CIC bioGUNE
MEMBER OF BASQUE RESEARCH & TECHNOLOGY ALLIANCE

GOBIERNO DE ESPAÑA MINISTERIO DE CIENCIA E INNOVACIÓN

15 Doctoral Candidate Positions

CIC bioGUNE (www.cicbiogune.es) opens applications for Doctoral Candidates (DC). Fifteen FPI contracts, funded by the AEI (State Agency for Research, Spain) are open for applications from December 19th. The positions will hold 4 years contract, social security, and health insurance.

CIC bioGUNE is a research center in biosciences located in Bilbao (Spain), where fundamental research goes hand in hand with oriented and applied perspectives. It offers an international, multidisciplinary scientific environment, hosting over 200 researchers working on chemical biology, cancer, genomics, biophysics, immunology, and many more. CIC bioGUNE is also equipped with state-of-the-art facilities for metabolomics, proteomics, genomics, structural biology (CryoEM, X-Ray, 800 MHz and 1 GHz NMR, computing cluster), and animal facility.

CIC bioGUNE is recognized with the Severo Ochoa Excellence Accreditation (2023-2026).

We welcome applications from motivated young scientists who wish to get their PhD degree in an international scientific environment in one of our 19 laboratories, carrying out cutting-edge research in the frontiers between chemistry, biology, and biomedicine within a highly collaborative environment. More than 80 doctoral candidates are currently developing their PhD Thesis with us.

Candidates should hold a degree in Biology, Biochemistry, Biotechnology, Chemistry, Pharmacy, Medicine, or related topic. They should have completed their MsC degree at the time of incorporation (expected summer 2023).

Research topics for the applications include:

1.-Liver Diseases lab: https://www.cicbiogune.es/people/mlmartinez

The role of the magnesium transporter CNNM1 in hepatic cancer (HCC)
Based on available information and our preliminary data, we propose that impaired magnesium homeostasis is involved in determining several traits of malignancy that are characteristic of HCC, which accounts for the poor prognosis of this cancer. The general objective of this project is 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.

2.-Cancer Heterogeneity Lab: https://www.cicbiogune.es/people/mdmvivanco

Novel combination studies to deconstruct development of resistance to therapy
Breast cancer is the most frequently diagnosed cancer and still 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 Doctoral Candidate (DC) will investigate cancer cell signalling networks, their crosstalk with the tumour microenvironment and their impact on resistance to therapy and how these contribute to increased risk of tumour progression and the development 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 DC will develop and characterise three-dimensional human cell models derived from cell lines,

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patient tissue samples and patient-derived xenografts. (S)he will use a variety of specialised techniques, including flow cytometry and cell-sorting, deep sequencing, proteomics and in vitro and in vivo functional assays.

3 & 4.-Chemical Glycobiology lab (2 positions): https://www.cicbiogune.es/people/jjbarbero

Deciphering glycan-protein interactions. From Chemistry to Biomedicine.
The DCs will be involved in highly multidisciplinary projects at the international level to elucidate the role of glycan-protein interactions in cancer and infection-diseases by using a combined methodology that includes chemical synthesis, molecular recognition methods (NMR, biophysical techniques and computations) and biological protocols. Target systems will be galectins and siglecs, deeply involved in inflammation and cancer, and the Influenza hemagglutinin.

5.-Exosomes Lab: https://www.cicbiogune.es/people/jfalcon

Development of three-dimensional culture models for studying extracellular vesicle (EV) biology.
Research in Extracellular Vesicles (EVs) mainly employed isolation of vesicles from conventional, bi-dimensional (2D) cell culture conditions. However, it is well known that cells arranged in complex structures display more physiological features, becoming better models to study cell biology and cell-to-cell interactions. Different 3D cultures, such as organoids, spheroids, bioreactors, and functionalized biological scaffolds can be implemented, to study the cross-talk between parenchymal and matrix cells, in both physiological and pathological conditions. The PhD candidate will focus on the study of EVs as the main element in cell communication in 3D culture models, by biochemical, molecular and cellular biology applying also omics technologies. The goal of the project will be to develop more efficient diagnostics and therapeutics EV-based tools for early detection and targeted drug release of cancer, neurological and metabolic diseases.

6 & 7.-Computational Chemistry Lab (2 positions): https://www.cicbiogune.es/people/gjoses

Molecular recognition and host pathogen interactions.
The DCs will be involved in multidisciplinary highly collaborative projects in the interphase between Chemistry, Biology and Computation, devoted to the accurate simulation of chemical and biochemical phenomena, with strong emphasis on functional protein design, metalloenzyme engineering and site-selective bioconjugation and decaging with therapeutical applications.

8.-Inflammation & Macrophage Plasticity Lab: https://www.cicbiogune.es/people/janguita

The role of microbiota-derived metabolites in the generation of central trained immunity.
The Inflammation and Macrophage Plasticity lab studies immunological processes associated with infectious diseases and homeostasis. The project is focused on the identification of transcriptional traits associated with the development of central trained immune responses and the role played by microbiota and their associated metabolome. The successful candidate will be part of a multidisciplinary group with interests in general Microbiology, Immunology, Host defense mechanisms, and inflammatory processes associated with infection, as well as the maintenance of homeostatic conditions. We use extensive Biochemical, Molecular Biology, and multiomics technologies in a highly collaborative environment.

9.-Ubiquitin-likes and Development Lab: https://www.cicbiogune.es/people/rbarrio

Role of the ubiquitin protein family in rare diseases.
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.
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).

10&11.-Precision Medicine & Metabolism Lab (2 DCs): www.cicbiogune.es/people/omillet

10.- Development of new biosensing tools for continuous, real-time measurement of drugs, biomarkers and metabolites.
Biosensors have the potential to radically transform our healthcare system. By providing cheap and easy to use measurement tools, biosensors will enable the deployment of fully personalized medicine in our daily life, empowering patients to make more informed decisions on their health. Pursuing this vision, our goal is to develop new biosensing technologies capable of performing real-time, continuous, in vivo measurements, and that are universally applicable to the detection of many different molecules. To achieve this, our lab combines biochemistry, biophysics, and analytical chemistry. In particular, the DC will be involved in a project to develop new biological receptors, and then implement them in electrochemical signaling devices to measure important drugs, hormones, and biomarkers. The project will cover all stages of biosensor development, so that the DC will acquire skills in biomolecular engineering, biophysical characterization of biomolecular receptors, sensor manufacturing, and in vivo studies.

11.- Quantitative analysis of metabolism using ^{31}P-NMR spectroscopy. Applications to NAFLD and tyrosinemia type I.
The DC will be involved in a project to develop a set of techniques, based on Nuclear Magnetic Resonance spectroscopy (NMR), to simultaneously measure, in a specific and quantitative way, the concentration of dozens of phosphorylated metabolites and integrate these data into a topological network of the metabolism; that is, a graphic representation that, in a visual, quantitative and precise way, answers the question of what alterations in metabolism occur in response to a logical physio (patho) change or to a specific treatment. This approach represents an alternative to a holistic (but complex) view of metabolism and is based on the fact that much of the logic behind the metabolic pathways that constitute metabolism and their cross-linking can be understood by focusing on the set of phosphorylated metabolites, or phosphorome. The project will cover all stages of methodology development, data analysis using AI algorithms and application to different animal models of disease of NAFLD and tyrosinemia type I.

12.-Prion Diseases Lab: https://www.cicbiogune.es/people/jcastilla

Development of a gene-therapy based approach for the treatment of Transmissible spongiform encephalopathies.

Transmissible spongiform encephalopathies (TSE) or prion diseases are a group of rapidly progressing and invariably fatal neurodegenerative disorders affecting humans among other mammals and for which no treatment is available. The DC will be immersed in a project to develop a therapy for these disorders based on the discovery of PrP^C variants that, due to their amino acid sequence, are unable to misfold into the prion isoform and additionally, can block the misfolding of susceptible PrP^C variants, acting as dominant negative (DN) proteins delaying or even stopping disease progression. To introduce these DN-PrP^C variants in the brain, where they need to be expressed in sufficient amounts during long periods to exert their inhibitory effect, a gene therapy approach will be developed. For that, adeno-associated virus (AAV) engineered to cross the blood brain barrier will be employed, carrying the genetic construct necessary for DN-PrP^C expression, in collaboration with a research group from CIMA, Pamplona. Throughout the project, distinct AAVs and DN-PrP^C will be tested in cell and animal models, with experts from NEIKER and CReSA-IRTA, to assess their efficacy and the best administration ways and dosages among other pre-clinical parameters (joint effort with clinicians from Bioaraba), necessary for the development of a future therapy for human prion diseases.

13.-Cancer Cell Signalling and Metabolism Lab: https://www.cicbiogune.es/people/acarracedo

Cancer Cell Signalling and Metabolism

Prostate cancer is among the most prevalent tumor types. Despite the effectiveness of first line treatments, disease recurrence affects a considerable number of men, and this tumor type still represents an important fraction of cancer-related mortality. The identification of molecular alterations the drive, sustain and nurture prostate cancer is a source of new strategies for disease prevention, diagnosis and treatment. This proposal will focus on the mechanistic study of molecular processes relevant to prostate cancer, encompassing the use of computational biology, molecular and cellular biology, mouse modelling and the analysis of human prostate cancer data and specimens. Our overarching goal is to generate high quality evidence around the molecular alterations that emerge during pathogenesis and progression of the disease, so that this valuable knowledge can fuel the future of innovative prostate cancer management. The Carracedo lab is structured as a multidisciplinary group of scientist, with an environment that favors critical thinking, creative research, teamwork and high quality training in cancer research.

14.-Structural and Cell Biology of Viruses Lab: https://www.cicbiogune.es/people/nabrescia

Modulating the conformational plasticity of the human cellular receptor tetraspanin CD81 by chemical binders

Tetraspanins are transmembrane proteins that form large signalling complexes known as tetraspanins-enriched microdomains (TEMs) or tetraspanins webs. They are involved in many important cellular processes including cell proliferation, migration, adhesion, B cell signalling and T-cell activation, virus assembly (HIV and Influenza A virus assembly) and entry (Hepatitis C virus). Our focus is on the tetraspanin CD81 as it is a cellular receptor for Hepatitis C virus entry, but also a potential target for antiproliferation in cancer progression.

The primary responsibility of the DC will be to lead a structure-function project firmly based on the current power of the drug-screen fragment-based approach to identify potential binders to the CD81 long-extracellular-loop ectodomain with the goal of modulating its plasticity. The project will involve adaptation of pre-existing information generated in our laboratory (e.g. several hundreds of crystals were individually soaked with about 900 compounds and diffracted

to high-resolution) and evaluation (through specialised analysis's software) of which of these candidates to take to the next level for initiating the medicinal chemistry process.
The DC will acquire skills in protein production and purification, X-ray crystallography data collection strategies, conduct data processing and analysis, in molecular cell biology (cell-based assay) and interpret results. The results gathered will ultimately serve to impact on our society providing a response to societal challenges affected by diseases related to cellular signalling and virus entry.

15.-Cancer Immunology & Immunotherapy lab: https://www.cicbiogune.es/people/apalazon

New therapeutic tools to overcome resistance to CAR-T cell therapy in solid tumors.
Adoptive cellular therapy (ACT) to treat cancer by modulating the immune response have led to unprecedented responses in patients with advanced-stage tumors, but only a minority of patientsrespond to them. ACT of T cells engineered to express artificial chimeric antigen receptor (CAR) targeting tumor antigen (Ag) is an exciting new approach for cancer immunotherapy. CAR-T cells have shown impressive clinical results in some hematological malignancies but have limitations in treating solid tumors, partially due to the immunosuppressive tumor microenvironment (TME). Thus, understanding the hostile signals that CAR-T cells are faced in TME is critical to prevent loss of T-cell function or persistence and to further improve the efficiency of current immunotherapy. In this context, interleukin-4-induced gene 1 (IL4I1) is an immunosuppressive enzyme that is upregulated by several cancer tissues and is emerging as a novel target to be block for cancer therapy. An interesting therapeutic strategy to enhance CAR-T cell efficacy could be to equip CAR-T cells with a CAR against IL4I1 (IL4I1-CAR) to convert IL4I1 immunosuppressive signal into a stimulatory one for T cells in the TME as a proof-of-concept technology prototype. We envision a IL4I1-binding CAR as synthetic membrane-bound receptor with the scFv of a IL4I1-blocking mAb. To date, the contribution of IL4I1 in CAR-T cell therapy for lung cancer (LC) remains unexplored. We hypothesize that LC TME is immunosuppressive and inhibit CAR-T cells through IL4I1, so we propose the simultaneous expression of a CAR against a specific tumor Ag and IL4I1-CAR on T cells. This cell therapy strategy will exploit the ability of CAR-T cells to remove soluble IL4I1 and improve its antitumor activity and that from neighbor cytotoxic T cells. This approach would serve as a proof-of-concept technology prototype that could be applied to treat other tumors and to block other targets as a technology platform.

Please, if you are interested send, before Jan 20th, your CV, along with a motivation letter (1 page, including up to five preferred topics) using the following form and indicating 44611 + name of the most preferred laboratory as reference