CIC bioGUNE
CENTER FOR COOPERATIVE RESEARCH IN BIOSCIENCES

EXCELENCIA SEVERO OCHOA

"la Caixa"

INPhINIT
"la Caixa" Fellowship Programme

Doctoral *INPhINIT* INCOMING Fellowship Program

CIC bioGUNE, located in the Science and Technology Park of Bizkaia (Derio), is a key research center within the national and international scientific landscape in the area of health science. The cutting-edge scientific activity of CIC bioGUNE researchers explores the interface between Chemistry and Biomedicine, with emphasis on Structural, Molecular and Cell Biology. 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:

- Addressing Hendra Virus attachment glycoprotein glycosylation (Dr. Ana Ardá)

- Bio-drilling phage-derived nanotubes against bacteria (Dr. Nicola GA Abrescia)

- Characterizing the recognition mode of sialoglycans by Siglec-6 immune checkpoint (Dr. June Ereño Orbea)

- Exploring the link between breast cancer heterogeneity and obesity / PhD Student position (Dr. María dM Vivanco)

- Full-atom virtualization of biochemical phenomena through 4D computer modeling (Dr. Gonzalo Jiménez-Osés)

- Impact of neddylation and its modulation on the antitumor immune response: opportunities in liver cancer for combined immunotherapeutic intervention (Dr. Malu Martínez Chantar)

- Implementation of extracellular vesicles as pharmacological nano-vehicles for targeted therapeutics (Dr. Juan Manuel Falcón)

- MS/NMR Metabolomics based Tests for COVID-19 Research (Dr. Óscar Millet)

- 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)

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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Addressing Hendra Virus attachment glycoprotein glycosylation

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

Protein glycosylation is an important post-translational modification, which have important implications for both protein physicochemical properties and biological functions. Although viruses do not have their own glycosylation machinery, they exploit the host cellular glycosylation capacities to decorate many of their viral proteins. These chemical modifications have important implications in viral pathology. The mechanisms by which viral proteins are glycosylated and how these modifications influence viral pathology remain largely unknown, especially for zoonotic viral causing diseases. Viral zoonosis, such as SARS-CoV-2, is expected to become a recurrent threat to human health due to the ongoing biodiversity loss. Glycans on viral proteins have been shown to affect protein folding and stability, to participate in viral attachment, and to modulate immune responses. Knowledge about the glycan determinants responsible for these functions is important for the rational design of antivirals and immune therapeutics.

This project will be focused on the *Hendra virus*, a highly pathogenic virus that has caused serious disease outbreaks in humans. The viral surface contains two proteins, the fusion (F) and the attachment (G) proteins, necessary for efficient entry. The project will be centered on the HeV-G glycoprotein, which will be produced recombinantly from mammalian HEK cells with specific ^{13}C-labeling. Nuclear Magnetic Resonance (NMR)-based strategies will be used to characterize the structure and dynamics of the glycans on the viral glycoprotein. The influence of the protein tertiary structure on the glycosylation profile will be evaluated. Additionally, NMR glycan signatures will be exploited to identify the specific glycan epitopes recognized by different C-type lectins and galectins, important players in host immunity and inflammation processes. Likewise, the site-specific glycosylation pattern and roles in lectin recognition will be evaluated through mutagenesis.

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Bio-drilling phage-derived nanotubes against bacteria

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

Bacterial infection is a re-emerging health concern, in particular since the widespread overuse of antibiotics. Novel biomedical strategies are required to fight the resistance that Bacteria have raised against antibiotic prophylaxis. The social belief that antibiotics could resolve almost any microbial infection has been fading away in recent years. Not least to undermine this social belief was the cucumber crisis in 2011, a foodborne bacterial infection occurred in Germany, caused by a deadly E.coli strain. This infection affected ~3,950 people, 53 of whom died.

Bacteriophages are viruses that infect and kill bacteria. The idea of using phages to treat bacterial infections is not new, but its pharmaceutical success has been hampered by several factors among which social acceptance, the CRISPR bacterial immune defence and the highly specificity of a phage for its host. Complementary to the current phage applications, here, we propose to explore and exploit the ability of self-assembling viral proteo-lipid tubes in perforating the cell wall of bacteria. We showed that the lipid-containing bacteriophage PRD1, infecting E.coli and Salmonella enterica harboring a conjugative IncP plasmid, is capable of assembling a proteo-lipidic tube that perforates the cell membrane for genome translocation. This phenomenon appears to be related to properties of lipids and to a specific set of candidate viral membrane proteins: P18, P32 and P7/14.

The goal of this proposal is to determine the molecular mechanisms governing the assembly of these proteo-lipidic tubes to be used as drilling devices of the bacterial cell wall causing the death of the bacteria using integrative biochemical, cellular and structural methods. This study serves (i) to exploit the effectiveness of new phage-derived biotechnological tools through a cross-sectional project; (ii) to impact on our society providing not only fundamental knowledge but also enabling the development of new therapeutic strategies.

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Characterizing the recognition mode of sialoglycans by Siglec-6 immune checkpoint

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

Immunotherapy has positively revolutionized oncological treatments. Most of such breakthroughs are due to the discovery of key checkpoints at the interface between immune cells and cancer cells. The Siglec receptors expressed on immune cells, have emerged as immune checkpoints. This family of receptors recognize sialic acid monosaccharides attached to proteins or glycolipids, as self-associated molecular patterns(*1*). The interaction between Siglecs and sialic acids is usually transduced in inhibitory signals. Interestingly, tumor cells, by being covered with sialic acids, can exert inhibitory responses on immune cells through Siglecs to prevent their death. In colorectal cancer, mast cells (MCs) at the tumor microenvironment (TME) are known to overexpress Siglec-6(*2*). Functionally, upon engagement to unidentified sialylated ligands on cancer cells, Siglec-6 induces a reduction of IgE-dependent ß-hex release and GM-CSF production on MCs (*2*). Hence, a better understanding of the binding mode of Siglec-6 to cancer cells will help our knowledge about its involvement in the development of the disease.

This project will combine structural biology and biochemical techniques to get insights into the binding mode of Siglec-6 to sialylated ligands. The information obtained will set the ground for the rational design of therapeutic molecules (e.g. glycan-based ligands) targeting Siglec-6.

References

1. S. Duan, J. C. Paulson, *Annu. Rev. Immunol.* **38**, 365–395 (2020).
2. Y. Yu *et al.*, *Front. Immunol.* **9**, 1–11 (2018).

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Exploring the link between breast cancer heterogeneity and obesity / PhD Student position

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Life Sciences

Medicine, Public Health, Sport Sciences, Nutrition, Clinical Psychology, Health Management

Obesity is a recognized risk factor for breast cancer and development of recurrence. Moreover, endocrine therapy is less effective in obese women, thus posing greater challenges in disease management (1). We have previously shown that cancer stem cells (CSCs), and the Sox2-Sox9 axis in particular, are implicated in resistance to hormone therapy and tumour recurrence (2, 3).

The goal of this project is to investigate the links between obesity and CSCs in breast cancer resistance to therapy, identifying molecular pathways and mechanisms that contribute to increased risk of recurrence and poor prognosis in breast cancer patients. To this aim, the project will employ a wide variety of *in vitro* and *in vivo* assays in order to obtain further insight into the mechanisms underlying the effects of obesity on increasing the risk of tumorigenesis and recurrence, an escalating problem in our society.

The Cancer Heterogeneity lab is working towards understanding tumour heterogeneity from the perspective of uncovering novel biomarkers and therapeutics in the treatment of cancer, and in particular breast cancer, which has the highest incidence and mortality in women worldwide. CSCs are implicated in tumorigenesis, metastasis and resistance to current cancer treatments. Work in the lab has shown that development of resistance to hormone therapy involves enrichment of CSCs and activation of SOX transcription factors (2,3), and that obesity stimulates expansion of CSCs (4). The lab is exploring the influence of hormones, signalling pathways and the microenvironment on breast stem cells in normal breast tissue and during tumour development.

References

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3. Domenici, G. et al. Vivanco MdM (2019). *Oncogene* 38:3151
4. Qureshi R et al., Vivanco MdM, Slingerland JM. (2020) *Cell Metab*. Jun 2;31(6):1154

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Full-atom virtualization of biochemical phenomena through 4D computer modeling

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Physical Sciences, Mathematics and Engineering
Chemistry and Chemical Engineering

The Computational Chemistry Group (CIC bioGUNE) uses state-of-the art computer modeling techniques for the theoretical prediction of new bioconjugation strategies, design of therapeutic peptides and antibodies, and understanding molecular recognition and glycobiology processes. A strong emphasis is also made on computer-aided enzyme engineering and directed evolution for abiological reactions. The immense power of the so-called computational microscope allows us to visualize complex biological phenomena in 4D (spatial and temporal) with atomic resolution expanding the limits of experimental techniques such as x-ray crystallography, cryo-EM and NMR. These are the main research lines in which this project will be integrated:

✓ Enzyme engineering and evolution: we use computational mutagenesis tools to predict and understand the structure-activity role of mutations in the catalytic performance of enzymes, both for biologically relevant processes and unnatural reactions with potential industrial application. We collaborate with leading biochemistry labs to guide and/or explain laboratory evolution towards stable, selective and highly active biocatalysts. We also apply our computational techniques to unveil the consequences of pathological mutations in the structure and dynamics of critical proteins associated to diseases.

✓ Bioorthogonal Chemistry: we develop new concepts and methods based on fundamental chemical processes for the site-selective modification of proteins and antibodies, with strong emphasis on improving stability, bioavailability and spatiotemporal control of therapeutic Antibody-Drug Conjugates (ADCs) with potential clinical applications.

✓ Molecular recognition and glycobiology: we provide detailed insights on the mechanisms of chemical and biochemical glycosylation processes and develop methods for the structural elucidation of complex glycocalyx components. These processes are at the core of host infections by microbial pathogens (virus and bacteria).

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Impact of neddylation and its modulation on the antitumor immune response: opportunities in liver cancer for combined immunotherapeutic intervention

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Life Sciences
Medicine, Public Health, Sport Sciences, Nutrition, Clinical Psychology, Health Management

Liver cancer is the 5th most common cancer worldwide and the 2nd leading cause of cancer death. This is a global health problem affecting up to 1% of the worldwide population.
In liver cancer, innate and adaptive immunity are part of a highly differentiated tumor microenvironment, which can have both pro- and anti-carcinogenic effects and thus contribute decisively to the effectiveness of antitumor therapy. Influencing the immune system and thereby shaping the tumor microenvironment toward the anticancerogenic side might help to control tumor growth and to improve patients' prognosis.
The importance of a crosstalk between transcriptional, posttranscriptional and posttranslational regulation in the wide spectrum of signaling pathways involved in the malignant transformation is a cutting-edge research topic that has only recently been suggested in liver disease. Neddylation modification was originally identified as a posttranslational regulator that highly conserved exists in a variety of cell types and species. Neddylation is an essential influencing factor on innate and adaptive immune cells in aspects of survival, differentiation, recruitment, and effector function. In addition, it served in an indirect manner by modulating the crosstalk between immune cells and others. Regarding liver disease, neddylation conjugation was shown to be aberrant both in early stages of the disease, such as during progression of the fibrosis stage of the disease as well as in liver cancer. Herein, we aim to deeply clarify the underlying mechanisms and the immunotherapy tool of neddylation in the treatment of liver cancer.

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Implementation of extracellular vesicles as pharmacological nano-vehicles for targeted therapeutics

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Life Sciences
Medicine, Public Health, Sport Sciences, Nutrition, Clinical Psychology, Health Management

The objective is the study of the use of extracellular vesicles (EVs) as pharmacological nano-vehicles for clinical use. Extracellular vesicles (EVs) are nano-sized membrane vesicles naturally secreted by cells. These vesicles have unique characteristics due to their cellular origin, including organotropic components that provide them with affinity for certain tissues, which could be exploited to direct therapeutic treatments towards specific objectives. Furthermore, as they are secreted by the body's own cells, this could also reduce the problem of immune rejection of treatment. Specifically, we will study the capacity of EVs produced by cells to encapsulate drugs, as well as to evaluate their functionality on acceptor cells using cellular, biochemical and molecular techniques. We will also pursue obtaining as much as possible pure preparations of EVs, a fact especially important in clinical applications. Therefore, we will also focus on the application of techniques that increase the purity of EV preparations with the aim of generating protocols that can be used in the clinic.

EXOSOMES laboratory and the METABOLOMICS platform at CIC bioGUNE (Derio, Bizkaia, Spain) led by Ikerbasque Research Professor leading the of the center. Biologist (by Sevilla University) with broad biochemical and cellular biology backgrounds, and wide experience in performing high-content omics-based analyses. Research in the study on EXTRACELLULA VESICLES - exosomes, microvesicles- as a source for biomarker discovery and a tool for therapeutic applications. Dr. Falcon´s group has characterized since 2005 exosomes secreted by many in vivo and in vitro experimental models of several diseases, as well as, from different body fluids. Board member of national (GEIVEX) and international (ISEV) associations for the study of extracellular vesicles.

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MS/NMR Metabolomics based Tests for COVID-19 Research

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Life Sciences
Medicine, Public Health, Sport Sciences, Nutrition, Clinical Psychology, Health Management

Coronavirus disease 2019 (Covid-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was first observed in Wuhan, and has since spread globally. The infection detection problem becomes a first-order priority by acknowledging that *currently there are no available methods for the early detection of COVID-19 progression* (i. e. methods to predict which patients will develop ARDS and at which severity level their infection will be). A growing body of evidence suggests that SARS-CoV-2 is not only a disease of the lungs but rather a systemic syndrome, showing many metabolic manifestations. This project aims to develop analytical methods based on the metabolic analysis of a serum samples by NMR spectroscopy and liquid chromatography/mass spectrometry (LC/MS). The methodology will exploit a unique metabolic fingerprint observed in COVID-19 patients in order to: i) diagnose COVID-19 in a robust mode, showing less false-positives and less false-negatives than the currently available methods; ii) predict the development of Acute Respiratory Distress Syndrome (ARDS) 7-10 days in advance; and iii) potentially useful in the prediction of the long-term sequels produced by this devastating disease. This project and our research group participation is part of an international consortium, led by Prof. Jeremy Nicholson (Murdoch University, Australia) and sponsored by BRUKER corporation.

Our group runs two 600 MHz IVDr spectrometers, equipped with a SampleJet autosampler and coupled to a SamplePro robot for sample preparation. This set-up ensures maximum efficientcy for sample preparation, with minimum handling and optimal reproducibility, according to the international SOPs generated by the Phenome Center Consortium. The NMR laboratory of CIC bioGUNE has been accredited as a *National Large Scale Infrastructure* by the Science and Technology Ministry of Spain and, recently, the ISO9001 regulation as well.

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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.

Dr. Castilla has remarkable experience training both pre-doctoral and post-doctoral scientists. Since 1998, Joaquín has been intensely involved in teaching PhD students and post-docs being directly involved in the scientific formation of more than 30 students. Moreover, the excellent scientific environment of Castilla's group at CIC bioGUNE, provides an excellent ground for them. Besides, through collaborations with other groups in the Institution, they will have access to the most advanced equipment for biophysical studies along with the guidance of experts in each area. 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.

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