CIC bioGUNE
CENTER FOR COOPERATIVE RESEARCH IN BIOSCIENCES

EXCELENCIA SEVERO OCHOA

INPhINIT
"la Caixa" Fellowship Programme

Doctoral *INPhINIT* INCOMING Fellowship Program

"la Caixa"

CIC bioGUNE 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 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.

Located in the Science and Technology Park of Bizkaia (Derio), the activity of CIC bioGUNE includes generation of both fundamental and oriented knowledge, training of research talent, and collaboration-building with local, national and international institutions. The center always places their technical advances, infrastructure, and scientific personnel at the service of society, health and business networks, and the global scientific community.

CIC bioGUNE has modern scientific infrastructures, led by prestigious scientists, which allow it to compete with the main European research institutes. These include advanced equipment for nuclear magnetic resonance (NMR), electron microscopy and X-ray diffraction, as well as different core technology platforms where genomes, proteomes and metabolomes can be analyzed.

INPhINIT Incoming **PhD Positions**:

- Bio-drilling phage-derived nanotubes against bacteria (Nicola GA Abrescia´s Lab)
- Chemoenzymatic glycoengineering of therapeutic monoclonal antibodies (Marcelo Guerin´s Lab)
- Deciphering Chemical and Biological Complexity Through Computer Modeling (Gonzalo Jiménez-Osés´s Lab)
- Pan-disease development of risk scores for longitudinal profiling of health status (Urko M Marigorta´s Lab)
- REWARDING: Articulating REverse WArburg vs Warburg and ROS proDuctIon In CaNcer; Role of DNAJC15 (Malu Martínez-Chantar´s Lab)
- Role of retrotransposition in Schwann cell development and pathology (Ashwin Woodhoo´s Lab)
- Study of the molecular mechanisms involved in the spontaneous misfolding of prion protein / Predoctoral position at Prion biology laboratory at CIC bioGUNE (Joaquín Castilla´s Lab)
- The impact of obesity on the development of resistance to therapy in breast cancer (María dM Vivanco´s Lab)
- Understanding the mode of action of ribosome targeting antibiotics using cutting-edge cryo-EM methodologies: A path to discovering new clinically relevant antibiotics (Sean Connell and Paola Fucini´s Lab)

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:

Itziar Gil de la Pisa (Project Manager)
ipisa@cicbiogune.es

CIC bioGUNE
Parque Científico y Tecnológico de Bizkaia, Edificio 801-A
48160 Derio (Bizkaia)
Tel.: +34 944 061 300 · Fax: +34 944 061 301
Email: info@cicbiogune.es · www.cicbiogune.es

Bio-drilling phage-derived nanotubes against bacteria

Research Professor Nicola GA Abrescia
(nabrescia@cicbiogune.es)

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 serve (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.

http://www.ikerbasque.net/es/nicola-g-abrescia
https://www.cicbiogune.es/org/research/Research

Chemoenzymatic glycoengineering of therapeutic monoclonal antibodies

Research Professor Marcelo Guerin
(mguerin@cicbiogune.es)

Life Sciences
Biotechnology, Bioinformatics, Pharmacy, Food Technology

Therapeutic immunoglobulin G (IgG) antibodies are a prominent and expanding class of drugs used for the treatment of several human disorders including cancer, autoimmunity, and infectious diseases. IgG antibodies are glycoproteins containing a conserved N-linked glycosylation site at residue Asn297 on each of the constant heavy chain 2 (CH2) domains of the fragment crystallizable (Fc) region. The presence of this N-linked glycan is critical for IgG function contributing both to Fc γ receptor binding and activation of the complement pathway. The precise chemical structure of the N-linked glycan modulates the effector functions mediated by the Fc domain. IgG antibodies including those produced for clinical use typically exist as mixtures of more than 20 glycoforms, which significantly impacts their efficacies, stabilities and the effector functions. To better control their therapeutic properties, the chemoenzymatic synthesis of homogeneously N-glycosylated antibodies has been developed. EndoS and EndoS2 secreted by Streptococcus pyogenes, have been successfully used as chemoenzymatic tools to glycoengineer antibodies. Both enzymes are highly specific and efficient against IgG, the most abundant antibody in serum. Thus, the scope of this research proposal is study the mechanism by which these enzymes specifically recognizes IgG, that still remains unknown, in order to engineer novel antibody-modifying enzymes. We will use a multidisciplinary approach, to gain information on the structural and conformational factors that govern the molecular mechanism substrate recognition of EndoS and EndoS2, and to engineer new endoglycosidases/glycosynthases specific for IgG.

http://www.cicbiogune.es/
https://sites.google.com/site/guerinlab/home
http://www.ikerbasque.net/marcelo.guerin

Deciphering Chemical and Biological Complexity Through Computer Modeling

Dr. Gonzalo Jiménez Osés
(gjoses@cicbiogune.es)

Physical Sciences, Mathematics and Engineering
Chemistry and Chemical Engineering

The Computational Chemistry Group (CCG) at CIC bioGUNE aims to create a solid platform for the theoretical prediction of chemical reactions for bioconjugation, designing and simulation of therapeutic peptides and proteins, and understanding Glycochemistry processes. A strong emphasis is also made on the Computer-Aided Enzyme Engineering and Directed Evolution. These are the main research lines developed at our group:

- *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.
- *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.
- *Drug Discovery*: we use synthetic chemistry and in silico tools to generate small molecules and peptides with therapeutic potential for neurodegenerative disorders (amyloidogenesis inhibitors) and infectious diseases (antimicrobial agents).
- *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.

www.cicbiogune.es/people/gjoses
www.gonzalojimenezoses.com

Pan-disease development of risk scores for longitudinal profiling of health status

Dr. Urko M Marigorta

(umartinez@cicbiogune.es)

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

The study of the genetics of complex disease has undergone a frenetic transformation in the last few years. Less than a decade ago, for instance, we knew about only three genes robustly associated with type 2 diabetes, one for cardiovascular disease, and even none for many other maladies. In sharp contrast, we now know hundreds for each of these diseases. For quite some time, the main business in the community will consist of making sense of all this wealth of data, a task necessary to improve our understanding of the etiology of disease and find new drug targets.

Another emergent and exciting use of this data, however, lies in gearing this information towards development of predictors that can serve to track disease in each individual. Bridging genomics with the clinic through precision medicine approaches is very challenging though. Among many others, one of the main obstacles for this goal is that all the wealth of genetic findings has been achieved through gigantic studies that necessarily miss the ample heterogeneity in disease symptoms that occurs in patients.

The **main goal of the proposed project** will be to test a new framework that can accommodate more realistically the longitudinal nature of disease risk. The cornerstone of the project is that disease is not a single entity but a symptom-based endpoint to which patients arrive through different etiological paths. Through integration of the latest datasets available in genomics, including whole-genome sequencing, single-cell RNA-Seq, and chromatin accessibility assays from patients, the PhD student will develop new biologically-informed genetic predictors for a range of complex diseases, and will test their transferability for risk stratification and longitudinal prediction of disease trajectory with clinical data.

https://www.cicbiogune.es/people/umartinez

REWARDING: Articulating REverse WArburg vs Warburg and ROS proDuctIon In CaNcer; Role of DNAJC15

Dr. Malu Martínez-Chantar
(mlmartinez@cicbiogune.es)

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

Although Warburg effect has been the pillar of the metabolism in Cancer, oxidative phosphorylation has appeared as an essential contributor in the overall ATP generation in determined types of cancers. The new hypothesis "*reverse Warburg effect*" has emerged in the field of tumor metabolism emphasizing the impact of the mitochondria-dependent energetic contribution in the proliferation and tumor invasiveness. In this new model, a cooperative communication is established between the tumor cells themselves and the stroma cells where the fibroblasts associated with cancer (CAF) play a fundamental role.

Methylation-controlled J protein (MCJ), also known as DnaJC15, is a small protein that belongs to the DnaJ family of co-chaperones. MCJ is not soluble, since it contains a transmembrane domain and localizes in the inner mitochondrial membrane. MCJ was first discovered in ovarian cancer cells, where it was found to be negatively regulated by methylation of CpG island. Human MCJ is highly expressed in tissues with active mitochondrial metabolism such as heart, liver and kidney. MCJ interacts with and represses the function of complex I of the ETC, making it the first endogenous inhibitor of complex I. MCJ deletion in vivo results in increased complex I activity without affecting mitochondrial mass. Indeed, MCJ interferes with the formation of respiratory Super Complex facilitating an efficient transfer of electrons and minimizing ROS production. Being the only endogenous inhibitor of complex I activity of the ETC, converts MCJ in the perfect candidate to be the nodal modulator of the Warburg and reverse Warburg effects in cancer cells, to regulate glycolysis and OXPHOS, controlling the redox balance and garner support from the CAFs. **This project will analyse the conceptual framework for MCJ contribution to the three main hallmarks of a tumor: support from surrounding stromal cells, attract new blood vessels to bring nutrients and oxygen and ultimately, metastasize**.

http://www.ciberisciii.es/
http://www.womeninhepatology.org/
https://www.easl.eu/
https://www.aasld.org/
http://cost-proteostasis.eu/

Role of retrotransposition in Schwann cell development and pathology

Dr. Ashwin Woodhoo
(awoodhoo@cicbiogune.es)

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

Schwann cells, the main glial cells of the peripheral nervous system, are highly plastic cells and have a remarkable ability to radically change their cellular identity in pathological situations, a feature that is highly unusual in mammals. The fundamental aim of the work in the group is to deconstruct the essential mechanisms that govern this plasticity, which forms the cornerstone of several debilitating and even fatal PNS neurological disorders that include demyelinating neuropathies e.g. Charcot-Marie-Tooth disease, and PNS cancers, including Neurofibromatosis.

The research project we are offering is to examine the role of transposable elements in regulating gene expression patterns during Schwann cell development and in pathological situations. New research is showing that transposition of mobile elements can have significant impact on human development and physiology (e.g. see Elbarbary et al., Science 2016). This project is focused on 3 key interlocking aspects of retrotransposition on Schwann cell development, myelination and pathology: (1) generation and analysis of different mice mutant models to examine the impact of retrotransposition, (2) identification of key retransoposition events, and (3) harnessing the potential of these mobile elements for controlling these processes using CRISPR-Cas9 technology.

The Biology of Schwann cell disorders laboratory is a young and vibrant group, headed by Dr Woodhoo. He received outstanding training and mentoring on Schwann cell biology by Profs R. Mirsky and K.R. Jessen at University College London, some of the most eminent scientists in the field. During this time, he published some seminal publications in the field, e.g. Woodhoo et al., Nature neuroscience 2009; Authur-Farraj et al., Neuron 2012; Napoli et al., Neuron 2012. His group at the CIC bioGUNE has also produced excellent publications (Iruarrizga et al., J. of Neuroscience 2012; Varela-Rey et al., Neuron 2014; Gomez et al., Journal of Cell Biology 2015).

https://www.cicbiogune.es/people/awoodhoo

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

Research Professor Joaquín Castilla
(jcastilla@cicbiogune.es)

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.

https://www.cicbiogune.es/people/jcastilla

The impact of obesity on the development of resistance to therapy in breast cancer

Dr. María dM Vivanco
(mdmvivanco@cicbiogune.es)

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

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women worldwide. Obesity is highly prevalent in developed countries, with approximately 26% of both men and women in Spain categorised as obese. Obesity has been associated with increased risk of breast cancer and, in established breast tumours, resistance to endocrine therapy. We have previously shown that cancer stem cells (CSCs), and the Sox2-Sox9-Wnt axis in particular, are implicated in resistance to therapy and tumour recurrence. 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 tumorigenesis in obese patients, as well as resistance and poor prognosis in breast cancer patients.

Insight gained from this research, while furthering our knowledge of CSCs and breast cancer, will be used to identify potential biomarkers and novel therapies in the diagnosis and treatment of breast cancer, thus providing new tools to fight the aggravating influence of obesity, an escalating problem in our society, on increasing the risk of breast cancer development and recurrence.

The Cancer Heterogeneity lab at CIC bioGUNE is working towards understanding tumour heterogeneity from the perspective of uncovering novel biomarkers and therapeutics in the treatment of cancer, particularly breast cancer. In recent years the identification and characterisation of CSCs has allowed for renewed efforts into anti-cancer therapies, with CSCs being implicated in tumorigenesis, metastasis and resistance to conventional cancer treatments (endocrine, chemotherapy and radiotherapy) in many tumour types, including breast cancer. The lab explores the influence of hormones, signalling pathways and the microenvironment on breast stem cells in normal breast and tumorigenesis.

https://www.cicbiogune.es/people/mdmvivanco

Understanding the mode of action of ribosome targeting antibiotics using cutting-edge cryo-EM methodologies: A path to discovering new clinically relevant antibiotics

Dr. Sean Connell and Dr. Paola Fucini
(sconnell@cicbiogune.es and pficini@cicbiogune.es)

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

Do you dream of glimpsing into the core of a cell and seeing nature's machines at work making proteins, lipids and other complex molecules? Our ability to realize this dream is rapidly approaching and cryo-electron microscopy (cryo-EM) is one of the biophysical techniques leading the way. The power of cryo-EM was recognized in the **2017 Nobel Prize in Chemistry** and has recently undergone a technical revolution hallmarked by a dramatic increase in the resolving power. Until few years ago, cryo-EM was limited to providing low resolution structures (10-20 Å) but today cryo-EM has the power to resolve the atomic structure of nature's biological machines (>3 Å). At this resolution we can describe the molecular structure of vital macromolecular complexes and understand how their structure changes to elicit a functional activity. Moreover, we can observe substrates bound in catalytic sites and begin to define how interactions and reactive centers drive reactions or promote conformational changes essential to the machine's cellular role. Understanding these details allows one to harness the activity of the machine for applications in biotechnology (chemical biology) or designing molecules that regulate the activity of the machine for biomedical applications (i.e. antibiotics).

The research conducted in the Connell and Fucini groups aims at understanding and further developing the mechanism of action of clinically relevant or newly discovered antibiotics that target the ribosome, one of the most vital macromolecular machine of the cell, devoted to protein synthesis. The perspective student will join a highly collaborative and multi-disciplinary research team to study at the structural level the assembly and initiation phases of protein synthesis to identify targets and describe the mode of action of novel antibiotics with clinical potential. Uncovering the structural basis of antibiotic action can yield solutions to the ever-threatening problem of growing antibiotic resistance.

https://www.cicbiogune.es/people/sconnell