiency (KO) or its overexpression (TG) has on the Mitochondrial function (MF) in the NIT-1 insulinoma cell line upon exposure to r pro-inflammatory cytokines. Assessment of C2 activity.

2. Specific Aim 2 (SA2): To study the effect that either the cyclin D3 deficiency (KO) or its overexpression (TG) has on the Mitochondrial function (MF) in the NIT-1 insulinoma cell line upon exposure to high glucose. Assessment of C2 activity.

Additional information:

Possibility of PhD development.

DADES DELS SUPERVISORS i GRUP DE RECERCA	
NOM DEL(s) SUPERVISOR(s)*: Ferran Barbé	
DEPARTAMENT*: Medicina	
ADREÇA: Av. Alcalde Rovira Roure, 80 IRBLleida 3.17	
GRUP DE RECERCA*: Translational Medicine in Respiratory Diseases	
E-mail del supervisor(s)*: febarbe.lleida.ics@gencat.cat	Telèfon: 973735929

*Dades Obligatòries.

MASTER'S THESIS PROPOSAL
TITLE*: Normotensive Patients with Sleep Apnea: Differential Impact of CPAP Treatment According to the Circadian Blood Pressure Pattern. A Randomized Controlled Trial. The MOISÉS study.
SUMMARY: Sleep apnea is a frequent condition in patients with an altered circadian blood pressure (BP) pattern. The non-dipping BP pattern is related to high cardiovascular risk. The response to treatment of sleep apnea with continuous positive airway pressure (CPAP) is heterogeneous. The overall objective of the project is to evaluate the differential effect of CPAP treatment on BP according to the circadian BP pattern in normotensive patients with severe sleep apnea. We will characterize the clinical and proteomic profile associated with the circadian regulation of BP in patients with sleep apnea, aiming to develop a non-invasive model integrating information from the clinical and biological data, to predict response to the treatment, allowing to delve into the pathophysiological mechanisms that relate sleep apnea and hemodynamic response to CPAP treatment. METHODOLOGY: Open-label, parallel, prospective, randomized, and controlled trial including 128 normotensive subjects newly diagnosed with severe sleep apnea. The patients will be classified according to their dipping pattern, defined by a drop in BP at night measured in 24-h ABPM, and will be randomized to receive CPAP or conservative care for 3 months. 24-h ABPM measurements and peripheral blood samples collection will be performed at the initial visit and after the follow-up period. Changes in 24-h ABPM BP will be evaluated, and a complete plasma molecular proteomic-based profiling will be carried out, followed by a functional bioinformatic pathway enrichment analysis.
Additional information:

DADES DELS SUPERVISORS i GRUP DE RECERCA	
NOM DEL(s) SUPERVISOR(s)*: Diego Arango del Corro / Águeda Martínez Barriocanal	
DEPARTAMENT*: Ciències Mèdiques Bàsiques	
ADREÇA: IRBLleida, Avinguda Alcalde Rovira Roure 80	
GRUP DE RECERCA*: Oncologia Molecular	
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*Dades Obligatòries.

MASTER'S THESIS PROPOSAL
TITLE*: Investigation of the molecular mechanisms underlying the initiation and progression of gastrointestinal tumors (colorectal and gastric), head and neck tumors or endometrial tumors.
SUMMARY: In the laboratory we try to understand the molecular mechanisms controlling the tumorigenic process with the ultimate goal of improving the diagnosis and treatment of patients. The group is currently investigating the role of several proteins and their cell signaling pathways. The selected candidate will join any of the following research lines (according to his/her personal interests): ○ RhoA: Study the role of the mutations in the GTPase RhoA found in gastric tumors with diffuse histology, and head and neck tumors. Recurrent mutations in the *RHOA* gene have been identified in these tumor contexts, but their contribution to tumor development is unknown. The study of these mutations in diffuse gastric cancer has led a line of research focused on the therapeutic value of RhoA signaling. ○ Unconventional non-muscular myosins: the group has made important contributions on the role of different non-conventional myosins in intestinal tumor cells. The role of myosin Vb in colorectal cancer is currently being investigated, and how the levels of expression of the protein contribute to build a cellular vulnerability that can be exploited therapeutically. ○ Ephrin receptors: Our group has made significant contributions to understand the role of the signaling of different EPH receptors in colorectal cancer. Our data indicate that some of these receptors may also play a key role in endometrial cancer. Specifically, we study the value of these receptors to improve the stratification of patients and their therapy.
Additional information:

DADES DELS SUPERVISORS i GRUP DE RECERCA	
NOM DEL(s) SUPERVISOR(s)*: Robert Montal Roura	
DEPARTAMENT*: Ciències Mèdiques Bàsiques	
ADREÇA:	
GRUP DE RECERCA*: Cancer Biomarkers Research Group (GReBiC).	
E-mail del supervisor(s)*: montalrobert@gmail.com	Telèfon:

*Dades Obligatòries.

MASTER'S THESIS PROPOSAL

TITLE*: **Biomarkers of Response to Immunotherapy through Comprehensive Immunophenotyping of Gastric Adenocarcinoma**

SUMMARY:

Gastric adenocarcinoma (GAC), the fifth most common cancer worldwide, imposes a considerable **global health burden**. Despite improvements in multidisciplinary therapies, 5-year survival rates remain unsatisfactory (~25%). In advanced clinical stages, cytotoxic chemotherapy is still the cornerstone of treatment. However, **immunotherapy** with PD-1 inhibitors has recently shown **durable responses in some cases** of GAC. Identifying those patients more likely to benefit from immune checkpoint inhibitors (ICIs) through **predictive biomarkers** is an unmet medical need. In this regard, genomic profiling of GAC has illustrated the biologic diversity of this disease, with a plethora of deregulated oncogenic pathways converging in **four main molecular subtypes**.

With the aim to better understand the **relationship between cancer and immune cells** we have identified a **discovery cohort** (HUAV-E, n=82; TCGA, n=295) of surgically resected GAC. Gene-expression deconvolution of immune cells and multiplex immune checkpoint protein spatial profiling will be used to identify tumor microenvironment features associated to known somatic alterations and molecular subtypes of GAC. Candidate **biomarkers recapitulating decoded immunophenotypes** will be tested in a **prospective cohort** (HUAV-A, n=24) of advanced GAC treated with ICIs and with available liquid biopsy at multiple time points. The final goal will be to provide biomarkers of response/resistance to ICIs in order to tailor a **personalized treatment for patients with GAC.**

Additional information:

Particularly suitable for TFM students with an interest in bioinformatic analysis of multi-omics data.

If interested, funding for developing the PhD in the group could be requested from competitive grants (FPU or similar).

DADES DELS SUPERVISORS i GRUP DE RECERCA	
NOM DEL(s) SUPERVISOR(s)*: Marta Llovera / Daniel Sanchis	
DEPARTAMENT*: Ciències Mèdiques Bàsiques	
ADREÇA: Edifici Biomedicina-I 2a planta	
GRUP DE RECERCA*: Senyalització Cel·lular i Apoptosi	
E-mail del supervisor(s)*: marta.llovera@udl.cat	Telèfon: 973702949

*Dades Obligatòries.

MASTER'S THESIS PROPOSAL
TITLE*: TATDN1: Characterization of cellular distribution and physiological roles, using different experimental models.
SUMMARY: Our group has been working on TATDN1, the mammalian homolog of bacterial TatD. TatD homologs in E coli, yeast and protist models have been related to DNA degradation in overexpressing experimental settings. However, our previous results show that TATDN1 is a cytoplasmic protein and is not involved in DNA degradation in the assessed setings. On the contrary, *Tatdn1*-deficient mice show alterations in motor coordination and dilated cardiomyopathy with no evident alterations in DNA degradation processes. We want to get further insight on TATDN1 functions and physiological roles. For that, we offer a Master's degree experimental project that will include 1) detailed characterization of intracellular distribution of TATDN1, using GFP tagged TATDN1 overexpression, and immunofluorescence and subcellular fractionation techniques in cell cultures, and 2) Production and phenotypical characterization of the fruit fly CG3358 (DmTatd) deficient mutant.
Additional information:

DADES DELS SUPERVISORS i GRUP DE RECERCA	
NOM DEL(s) SUPERVISOR(s)*: Ferran Barbé (Tutor, UdL), David de Gonzalo Calvo (Supervisor, IRBLleida), Adriano Targa (Supervisor, IRBLleida).	
DEPARTAMENT*: Neumología	
ADREÇA: Alcalde Rovira Roure, 80, 25198	
GRUP DE RECERCA*: Grupo de Investigación Traslacional en Medicina Respiratoria (TRRM)	
E-mail del supervisor(s)*: dgonzalo@irblleida.cat, adrianotargads@gmail.com	Telèfon: 973702491

*Dades Obligatòries.

MASTER'S THESIS PROPOSAL
TITLE*: Unraveling the mechanisms underlying long-term sequelae of critical COVID-19 patients
SUMMARY: COVID-19 affected more than 600 million people worldwide. During the acute phase of the disease, approximately 30% of the patients develop severe complications, which increase the risk of hospitalization, ICU admission, and death. Additionally, critical patients report a set of symptoms observed months after hospital discharge including fatigue, dyspnea, cough, sleep disturbances, anxiety, depression, and cognitive impairment, among others. The aim will be to evaluate potential mechanisms underlying the respiratory sequelae of critical COVID-19 patients considering clinical and molecular aspects. From the clinical perspective, we will evaluate the impact of sleep, circadian rhythms, mental health, and the previous respiratory condition on the respiratory function of these patients in the long-term (12 and 24 months after hospital discharge). From the molecular perspective, transcriptomic approaches will be implemented to decipher the biological pathways implicated in the pathogenesis of the sequelae and to identify potential biomarkers for improving clinical decision-making. We are seeking for a highly motivated student to be part of the Translational Research in Respiratory Medicine (TRRM) research group. Most of the tasks will be performed at the Biomedical Research Institute of Lleida (IRBLleida), in collaboration with the Pneumology Department of Hospital Arnau de Vilanova-Santa Maria de Lleida and the Sleep Unit of the Hospital de Santa Maria de Lleida. The tasks and acquired knowledge will include the evaluation of sleep and circadian rest-activity rhythm data provided by actigraphy, execution of molecular techniques such as RNA profiling, statistical analysis of the data, presentation of findings during seminars of the research group, and writing of scientific papers.
Additional information:

DADES DELS SUPERVISORS i GRUP DE RECERCA	
NOM DEL(s) SUPERVISOR(s)*: Dra. Sara Hernández i Dr. Jordi Calderó	
DEPARTAMENT*: Medicina Experimental	
ADREÇA: Avda. Rovira Roure 80 25198 Lleida	
GRUP DE RECERCA*: Patologia Neuromuscular Experimental	
E-mail del supervisor(s)*: sara.hernandez@udl.cat	Telèfon: +34973702416

*Dades Obligatòries.

MASTER'S THESIS PROPOSAL
TITLE*: Effect of drug-based combinatorial therapies targeting neuroinflamation in spinal muscular atrophy.
SUMMARY: Spinal muscular atrophy (SMA) is an autosomal recessive disease that represents the leading genetic cause of infant mortality. SMA is characterized by the degeneration of α-motoneurons (MNs), which results in progressive muscular atrophy, denervation and paralysis. In the most severe cases, the disease culminates in respiratory failure and death. Although SMA is an hereditary disease caused by mutations in the survival motor neuron 1 gene, SMN1, other factors are underlying MN degeneration, such as astroglia and microglia activation, so-called neuroinflamation. The main goal of this project is to test different drugs that could be used as a therapeutic strategy because they target neuroinflamation-related mechanisms described in MN pathology in the SMA background.
Additional information:

DADES DELS SUPERVISORS i GRUP DE RECERCA	
NOM DEL(s) SUPERVISOR(s)*: Manel Portero	
DEPARTAMENT*: Medicina Experimental	
ADREÇA: Ed Biomedicina I, Avda Rovira Roure 80 E25196 Lleida	
GRUP DE RECERCA*: Fisiopatologia Metabòlica	
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*Dades Obligatòries.

MASTER'S THESIS PROPOSAL
TITLE*: Cell senescece , autophagy and membrane lipid composition in the pathophysiology of age-related neurodegenerative diseases
SUMMARY: In a recent work (Torres et al., 2022), we have shown that cell senescence of mouse fibroblasts in vitro is associated to buildup of cryptic exons, whose level is usually controlled by the activity of Tdp-43 (Torres et al. Autophagy 2018). In vivo, we also found this specific trait in the motor neuron disease model achieved by overexpressing SOD-G93A. These mice express an age-related increase in the p21 and p16 mRNA levels, with enhanced expression of these markers of senescence in the cytosol of several cells of lumbar spinal cords. Most of the cells showing increased p16 immunoreactivity were identified as astrocytes and microglia, with neuronal cells being relatively spared from the buildup of this senescence biomarker. These phenomena are associated to changes in membrane lipid composition, driven by the loss of the lipid composition sensor *AdipoR2*. Given the importance of autophagy process in the pathophysiology of age-related diseases in this master theses, the candidate will explore, employing cell culture, click-chemistry supported lipid-composition analyses and molecular biology techniques, whether the loss of RNA-binding proteins could be relevant in the autophagy changes related to cell senescence.
Additional information: Torres P, Anerillas C, Ramírez-Núñez O, et al. A motor neuron disease mouse model reveals a non-canonical profile of senescence biomarkers. *Dis Model Mech*. 2022;15(8):dmm049059. doi:10.1242/dmm.049059 Torres P, Ramírez-Núñez O, Romero-Guevara R, et al. Cryptic exon splicing function of TARDBP interacts with autophagy in nervous tissue. *Autophagy*. 2018;14(8):1398-1403. doi:10.1080/15548627.2018.1474311

DADES DELS SUPERVISORS i GRUP DE RECERCA	
NOM DEL(s) SUPERVISOR(s)*: Jordi Tamarit	
DEPARTAMENT*: Ciències Mèdiques Bàsiques	
ADREÇA: Edifici Biomedicina 1, Rovira Roure 80, Lleida	
GRUP DE RECERCA*: Bioquímica de l'Estrès Oxidatiu	
E-mail del supervisor(s)*: jordi.tamarit@udl.cat	Telèfon: 973702475

*Dades Obligatòries.

MASTER'S THESIS PROPOSAL
TITLE*: Evolution of an iron-detoxifying protein: uncovering the function of a group of conserved amino acids in eukaryotic frataxins.
Friedreich Ataxia is a rare, inherited recessive disease caused by mutations in the frataxin gene. Frataxin is a highly conserved protein, and homologous can be found in virtually all living organisms. It has been proposed that frataxins play a fundamental role in iron homeostasis, either regulating iron assembly into metaloproteins or contributing to iron detoxification. Nevertheless, several functional differences exist between eukaryotic and bacterial frataxins, notably in its ferroxidase activity. Recently, we have noticed that eukaryotic proteins contain a cluster of four amino acids which are not present in their bacterial homologues. This potential functional site is also present in Rickettsia, suggesting that it was already present in the endosymbiont ancestor of mitochondria. In the present project we will analyze the funcional relevance of these amino acids. By site-directed mutagènesis, we will modify the amino acids from this cluster and analyze its effect on frataxin stability and function.
Additional information:

DADES DELS SUPERVISORS i GRUP DE RECERCA	
NOM DEL(s) SUPERVISOR(s)*: JORDI TORRES ROSELL/NEUS COLOMINA GABARRELLA	
DEPARTAMENT*: CMB	
ADREÇA: Ed Biomed I, IRBLleida, Av. Alcalde Rovira Roure, 80	
GRUP DE RECERCA*: CICLE CEL·LULAR	
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*Dades Obligatòries.

MASTER'S THESIS PROPOSAL
TITLE*: Replication fork remodelling and genome integrity in cancer cells
SUMMARY: Mitotically growing cells devote most efforts to accurately duplicate and transmit their genome. Failures in this key process can give rise to aneuploidy and genome instability, a hallmark of cancer cells. DNA replication can be impeded by multiple challenges, including DNA lesions, limiting nucleotides, secondary structures or collisions with the transcriptional machinery. These type of interferences need to be properly addressed to maintain the stability of the genome and avoid tumorigenesis. Recent advances have revealed that forks are actively remodeled upon replicative stress. One of the mechanisms used, known as fork reversal, is mediated by fork remodelers, which slow down DNA replication, stabilize forks and promote lesion bypass in situations of DNA damage. The Smc5/6 complex is critical for the physical separation of sister chromatid during DNA replication. The yeast Smc5/6 complex controls fork remodeling through direct inhibition of the Mph1 helicase, a fork reversal enzyme. Our unpublished results indicate cells carrying mutation in the human Smc5/6 complex have slower forks. However, this function does not seem to be mediated by FANCM, the human orthologue of the Mph1 helicase. Human cells rely on a battery of fork reversal enzymes to remodel forks under conditions of replicative stress. Thus, human Smc5/6 might promote replication fork progression and genome integrity through inhibition of activities other than FANCM. To test this hypothesis, we plan to study the dynamics of DNA replication in *smc5/6* mutant cancer cells after genetic inactivation of specific fork reversal enzymes. In addition, we will explore the mechanisms involved in the suppression of fork remodeling activities.
Additional information: