ANEXO I

(PROYECTOS)

1. Understanding regulatory unfolded protein response (UPR) mechanisms and its therapeutic relevance in neurodegenerative disorders (NDs)

1. *Research / Project Description (Descripción de la línea de investigación al que se incorporaría el solicitante de la MCSA: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

Understanding regulatory unfolded protein response (UPR) mechanisms and its therapeutic relevance in neurodegenerative disorders (NDs)

Among all disorders caused/enhanced by aging, NDs stand out as one of our main biomedical challenges. NDs are caused by the progressive degeneration of neurons in the central nervous system, severely affecting motor and cognitive functions. While Alzheimer's disease and Parkinson's disease are the most frequent NDs, other devastating disorders such as Amyotrophic Lateral Sclerosis cause a severe symptomatology and a rapid disease progression (3-5 years). None of the current therapies can reduce neuronal death in NDs, and therefore current treatments cannot delay or stop disease progression.

One of the pathological hallmarks shared by most NDs is the accumulation of protein aggregates and the activation of a coping reponse known as the UPR. The UPR comprises a set of signaling pathways that communicate the endoplasmic reticulum (ER) with the nucleus. ER folding deficiencies activate UPR which in turn triggers a gene expression program. While the UPR acts first as coping response to stress, chronic/excessive UPR activation leads to apoptotic mechanisms and neuronal death.

In this project we will:

1) investigate UPR basic molecular regulatory mechanisms, specifically the non-canonical splicing of the mRNA encoding XBP1 transcription factor that plays a key role in UPR activation (*Aragón T, Nature, 2009; Argemí J, Gastroenterology, 2017*)

2) assess the therapeutic potential of UPR modulation for NDs. UPR targeting drugs will be tested in primary neuronal models of NDs based on longitudinal survival analysis (*Arrasate M, PNAS, 2005; Iñigo-Marco I, PNAS, 2017*) and in transgenic mouse models.

3) setup a CRISPR-Cas9-based genetic screen to identify genes that, when deleted, enhance neuronal survival in the neuronal models developed.

2. *Who can apply? (eligibility criteria)*

Specific requirements:

The Post-Doctoral fellow will participate in the study of the basic mechanisms of XBP1 splicing and in the functional screenings proposed. The project will involve the implementation of new methodologies, specifically the generation of sequencing libraries for RNAseq and ChIPseq approaches, where our team has some experience and collaborates with groups that will provide technical assistance. The candidate must have a strong background in molecular biology, expertise in the generation of libraries for deep sequencing will be appreciated.

2. Inflammatory mechanisms involved in the beginning and progression of the dopaminergic death and the functional and structural changes of the synapse

1. *Research / Project Description (Descripción de la línea de investigación al que se incorporaría el solicitante de la MCSA: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

Our laboratory is focused on the study of the origin and pathophysiology of Parkinson's disease using a model of progressive parkinsonism induced by the overexpression of mutated alpha-synuclein in the substantia nigra pars compacta (SNc). We are focused on the study of the **inflammatory mechanisms** involved in the beginning and progression of the dopaminergic death and the **functional and structural changes of the synapse** that take place during the beginning and progression of dopaminergic cells. We study the relationship between microglial and astrocytic activation and dopaminergic death using in vivo PET studies and post mortem studies with several approaches and techniques at different time points after the expression of alpha-synuclein in order to have a detailed temporal pattern of the relationship between neuroinflammation and dopaminergic death. Based on the results obtained we will treat the animals with antibodies directed to the inhibition of specific molecules to assess the impact of these novel approach in the beginning and progression of dopaminergic death. Our goal is to decipher if neuroinflammation has a role in the initiation of the dopaminergic cell or acts perpetuating the neurodegeneration once it has been initiated. Complimentary, we are studying the earliest functional modifications of the synapsis prior to the structural changes and the degeneration of the dopaminergic cells using different approaches: bioenergetics (seahorse), molecular (synaptosomes), synaptic plasticity (molecular and patch-clamp), electronic microscopy studies, flux cytometry, amperometry to study dopamine realise etc. We also plan to start the study of organotipic cultures comprising the SNc, striatum and cortex with overexpression of alpha-synuclein in order to study how the dopaminergic and the cortical synapsis are functionally are structurally affected by the expression of alpha-synuclein. Afterwards, we will used different therapeutic approaches (antiagregant of synuclein, inhibitors of autophagy or metabolic routes etc) to test a potential benefit in the function and survival of the cells. The candidate will work in the two lines with the objective to foster the current research and enhance the development of therapeutic strategies.

2. *Who can apply? (eligibility criteria)*

Specific requirements:

PhD in neuroscience. Cellular and/or Molecular Biology, Strong theoretical and practical background in Microscopy of last generation (two photon, multiphoton, STED etc) and histological analysis.
Practical experience on viral vector injections, cell cultures, and animal models of neurodegenerative diseases.
Knowledge of autophagy, neuroinflammation, and synapsis would be an asset.

Autonomous person with a good sense of initiative, curiosity, creativity, and perseverance.--
Good communication skills, good written and oral English skills.

3. Magnetic resonance compatible immersive virtual reality system and its application to brain activity during locomotion

1. *Research / Project Description (Descripción de la línea de investigación al que se incorporaría el solicitante de la MCSA: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

Magnetic resonance compatible immersive virtual reality system and its application to brain activity during locomotion

Immersive virtual reality (iVR), represented by modern head mounted virtual reality displays, is a visualization tool that allows for great realism and sensory immersion, which has mainly been used in the entertainment business, has become of scientific interest, where in clinical fields has become a potential tool for motor training and rehabilitation tasks, like in human gait. iVR induced changes in brain activity while walking are unknown to this day, mainly due to two reasons: the lack iVR systems compatible with a magnetic resonance (MR) environment and because studying human locomotion inside an MR machine has proven difficult due to technical reasons. On the other side, the study of locomotion represents one of the iVR´s areas of interest, mainly in clinical areas, justified by its potential application as a rehabilitation tool to gait disorders. Recently, our group validated a MR-compatible locomotion model [1,2] and has also explored the physiological response to immersive virtual reality [3]. In this project, we propose the construction of a MR-compatible iRV visual stimulation system that, together with our locomotion model, could allow us to explore the impact of iRV in healthy young and elderly adults' brain activity while executing a locomotion task. This approach would allow us to understand how immersion in VR changes brain activity when walking, and how these changes are modulated when aging.

2. *Who can apply? (eligibility criteria)*

Specific requirements:

fMRI expertise (stimuli programming, collecting fMRI data, data analyses), virtual reality knowledge, motor control knowledge.

4. Identification of disease-modifying therapeutic targets for the treatment of Parkinson´s disease

1. *Research / Project Description (Descripción de la línea de investigación al que se incorporaría el solicitante de la MCSA: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

Our research line is focused in the identification of disease-modifying therapeutic targets for the treatment of Parkinson´s disease based on the modulation of neuron-glia crosstalk through the endocannabinoid system. Using different cannabinoid system modulators, we have identified those that have anti-parkinsonian properties either due to a symptomatic effect or to a neuroprotective effect using the chronic MPTP mouse model. At present, we are studying the mechanism of action of the neuroprotective compounds and how glial activity could be modulated for neuroprotective purposes using flow cytometry and RNAseq techniques. To determine the role of cannabinoid type 2 (CB2) receptors in neuroprotection, we are using $CB2^{eGFP/f/f}$ and $CB2^{-/-}$ mice. Studies of longitudinal survival analysis in primary neuron cultures allow us to investigate the effect of mutations causing Parkinson´s disease and inflammation and their relationship to neuronal survival.

2. *Who can apply? (eligibility criteria)*

Specific requirements:

The applicant must have experience in the use of experimental animals. Desired requirements include: background in neuroscience, experience in animal behavior, in flow cytometry, in cell culture, histological and molecular biology techniques.

5. Unraveling the pathogenesis of human multiple myeloma by integrative multi-OMICS and single-cell RNA-seq studies in transgenic mouse models

1. Research / Project Description *(Descripción de la línea de investigación al que se incorporaría el solicitante de la MCSA: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

Unraveling the pathogenesis of human multiple myeloma by integrative multi-OMICS and single-cell RNA-seq studies in transgenic mouse models

PI: Jose A. Martinez-Climent, MD, PhD
Hemato-Oncology Department, CIMA, University of Navarra, Pamplona (SPAIN)

Multiple myeloma (MM), a malignant plasma-cell disorder, evolves from a pre-malignant condition termed MGUS characterized by the progressive accumulation of clonal plasma cells in the bone marrow (BM). Studies to understand how pre-malignant MGUS transits into malignant MM may lead to develop preventive early-treatment approaches. However, because valid experimental models recapitulating MM development are lacking, a comprehensive analysis of the MGUS-MM transition has not yet been performed. The work of our group relies on the generation and characterization of experimental mouse models of B-cell malignancies (1-6). To model MM development in mice we conducted a cre-LoxP-based systematic screen by inducing the combination of eight gene mutations common in MM patients (i.e.: NF-κB, RAS, MAF) at different stages of B-cell differentiation. In mice carrying different mutant combinations, progressive BM disease classified as MGUS-like was observed, which eventually induced fatal MM, therefore recapitulating the nature history of human disease. In this multidisciplinary project, we will use these unique models to define how tumor-cell intrinsic features interact with BM immune cells to promote MGUS transition into MM. Within our Hemato-Oncology Department, high-throughput cellular and molecular analyses including single-cell RNAseq will be conducted both in mouse and patient samples. We will also evaluate in the mice responses to targeted drugs and immunotherapeutic agents that are in parallel being tested in clinical trials in MM patients. We expect this novel integrative research proposal will unveil the natural history and the biology underlying plasma cell tumor development, eventually contributing to accelerate the cure of MM.

References: 1) Beltran, PNAS 108, 12461-66 (2011); 2) Vicente-Duenas PNAS 109, 10534-39 (2012); 3) Sagardoy Blood 121, 4311-20 (2013); 4) Fresquet Blood 123, 4111-19 (2014); 5) Robles Nature Comm Jun 14;7:11889 (2016); 6) García-Barchino J Pathol 245, 61-73 (2018)

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2. Who can apply? (eligibility criteria)

Specific requirements:

- Strong publication record with at least 1 first-author article in D1
- Background in cellular and molecular biology, gene expression profiling, RNAseq, WES, or epigenomics will be an advantage
- Experience with mouse models of cancer and/or previous work experience in hematological malignancies and/or bio-informatics knowledge and interest will also be welcomed

6. Study of the epigenomes of multiple myeloma (MM), monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM)

1. *Research / Project Description (Descripción de la línea de investigación al que se incorporaría el solicitante de la MCSA: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

Multiple Myeloma (MM) is an incurable neoplasm preceded by pre-malignant stages termed monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). Although MM transformation has been relatively well characterized at the transcriptional and genetic level, its epigenome has only been partially characterized. In MGUS-MM, we have recently observed that DNA methylome was defined by a highly heterogeneous pattern globally characterized by regional DNA hypermethylation embedded in extensive hypomethylation. We also observed that MM acquired their malignant phenotype through widespread chromatin activation showing similarities with normal plasma cells. However, the epigenome of MGUS-SMM-MM transformation have not been studied so far. In this context, in this project we will study the epigenomes of MGUS, SMM and MM. We will analyze the DNA methylome and transcriptome together with a deep analysis of histone modifications with non-overlapping functions (H3K4me3, H3K4me1, H3K27ac) and the chromatin accessibility. Then, we will detect regulatory elements that become de novo (in)active in MM as a whole or in any of its clinical variants as compared to normal B cells. Based on the list of de novo (in)active regions (potential epigenetic drivers with oncogenic impact), the second objective of this proposal will be to select the top 500 candidates and perform a functional screening *in vitro* and *in vivo* using the CRISPR/Cas9 library and upon being challenged with chemotherapeutic agents and epigenetic drugs. This proposal will characterize the epigenome of MGUS-SMM-MM transformation, reveal novel regions with oncogenic potential and identify novel targets for treatment of these patients.

2. *Who can apply? (eligibility criteria)*

Specific requirements:

- Fundamental knowledge of Molecular Biology techniques.
- Knowledge about massive sequencing techniques.
- Knowledge about approaches based on CRISPR.
- Experience with programming languages (as R, Matlab, Python or Perl).
- Basic knowledge of data analysis of high-throughput experiments (RNA-seq, ChiP-seq, ATAC-seq).
- Fundamental knowledge of statistics.

7. Identifying transcriptional alterations in hematopoietic stem cells (HSCs) that guide the progression to clonal hematopoiesis and myelodysplastic syndromes (MDS)

1. *Research / Project Description (Descripción de la línea de investigación al que se incorporaría el solicitante de la MCSA: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

Clonal hematopoiesis and myelodysplastic syndromes (MDS) are hematological malignancies characterized by alterations in the differentiation of hematopoietic progenitor cells. These are age-related diseases that frequently occur in a successive fashion, and the mechanisms responsible for their pathogenesis and progression need further elucidation. Our hypothesis is that transcriptional alterations in the hematopoietic stem cell (HSC), already demonstrated in aging, continue to evolve through the evolution of these diseases contributing to progression. We aim to identify transcriptional alterations in HSCs that guide the progression to clonal hematopoiesis and MDS. To do so, we will characterize the transcriptome of HSCs in these entities, identify the regulatory mechanisms involved in the generation of aberrant transcriptomes, and finally, we will use genome editing to target candidate genes. This work may lead to the identification of aberrations with prognostic value for the progression of these diseases or that may represent novel therapeutic targets for the prevention or treatment of these patients.

2. *Who can apply? (eligibility criteria)*

Specific requirements:

- Molecular biology expertise
- Cell culture
- Experience in bioinformatic analysis

8. Therapeutic potential of induced cardiovascular progenitors in models of myocardial infarction

1. Research / Project Description

Heart disease remains one of the leading causes of mortality. Since there are not enough heart donors available for transplantation, in recent years new approaches have been explored, and most groups have been focused on the use of the stem cells. The success of cardiac cell therapy will be determined by the development of methods to improve engraftment and the generation of cells capable to regenerate the damaged tissue. The research of Dr. Xonia Carvajal-Vergara group is focused on the study of cardiovascular progenitors (CVP) obtained through cell reprogramming methodologies and the evaluation of their effectiveness in the treatment of infarcted hearts. The reprogramming towards induced pluripotent stem cells (iPSC) enable the generation of a variety of cells, including CVP. In this regard we demonstrated for the first time a cardiac disease modeling using iPSC-cardiomyocytes from LEOPARD syndrome patients. However the tumorigenic potential of iPSC is a handicap. We hypothesize that induced cardiovascular progenitors (iCVP) are the right population of cells for cardiac therapy since: iCVP are able to proliferate and produce all lineages of the heart; patient-specific iCVP could be obtained using a direct, low cost and short (weeks) process; and iCVP derivatives would be likely to couple electromechanically. The postdoctoral candidate will develop some of the main objetives pursued in a groundbreaking project entitled “Therapeutic potential of induced cardiovascular progenitors in models of myocardial infarction”, funded by the Ministry of Economy and Competitiveness (SAF2016-79398-R), which include: 1) to establish a direct reprogramming strategy to obtain human CVP; 2) to demonstrate the potential of iCVP to contribute to cardiac regeneration in models of myocardial infarction.

2. Who can apply? (eligibility criteria)

Specific requirements:
Degree: Doctor in Biomedicine, Genetics, Biochemistry or related areas. Degree in Biochemistry, Biology or Biotechnology.
Experience:

- Scientific trajectory and quality accredited by publications, presentations to congresses, participation in research projects, etc.
- Cell biology techniques (cell culture, transfection and infection, flow cytometry, immunohistochemistry, fluorescence microscopy) and molecular techniques (WB, conventional and quantitative PCR, cloning and genetic engineering techniques).

The following aspects will be valued and desirable: 1) previous experience in the reprogramming field; 2) high level of oral and written English; 3) leadership and ability to work in group.

9. Understanding the healing process that develops after myocardial infarction (MI)

1. *Research / Project Description (Descripción de la línea de investigación al que se incorporaría el solicitante de la MCSA: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

Myocardial infarction (MI) is one of the main causes of mortality and morbidity in developed countries. Medical advances have improved the survival and prognosis of patients with MI, nonetheless mortality remains as high as 13% and the 5-year mortality for patients with heart failure remains as high as 50%. After heart attack, dead cardiac tissue is replaced by a healing scar, which initially preserves the integrity of the cardiac wall but finally maturates into a disabling fibrotic scar, leading to chronic pathology. This derives in a further decrease in heart function which eventually can lead to end-stage heart failure. Current clinical solutions to this problem, beyond heart transplant, are different strategies to reverse the maturation process or manipulate the disabling scar, without any success until now.

Our line of work focuses on understanding the healing process that develops after MI, analyzing the molecular mechanisms that regulate the activation and differentiation of the cardiac fibroblast populations. This will allow us to identify new targets involved in the process of cardiac fibrosis on which to act in a therapeutic way. Furthermore, we will develop innovative treatment approaches based on the production of adeno-associated vectors and nanoparticles that will allow localized and specific targets to be modulated, thus achieving effective and long-lasting treatment.

The results obtained from these studies will be of great relevance not only for better understanding the mechanisms of fibrosis in the heart but also to develop these novel therapeutic strategies that if successful could be translated in the future to the clinic.

2. *Who can apply? (eligibility criteria)*

Specific requirements:

Solid experience in molecular and cellular biology and animal manipulation

Good organizational, communication and interpersonal skills

10. Characterization of epigenetic and co-transcriptional events dysregulated during progression from non-alcoholic fatty liver disease (NAFLD) to HCC

1. *Research / Project Description (Descripción de la línea de investigación al que se incorporaría el solicitante de la MCSA: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

Non-alcoholic fatty liver disease (NAFLD) affects 30-40% of the adult population, and its prevalence is much higher in obese individuals. NAFLD patients are at risk of progressing towards more advanced stages of the disease, which include liver cirrhosis and the development of hepatocellular carcinoma (HCC), a leading cause of cancer-related death worldwide. In the next few years NAFLD will be the first cause of liver transplantation in USA. The mechanisms underlying NAFLD progression are not completely understood, and this knowledge is fundamental for the development of effective diagnostic and therapeutic strategies. In this project, we propose to evaluate fundamental genetic mechanisms involved in the regulation of hepatocellular function in the face of dietary challenges. More specifically, and based on our preliminary observations, we will characterize epigenetic and co-transcriptional events dysregulated during NAFLD progression to HCC. We will study the impact of these alterations in the pathogenesis of the disease and the therapeutic potential of their molecular targeting.

2. *Who can apply? (eligibility criteria)*

Specific requirements:

The ideal candidate should have experience in (liver) metabolism. Experience in animal models of metabolic liver disease and molecular biology is also desirable.

11. Oncolytic virotherapy as an alternative therapeutic option for patients with lung cancer

1. Research / Project Description *(Descripción de la línea de investigación al que se incorporaría el solicitante de la MCSA: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

Oncolytic virotherapy as an alternative therapeutic option for patients with lung cancer

The promising results of therapies targeting immune-checkpoints have initiated a new era in the lung cancer treatment. However, this neoplasia is still the leading cause of cancer-related death worldwide, and combined therapies are being evaluated to reduce lung cancer mortality. Oncolytic adenoviruses, engineered to replicate in and selectively destroy tumor cells, represent a promising therapeutic strategy that could improve the outcome of lung cancer patients. Clinical trials with oncolytic virus have demonstrated survival benefits in glioblastoma patients, but no studies have been performed in lung cancer patients yet. Furthermore, the oncolytic effect of the virus may have a dual effect; killing tumor cells and inducing systemic anti-tumour immunity. In preliminary results, we have demonstrated that adenoviral treatment significantly reduces tumor growth in syngeneic models of squamous lung carcinoma of the cells. **We hypothesize that oncolytic virotherapy may have antitumor effect in lung cancer, generating efficient and safe tumor responses. The oncolytic capability of adenovirus, together with co-stimulatory ligands that activate the tumor infiltrating lymphocytes, may boost the patient´s immune system, significantly improving the effect of immune-checkpoint blockade strategies.**
The candidate will join the Program in Solid Tumors of CIMA, under the supervision of Dr Jackeline Agorreta and Dr Marta Alonso. Preclinical “in vitro” and “in vivo” models of lung cancer will be used to evaluate the efficacy of oncolytic virotherapy and its combination with immune-checkpoint inhibitors.

2. Who can apply? (eligibility criteria)

Specific requirements:

The successful candidate is expected to develop, deliver and manage a focused program of research that uses a range of techniques including molecular techniques and animal model development. Training in imaging and histological techniques as well as previous postdoc experience will add value to the candidate. The project includes the design, execution and reporting of his/her own experiments, contributing to the future research directions of the host group, and, when appropriate, the introduction and development of new systems, methods and technologies in pursuit of the scientific goals of the program. Apart from the necessary technical and scientific skills we are looking for candidates who are highly committed to develop the assigned project with independence and initiative, who are able to communicate ideas and results effectively, who are good at team work and are able to collaborate with different colleagues with mixed backgrounds and expertises.

12. Optimization of epigenetic inhibitors having promising biological activity. LC-MS/MS bioanalysis and Pharmacokinetic profiling of advanced compounds

1. *Research / Project Description (Descripción de la línea de investigación al que se incorporaría el solicitante de la MCSA: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

The post-doc will be responsible for all LC-MS/MS bioanalysis carried out at the Small Molecule Drug Discovery platform at CIMA. For the different projects, this involves:

- Pharmacokinetic profiling of advanced compounds from different projects in mouse models, using WinNonlin software.
- LC-MS/MS analysis of compounds in different matrices: cell culture media and biological samples (plasma, cerebrospinal fluid, tumor samples, different tissues and organs). Set up of the analytical and quantitation methods.
- Permeability studies (PAMPA)
- Plasma or brain protein binding studies
- Drug stability studies
- Quality control (purity determination) of compounds

Currently, our lab is strongly focused on the development of epigenetic therapies as an alternative to standard oncological treatments and other diseases.

We recently reported the discovery of a novel compound (CM-272) as a first-in-class inhibitor targeting the G9a and DNMTs methyltransferase activity with nanomolar potency (Nat. Commun. 2017; doi: 10.1038/ncomms15424). CM-272 significatly prolongs survival of acute myeloid leukaemia, acute lymphoblastic leukaemia and diffuse large B-cell lymphoma xenogeneic models. The in vivo efficacy of CM-272 in alternative cancers (e.g. solid tumors) is currently being investigaged, alone or in combination with other chemotherapeutic agents. In this regard, the candidate would support the design of in vivo efficacy experiments.

We are developing a second generation of epigenetic inhibitors (undisclosed target), having promising biological activity. The optimization of these compounds is on-going and the candidate will participate in all aspects concerning LC-MS/MS bioanalysis and will be integrated in the decision work-flow to progress compound candidates for in vivo efficacy testing.

2. *Who can apply? (eligibility criteria)*

Specific requirements:

- Ph.D. in Bioanalysis, Pharmacokinetics, Analytical Chemistry, Pharmacology, Drug Metabolism or related fields
- Experience in LC-MS/MS quantitative analysis
- Highly proactive, with ability to work independently and eager to learn
- Experience in sample preparation for bioanalysis is desirable
- Experience in developing in vitro ADME studies is desirable
- Experience with data analysis software (WinNonlin) is desirable
- Experience in drug discovery process is an advantage

13. Functional, molecular and clinical implications of cell and non-cell autonomous mechanisms regulated by novel synthetic-lethal interactions with RAS in lung cancer.

1. *Research / Project Description (Descripción de la línea de investigación al que se incorporaría el solicitante: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

The Oncogenes and Effector Targets lab is interested in understanding the cellular and molecular mechanisms driving oncogenesis and therapy resistance of lung and pancreatic tumors harboring mutations in RAS, the most prevalently mutated oncogene in human cancer. To do this, we recently implemented an integrative approach to unveil a pan-cancer RAS gene signature critically convergent and necessary for tumor homeostasis. This pan-cancer signature has been queried to identify novel pharmacological approaches based on drug repurposing strategies. Additionally, we have generated multiple *in vitro* and *in vivo* models, including genetically-engineered mouse models (GEMMs), to test the functional relevance of the RAS signature genes as well as of novel combinatorial strategies built upon targeted agents or immunotherapy (Vallejo et al, Nat. Comms, 2017; Ajona et al, Cancer Discov, 2017).

A current line of research aims to dissect the functional, molecular and clinical implications of cell and non-cell autonomous mechanisms regulated by novel synthetic-lethal interactions with RAS in lung cancer. The project will:
1) characterize the role of RAS dependencies on tumor cells and tumor microenvironment through loss-of-function experiments (via CRISPR strategies) in homotypic and heterotypic models *in vitro* (2D and 3D) and *in vivo* (patient-derived xenografts, allografts of murine cells and GEMMs).
2) identify the molecular network regulated by these genes through co-immunoprecipitation, co-immunolocalization, immunoblotting, semi-quantitative mass-spec and RNA-seq approaches.
3) determine their translational-clinical value through analysis of several patient cohorts as well as its functional significance as disease biomarkers and/or molecular targets in lung cancer GEMMs and patients.

2. *Who can apply? (eligibility criteria)*

Specific requirements the candidate should have:
• at least one first-author publication in respected journals.
• practical skills *in vitro* with cancer cells and modulating gene expression via iRNA/CRISPR.
• experience with *in vivo* cancer models, primary cell culture and FACS would be advantageous.
• expertise in statistical and computational approaches for analysis of large datasets would be a plus.
• a desire to work in a collaborative environment.
• flexibility to collaborate in other projects.
• competence to communicate in English or Spanish.

14. Development of novel gene therapy strategies for inherited diseases based on recombinant AAV vectors

1. *Research / Project Description (Descripción de la línea de investigación al que se incorporaría el solicitante de la MCSA: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

We are looking for a self-motivated and dedicated individual with interests in gene therapy, molecular biology, and immunology for a project involving the development of novel gene therapy strategies for inherited diseases based on recombinant AAV vectors. Strategies to increase vector transduction efficiency in human cells, organ targeting and modulation of the immune response will be explored.
Overall responsibilities include: helping to plan, design, execute, trouble-shoot, and interpret experiments aimed at generating novel gene therapy reagents, virus production and testing the efficacy of gene therapy reagents in cell culture or mouse models; follow detailed experimental protocols, make observations, record data and present results; assist others in the laboratory, and help maintain a constructive laboratory environment.

2. *Who can apply? (eligibility criteria)*

Specific requirements:

The ideal candidate will have experience in the techniques we use regularly including molecular biology, vector production, transcriptome profiling, confocal microscopy, immunohistochemical techniques, in situ hybridization, and work in mouse models.
The applicant should have a good publication record in terms of papers in peer-reviewed journals and other relevant international publication channels.

Good communication, organization, interpersonal and creative thinking skills are a must**.**

15. Role of lung stem cells in the development of pulmonary fibrosis

1. *Research / Project Description (Descripción de la línea de investigación al que se incorporaría el solicitante de la MCSA: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

Idiopathic pulmonary fibrosis (IPF) is a progressive chronic lung disease with a median survival of 2.5-3.5 years. Currently, there is no treatment for this disease due to the limited insight into its pathophysiological mechanisms. IPF is characterized as every fibrotic process in other organs by an excess of ECM deposition that results in scar tissue causing the distortion of the lung architecture that compromises its normal function of gas exchange. In addition, there is cell death of epithelial and endothelial cells, vascular leakage, an unbalanced inflammatory response and an abnormal epithelial repair. Although the cause of IPF remains unknown, it is becoming clear that important clues lie in the complex crosstalk between the alveolar epithelium, that includes a population of stem cells, and the neighboring mesenchyme.

Our research seeks to study the role of lung stem cells in the development of pulmonary fibrosis. We aim to understand the contribution of the different lung stem/progenitor cell populations to the initiation of the inflammatory response and fibrogenesis that lead to the development of pulmonary fibrosis. Also, we aim to unravel the molecular mechanisms involved in this pathogenesis exploring the role of the Notch pathway as a mediator of the above mentioned cellular interactions. Taking advantage of lineage tracing techniques, cell ablation models and genetic signaling pathway modulation, the proposed study will provide a better understanding of the pathophysiology of lung fibrosis that may result in the development of effective therapies for IPF.

2. *Who can apply? (eligibility criteria)*

Specific requirements:

We are looking for a highly motivated postdoctoral scientist with an interest in stem cell biology and lung regeneration. We look for a candidate with proficiency laboratory research experience particularly in stem cell biology and development, molecular biology and imaging. The candidate is expected to work with mouse models of pulmonary fibrosis so experience in mouse genetics and in vivo models of injury is required. The position will require independent work at the laboratory as well as extensive ability to analyze, interpret and present results.

16. Study of signaling, transcriptional and epigenetics of potential pluripotent stem cells to create new the chimeras

1. *Research / Project Description (Descripción de la línea de investigación al que se incorporaría el solicitante de la MCSA: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

Our research line aims to generate inter-specific organs using the blastocyst complementation approach, with special focus on the cardiovascular system. Blastocyst complementation is a technique based on the microinjection of pluripotent stem cells in a genetically modified preimplantational embryo incapable to form a certain cell type/organ, allowing the generation of these cell type/organ from the exogenous pluripotent stem cells. Empirically, it has been demonstrated that certain mouse ES cell lines give higher levels of chimerism than others, and that mouse ES cells give higher levels of chimerism than rat or human ES/iPS cells injected into a mouse embryo. Nevertheless, little is known about the mechanisms that allow the exogenous cells to form a chimera and how these mechanisms can be potentiated to improve chimerism, especially in the generation of inter-specific chimera. The project that we offer for a post-doc applicant will be focused on the study of cell signaling, transcriptional networks and epigenetics regulating the chimerism potential of pluripotent stem cells of different species like mouse, rat and human, using different –omic technologies.

2. *Who can apply? (eligibility criteria)*

Specific requirements:
Qualified candidates with a strong background in stem cell biology, epigenetics, telomeres, molecular cell biology or computational biology (‘omics’) are encouraged to apply. The postdoc fellow is expected to have strong work ethic and commitment, critical thinking abilities, and excellent organization and communication skills.

17. Development of a non-genotoxic conditioning method for new treatments in Ataxia Telangiectasia (AT).

1. *Research / Project Description (Descripción de la línea de investigación al que se incorporaría el solicitante de la MCSA: objetivos perseguidos, impacto deseado, etc). MÁX: 1.800 caracteres (espacios incluidos)*

Hematopoietic stem cell transplantation (HSCT) can **alleviate the hematopoietic-associated alterations that occur in Ataxia Telangiectasia (AT)**. Nonetheless, HSCT is rarely used because allogeneic transplantation is fraught with life-threatening complications. The highly efficient new gene editing technologies in combination with autologous HSCT may constitute a curative alternative for AT patients. Autologous HSCT circumvent the risk of graft versus host disease but the **genotoxicity of conditioning regimens** remains a significant obstacle to the implementation of this approach. Current conditioning approaches depend on irradiation or its combination with chemotherapy. These methods are particularly undesirable in AT patients that have a defective DNA repair system. Hence to fully realize the **curative potential of HSCT in AT**, **the development of a non-genotoxic conditioning method that avoids undesirable toxicity is essential**. Towards this goal, we propose to explore the use of internalizing immunotoxins that specifically target the HSC compartment to efficiently condition immunocompetent mice for HSCT. We will evaluate the toxicities associated with the use of immunotoxins and compare them with classic conditioning approaches. We will demonstrate disease correction in an Ataxia Telangiectasia mouse model using gene therapy corrected HSCs and immunotoxin based conditioning. Lastly, we will describe novel targets in human HSCs by means of Cell SELEX and will validate their use as targets for specific immunotoxins and aptamers for HSCT conditioning in humanized mouse models. Upon completion of the project, **we expect to have in hand a novel immunotoxin ready for patenting, commercialization and/or clinical investigation**.

2. *Who can apply? (eligibility criteria)*

Specific requirements:

We are seeking for a creative, ambitious and highly motivated candidate for a fully supported postdoctoral fellowship to join the Hematopoietic Stem Cell and Bone Marrow Niche Lab headed by Dr. Borja Saez at CIMA.

The candidate will join a highly collaborative environment and is expected to lead a project aimed at understanding the process of hematopoietic stem cell engraftment upon transplantation and the development of safe conditioning regimens that may help expand the use of BMT to monogenic diseases of the blood.

Successful candidates will have a Ph.D. or M.D. degree, a strong background in hematopoietic stem cell biology and expertise in molecular and cellular biology, gene editing and/or flow cytometry. Experience with animal models is not essential but would be preferred.

The candidate must demonstrate an excellent writing and verbal communication skills in English, good organizational and communication skills and the ability to work independently (managing the project, supervise students, manuscript writing etc.).

Applicants must provide a cover letter explaining interest in this position, an up-to-date CV and a list of three references to Dr. Borja Saez (bsaezoch@unav.es).