CIC bioGUNE
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"la Caixa" Foundation

INCOMING Doctoral *INPhINIT* Fellowship Program 2023

CIC bioGUNE, member of the Basque Research and Technology Alliance (BRTA), is a key research center within the national and international scientific landscape and has emerged as a knowledge source in the area of health science. The cutting-edge scientific activity of CIC bioGUNE researchers explores the interface between **Chemistry, Structural, Molecular and Cell Biology**, with the aim of developing a more **Precise Medicine** for the future. Two **Research Programmes**, "*Molecular Recognition and Host-Pathogen Interactions*" and "*Metabolism and Cell Signaling in Disease*", are made up of more than a hundred scientists and technicians who concentrate on the molecular bases and mechanisms of disease to create new diagnostic methods and promote development of advanced therapies.

PhD open positions offered at CIC bioGUNE:

- Characterization of metastatic prostate cancer immune microenvironment to rationalize combinatorial therapy (Dr. Arkaitz Carracedo/Dr. Marco Piva)

- Characterization of new cellular (CRISPR/cas9) and animal study models in hereditary Tyrosinemia Type I. Development of pharmacological chaperones as a therapeutic strategy (Dr. Óscar Millet)

- Deciphering the structure of emerging viral threats to improve human and animal welfare (Dr. Nicola GA Abrescia)

- EMOTIONAL (ThE Role of impaired Magnesium hOmeosTasis In hepatOcellular carciNomA biology) (Dr. Malu Martínez Chantar)

- Study of the molecular mechanisms involved in the spontaneous misfolding of prion protein / Predoctoral position at Prion biology laboratory at CIC bioGUNE (Dr. Joaquín Castilla)

- Study of the molecular networks implicated in breast cancer resistance to therapy (Dr. María dM Vivanco)

- Targets identification of E3 ubiquitin ligases involved in rare diseases (Dr. Rosa Barrio)

For more information about **requirements for applicants**, please follow this link.

If you are **interested in applying** for it or need **further information**, please contact:

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Characterization of metastatic prostate cancer immune microenvironment to rationalize combinatorial therapy

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Life Sciences: Human Biology, Microbiology, Molecular Biology, Genetics, Cellular Biology, Genomics and Proteomics, Biochemistry

Prostate cancer (PCa) is the most commonly diagnosed cancer in men, representing one of the leading causes of cancer-related death worldwide. Although patients with localized disease are typically treated with definitive therapy, metastasis predominantly rises after the acquisition of resistance. Furthermore, treatment-naïve metastatic PCa, encompassing a tumor type that is metastatic at the time of first diagnosis, represent 9-20% of prostate cancer patients in Europe, but are responsible for more than 50% of lethal PCa. In the last two decades the clinical options to treat different cancers have grown exponentially, mainly due to introduction of immune checkpoint blockade (ICB) treatments and the specific signaling pathway inhibitors. However, these types of treatment have shown very limited clinical benefits against metastatic PCa and It is worth noting that little attention has been put into the applicability of these treatments in the context of treatment-naïve metastatic PCa. We will take advantage of genetic engineered mouse models that spontaneously develop metastatic PCa and using the most cutting-edge technologies characterize at the single cell level molecular alterations in tumor cells and in the tumor microenvironment involved in cancer progression and metastasis. We aim to dissect the contribution of cell signaling pathways and immune cell populations to the acquisition of an aggressive phenotype. This unprecedent view will set the basis to rationalize combinatorial treatments using targeted therapies and ICB in metastatic PCa that will be tested in pre-clinical setting.

This predoctoral position is focused on understanding of the role of immune suppressive tumor microenvironments mechanisms during prostate cancer progression. Multi-omics characterization of in vitro and in vivo models of metastatic prostate cancer with different degrees of aggressiveness will be used to identify candidates for functional characterization and pre-clinical studies. Moreover, clinical samples will be characterized to validate findings rom model systems in human disease. The project will involve a laboratory-based technics including mammalian tissue culture, FACS analysis, viral transduction, immune-blotting and others molecular and cell biology methods. This study will involve also working with mice, including orthotopic tumor formation, tumor growth and treatment response evaluation, metastatic capacity assay.

Arkaitz Carracedo | CIC bioGUNE | Center for Cooperative Research in Biosciences

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Characterization of new cellular (CRISPR/cas9) and animal study models in hereditary Tyrosinemia Type I. Development of pharmacological chaperones as a therapeutic strategy

Dr. Óscar Millet
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Life Sciences: Human Biology, Microbiology, Molecular Biology, Genetics, Cellular Biology, Genomics and Proteomics, Biochemistry

Hereditary Tyrosinemia Type I (HT1) is a rare disease that is inherited in an autosomal recessive manner. Its appearance is due to a deficiency in Fumarylacetoacetate Hydrolase (FAH), which catalyzes the last reaction of the Tyrosine degradation pathway. The inability to complete Tyrosine catabolism leads to the accumulation of toxic metabolic intermediates and by-products, such as Fumarylacetoacetate (FAA) and Succinylacetone (SA). This accumulation ultimately causes Hepatocellular Carcinoma and Renal Tubular Dysfunction, so that if the disease is not treated in time, it can lead to death before 2 years of age. At the molecular level, FAH is a homodimeric cytosolic protein made up of 2 subunits of 46 kDa each. Around 100 FAH mutations associated with HT1 have been described, most of which are of the missense type and are located in the C-terminal domain. Recently, our research group showed that only the dimeric species of FAH is active, while the monomeric species is unstable and tends to aggregate. This same study demonstrated that many of the previously mentioned missense mutations hinder FAH dimerization through structural destabilization. Pharmacological chaperones (PCs) constitute an attractive therapeutic approach for the treatment of HT1 patients whose mutations correspond to the group of those that affect the structural stability of FAH.

The hypothesis of this project is that FAH instability due to mutations that affect its dimerization can be corrected by pharmacological chaperones (PCs) that favour its dimeric and functional state. The objectives of the work are the following:1) Rational search for chemical compounds whose interaction with FAH favours the active dimeric state of the protein. 2) Characterization of the binding mechanism of the compounds that act as PCs of FAH. 3) Development of a cellular model of HT1 that serves as a validation system for in vitro results. 4) In vitro reconstitution of the Tyrosine degradation pathway. 5) Characterization of an animal model of HT1 carrying a missense mutation.

The methodology planned for this project includes recombinant protein expression and purification techniques. The purified proteins will be used for *in vitro* enzyme assays and their biophysical characterization by Nuclear Magnetic Resonance (NMR). On the other hand, cell cultures will be used using the CRISPR/Cas9 gene editing methodology, to obtain a cellular model of HT1. Finally, it is planned to carry out different experiments for the *in vivo* characterization of the effect of the FAH G337S mutation, which has been previously identified *in vitro* as one of those responsible for the structural destabilization of the active dimer, in a mouse model.

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Deciphering the structure of emerging viral threats to improve human and animal welfare

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Life Sciences: Human Biology, Microbiology, Molecular Biology, Genetics, Cellular Biology, Genomics and Proteomics, Biochemistry

If there is one thing that the past three years has shown us, is that ongoing, active research in virology and immunology is paramount. Readiness for action when such pandemic events occur rely on years of basic knowledge accumulated in time and constant technological development.

With the current climate change, global human transportation and livestock trading, combating viral infection in humans and animals cannot be underestimated. Strictly related to the human food-chain, to the agricultural activities of small, medium and large size farms, animal welfare represents a continuous challenge in both poor and rich countries. Indeed a great amount of emerging diseases have an animal origin; in a study of 1415 pathogens known to affect humans, 61% were zoonotic and in several cases animal and human diseases may become interconnected. We target Schmallenberg virus (SBV), an enveloped and pleomorphic virus infecting livestock, a member of the Peribunyaviridae family, and transmitted by midges. SBV, first identified in EU in 2011, serves us as a model system for studying Peribunyaviruses, which is one of the largest virus family on earth.

The goal of the proposal is to determine the molecular organization and structure of the glycoproteins composing the SBV virion using state-of-the-art cryo-electron tomography. The results gathered will ultimately serve to impact on our society providing a ONE HEALTH approach to societal challenges enabling the development of new therapeutic strategies.

The Structure and Cell Biology of Viruses Lab is seeking an outstanding scholar interested in infectious viral disease and state-of-the art structural imaging techniques. The Candidate will help drive this globally focused research by resolving the organization and the three-dimensional structure of the glycoproteins decorating the Schmallenberg virus envelope by cryo-electron tomography (cryo-ET) technique. The primary responsibility of this position will be to lead a structure-function project firmly based on the current power of cryo-electron microscopy and sub-tomogram averaging techniques. Among the requested activities, the Candidate will acquire skills in virus production and purification, cryo-ET data collection strategies, conduct data processing and analysis, and interpret results. The role of the Candidate will require reliability, adaptability, and flexibility in the scope of duties and responsibilities. The perspective PhD student must have a degree in fields related to biotechnology, biology, physics, or structural virology.

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EMOTIONAL (ThE Role of impaired Magnesium hOmeosTasis In hepatOcellular carciNomA biology)

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Life Sciences: Human Biology, Microbiology, Molecular Biology, Genetics, Cellular Biology, Genomics and Proteomics, Biochemistry

Perturbations in the homeostasis of several micronutrients are recognized as major cause for many diseases, including hepatocellular carcinoma (HCC), which constitutes a worldwide medical problem due to the late diagnosis and poor response to available pharmacotherapy. To date, several drugs are destined for HCC treatment, among which inhibitors of tyrosine kinase receptors (TKIs), mainly sorafenib and regorafenib, are at the first and second line of treatment, respectively. Besides, novel immune-enhancing therapies, in which treatment acting on PD-1 is the most advanced approach at clinical trials, in combination with TKIs are being evaluated. A better understanding of HCC biology is mandatory to improve treatment and prognosis.

Aim: To elucidate the role of the magnesium transporter "cyclin and CBS domain divalent metal cation transport mediator 1" (gene symbol *CNNM1*) in HCC biology and explore the usefulness of modulating magnesium content in cancer cells by pharmacological manipulation as a novel strategy to inhibit HCC development. *In vitro* and *in vivo* studies will be performed to substantiate the involvement of CNNM1 in the control of the epithelial-mesenchymal transition, metabolic rewiring, the defense of HCC against the host immune system and the activity of the resistome involved in the strong multidrug resistance phenotype of this tumor.

To reach this aim, the candidate will be involved in determine: **1)** In vitro characterization of the contribution of CNNM1 and Mg2+ homeostasis to tumor development, angiogenesis, metabolic fingerprint and epithelial-mesenchymal transition; **2)** Identification of the transcription factor that modulates CNNM1 expression in liver tumors associated with the epithelial-mesenchymal transition; **3)** Identification of the impact on the resistome of CNNM1-dependent magnesium perturbation; **4)** Development and in vitro evaluation of novel strategies to manipulate HCC biology by acting through CNNM1-mediated Mg2+ homeostasis; **5)** In vivo characterization of the contribution of CNNM1 and Mg2+ homeostasis to tumor development. Metabolic perturbation, immune system modulation and epithelial-mesenchymal transition; **6)** Evaluation in HCC biopsies of the relationship between CNNM1 expression and clinical characteristics of malignancy in HCC.

During her/his thesis, the candidate will gain extensive knowledge of cancer biology, metabolism, and bioinformatics, as well as the opportunity to complete training internships in other national and international laboratories.

Malu Martínez-Chantar | CIC bioGUNE | Center for Cooperative Research in Biosciences

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Study of the molecular mechanisms involved in the spontaneous misfolding of prion protein / Predoctoral position at Prion biology laboratory at CIC bioGUNE

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Life Sciences: Human Biology, Microbiology, Molecular Biology, Genetics, Cellular Biology, Genomics and Proteomics, Biochemistry

Prion diseases belong to a group of fatal neurodegenerative disorders that affect humans and animals and for which no therapy is available. They are characterized by an extreme variability in their clinical presentation, neuropathological patterns and the existence of molecular subtypes. The diseases of sporadic origin seem to imply the spontaneous misfolding of prion protein that results in a great diversity of prion strains, which show differential biological and physicochemical properties. To decipher what factors determine this misfolding and therefore the pathogenesis, in-depth knowledge of these spontaneous processes as well as the decrypting of the three-dimensional structure of the infectious protein are required, for what in vitro prion propagation methods are necessary. The main objective of this project is to understand the role of the biological and physicochemical factors that are involved in the spontaneous protein misfolding and the way in which they favor the generation of structural diversity.

The candidate will have the opportunity to do short stays out of his laboratory thanks to more than 20 international collaborations that Castilla's group has opened. His group is the leading expert in a unique technique able to replicate prions in vitro, what allows him to establish fruitful collaborations with laboratories all over the world.

The selected candidate will use a wide variety of prion protein species and polymorphisms in combination with different biological, chemical and physicochemical cofactors that will allow us to study which molecular elements are responsible for this phenomenon. For that, the candidate will be trained on molecular biology for protein variant generation, recombinant protein production and purification and on distinct amyloid propagation in vitro techniques, mainly focused on the new methodology developed. Through this methodology, the candidate will try to answer questions such as: 1) are there primary amino acid sequences that naturally favor or block the spontaneous infectious misfolding?, 2) is there an unlimited number of different misfoldings for the same amino acid sequence?, 3) can the variety of misfoldings generated spontaneously be modulated using chemical or physicochemical factors?, 4) what is the role of the transmission barrier in propagating the misfolding between different species?, and 5) what basic structure determines prion infectivity? The candidate will collaborate with several research groups to gain knowledge on different biophysical techniques, (i.e. FTIR, cryo-EM, CD). In addition, the candidate will obtain expertise on handling rodent models for transmissibility and infectivity studies and will be up to some degree trained on the identification of neurological signs and the histopathologic study of encephalon.

Joaquín Castilla | CIC bioGUNE | Center for Cooperative Research in Biosciences

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Study of the molecular networks implicated in breast cancer resistance to therapy

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Life Sciences: Human Biology, Microbiology, Molecular Biology, Genetics, Cellular Biology, Genomics and Proteomics, Biochemistry

The goal of the Cancer Heterogeneity Lab at CIC bioGUNE is to understand tumour heterogeneity from the perspective of uncovering novel biomarkers and therapeutics in the treatment of cancer, particularly breast cancer, but also in prostate and colorectal cancer. In recent years, much has been learnt about the roles of cancer stem cells (CSCs) in tumorigenesis, metastasis and resistance to conventional treatment (endocrine, chemotherapy and radiotherapy) in many tumour types, including breast cancer.

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women worldwide. We have previously shown that CSCs, and the Sox2-Sox9-Wnt axis in particular, are implicated in resistance to therapy and tumour recurrence. The PhD student will investigate the molecular networks that link these features in breast cancer resistance to therapy, identifying the mechanisms that contribute to increased risk of tumour progression, and the development as of resistance in patients. We anticipate that insights gained from this research will not only further our knowledge but also identify new biomarkers and potential therapies for cancer diagnosis and treatment.

The student will have the opportunity to develop and characterise three-dimensional human cell models derived from cell lines, patient tissue samples and patient-derived xenografts and use them in a variety of *in vitro* and *in vivo* assays. (S)he will use a variety of specialised techniques, including flow cytometry and cell-sorting, deep sequencing, gene reporter cells and *in ovo* tumour growth and metastasis assays. Scientific background in cellular biology is required. A basic knowledge of culture of mammalian cells would be useful. Additional training and support will be provided for specific techniques, as and when needed.

CIC bioGUNE brings together over 20 independent laboratories formed with a variety of scientists from different backgrounds, many of them from abroad, providing a stimulating and energetic environment for the training and scientific development of young investigators.
This is a pre-doctoral researcher position in the Cancer Heterogeneity Lab at CIC bioGUNE, situated close to Bilbao. Tasks (in addition to development of the research project as above) will further include attending, participating and presenting at lab meetings, journal clubs and seminars at CIC bioGUNE, as well as at appropriate conferences. Lab meetings and seminars are all in English, contributing to the international atmosphere in the lab.

María dM Vivanco | CIC bioGUNE | Center for Cooperative Research in Biosciences

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Targets identification of E3 ubiquitin ligases involved in rare diseases

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Life Sciences: Human Biology, Microbiology, Molecular Biology, Genetics, Cellular Biology, Genomics and Proteomics, Biochemistry

Protein homeostasis plays a determinant role in the regulation of animal developmental circuits, which are fine-tuned by posttranslational modification by members of the ubiquitin-like (UbL) family. Barrio Lab focuses on elucidating the roles of protein homeostasis driven by UbLs, i.e. SUMOylation, and on the diseases caused by homeostasis disruption, i.e. rare diseases such as ciliopathies. We use state-of-the-art technology in biochemistry, cellular and molecular biology and genetics, being experts in proteomics and molecular interactions, using cell culture, patient-derived samples and *Drosophila in vivo* model. We develop technology to analyse the consequences of the posttranslational modifications.

The group has great experience in training doctoral candidates and management of R&D projects. Drs Barrio and Sutherland are members of the MSc programme of the University of the Basque Country UPV/EHU, recognised with the Mention of Quality. Barrio is member the Training Committee at CIC bioGUNE and supervised 11 PhD and 11 MSc theses, 5 postdocs and numerous BSc students. Sutherland is Professor at the University of Deusto Medical degree and supervised 4 PhD and 6 MSc theses, 2 postdocs and numerous BSc students.

The candidate will develop a cutting-edge project in the field of biomedicine. Specifically, s/he will develop strategies to analyse the targets of E3 UbL ligases involved in rare diseases and with specific sub-cellular localization. This project will have high impact in the understanding of rare diseases and on the emerging technology of targeted protein degradation, where the cell degradation machinery mediated by ubiquitin is hijacked for the elimination of disease-causing proteins. The candidate will learn techniques of molecular biology (gene editing by CRISPR-Cas9, cloning), biochemistry (protein-protein interactions, immunoprecipitations, proximity proteomics), cell biology (cell culture, immunostainings, fluorescence and confocal microscopy), and genetics (model organisms). The candidate will find a collaborative and stimulating atmosphere in an international group that masters the state-of-the-art technologies required for the project.

The candidate will enrol the training programme at CIC bioGUNE where s/he will benefit of the advice of a tailored Training Advisory Committee. The candidate will benefit of the international contacts through the networks where the laboratory participates (i.e. ProteoCure COST Action, a European network on targeting proteolysis for proteome remodelling). The candidate will benefit from continuous education and training in scientific and soft skills, such are state-of-the-art technology, public presentations and scientific writing.

Rosa Barrio | CIC bioGUNE | Center for Cooperative Research in Biosciences

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