Master in Biomedical Research

2019-2020

List of potential laboratories

Other laboratories would also be accepted

(by alphabetical order using the last name of each principal investigator)

Note: admissions to the Master in Biomedical Research (BIOMED) are prioritized for students that have been accepted to do his/her research *practicum* in a research laboratory.

A main orientation of the BIOMED master is to continue towards a PhD thesis, and the majority of students enrolling in this master have, at the time of pre-registration, been accepted in research groups to do a PhD after they finish the master. However, there are students who have a motivation to do this master, and eventually a PhD, but who may not know how to contact a suitable laboratory.

This document contains a few guidelines to help candidate students in finding a research group, and also a list of potential laboratories to which they can submit applications.

This list is orientative, and students can do their research in another laboratory that they can find on their own. Also, this list is not just to choose a laboratory: you must contact the group you are interested in, arrange an interview, and get the written acceptance of the investigator in charge of that group.

“How to: getting accepted in a research laboratory”

1- You have to know what you would like to work on.

2- Be specific: you should be able to say what are the questions that are important to you and why.

Not very good: I want to work in neurosciences, I have always liked it.

Much better: I want to understand the processes and mechanisms that make neurons more sensitive to oxidative stress and oxygen deprivation in patients with neurodegenerative diseases such as...

Not very good: I want to work in regenerative medicine, I think that stem cells have a lot of potential to cure diseases.

Much better: I want to contribute to the identification of proteins that when expressed in a differentiated cell such as a fibroblast, can cause it to dedifferentiate and acquire functional characteristics of a pluripotent cell.

3- Find out who is working on what.

Websites of universities and research centers, PubMed searches, Google...

It takes time! (don’t wait till last minute to begin looking for your favorite lab)

4- Write to the group that interests you.

5- Contacting a group.

a) Motivation letter: tell them why you want to work with them (for this, you need to know something about what they do and about current questions in the field).

It takes time! (don’t wait till last minute to begin looking for your favorite lab)

Also tell them why you are good. Labs appreciate commitment, responsibility, ability to work in a team, ability to persevere and a strong motivation.

Ask them for an interview to show them how good you are.

Do not write a generic letter to copy-paste and send to ten different laboratories changing only the name of the group leader.

Choose your labs and send a personal, specific letter to each one.

b) Keep in mind that a person working full time in a cellular-molecular biology lab can spend more than 1000 euros/month in materials, besides a lot of time required to train you and supervise you until you begin to get solid results.

Expect that during the first 6 months it is more likely that you will produce more trouble and expenses than productive results. Laboratories are usually not financed by the university nor the research center, and they get the money from competitive grants that are given or denied based on publication in internationally respected journals.

Do not get discouraged with rejections, learn from them to improve your application.

c) Do not forget important details in your CV:

1- Give names of senior persons that can be a reference.

Be careful with “clone” reference letters from teachers that don’t really know you and will just say general things.

2- Include your university scores. If they are not too good, you should be ready to explain why, either in your application letter or in an interview. Be honest and realistic about it. If the teaching/exam system of your university hasn’t worked for you, you will know the reasons better than anyone else, so be prepared to speak frankly about it.

University scores are not an exact indicator of who will become a successful scientist, but they say that a person has gone through 4-5 years of serious effort with a better than average performance.

Most people will interpret this as a sign of self-discipline, organization, capacity to work even if you have a bad day, and to get things done regardless of whether they are more fun or plainly boring.

Project Title:
Human brain evolution modelled in iPSC organoids

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

Sandra Acosta
Postdoctoral fellow /Senior Scientist
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Summary of project summary or current research lines (less than 300 words).

The human brain is arguably the most sophisticated organ of our bodies and certainly one of the most amazing products of evolution. In this project we focus on the identification of regulatory elements that have play a central role in the acquisition of human brain traits. We use iPSC and/or ESC derived organoids to model the milestones of brain development, since animal models fail to recapitulate the human species-specific brain traits. Using comparative genomics we have identified a number of key variants located in enhancers that have evolved in an accelerated manner during the evolution of the human lineage. This accelerated evolution suggests that they might be involved in the acquisition of human brain traits. The purpose of the study is to unveil the function of the human enhancer variants introducing the ancestral mutations in the human iPSC/ESC genome using CRISPR/Cas9 directed tools for gene editing. Subsequently they will be differentiated into neural populations and analyzed for phenotypic differences that recapitulate the evolutionary processes involved in human brain function.

Project Title: Investigating deafness through crispr mutants in zebrafish

Project supervisor

Berta Alsina, PhD
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Summary of project summary or current research lines (less than 300 words).

The inner ear is the sensory organ responsible for the senses of hearing and balance. Hair cells (HC) are specialized mechanosensory cells of the inner ear that send the acoustic information to the brain through specialized sensory neurons. Thus, deafness is mainly due to the loss of these both cell-types. Several genes have been reported in humans to cause deafness but their functional role in inner ear physiology is not well-known. The clustered regularly interspaced palindromic repeats (CRISPR)/Cas9 technology is a powerful gene-editing technology that allows to edit in a directed manner any desired gene. We aim to recapitulate specific gene mutations causing deafness in humans by using crispr technology in zebrafish. For this we will create point mutation knock-ins into zebrafish genomic sites using CRISPR/Cas9 reagents and single-stranded oligodeoxynucleotides and genomic deletions of putative cis-regulatory elements. The zebrafish is a great model to generate high-throughput analysis of mutants due to its easiness to inject crispr/cas9 reagents at 1-cell stage, rapid development, availability of reporter lines and transparency. Our laboratory has large experience in investigating inner ear development in zebrafish and recently we have set up the technology of crispr/cas9 mutation of deafness genes with success. Moreover, we have already reporter lines that specifically label hair cells and sensory neurons to follow their phenotypic disruption.
The student should have interest in disease models, developmental biology and crispr technology. He/She will be able to acquire state of the art skills such as crispr design, confocal imaging, immunostaining, in situ hybridization and zebrafish injection.
The Alsina lab is located at the PRBB with excellent facilities available to carry on the proposed project.

Project (generic): New mechanisms of transcriptional control of inflammatory responses

Project supervisor: Jose Aramburu and Cristina López-Rodríguez, Immunology Unit, Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona
Tel: 93316-0810 (CLR) / -0809 (JA)/ -0822 (LAB)
E-mail: jose.aramburu@upf.edu and cristina.lopez-rodriguez@upf.edu

Summary of project summary or current research lines

A main focus of our group is to identify new mechanisms of transcriptional control of inflammatory responses. We study various processes such as cancer immunotherapy, inflammatory defense against pathogens, inflammation during tissue regeneration and communication between immune cells in transplant rejection.

For more information, see:
https://www.upf.edu/web/biomed/entry/-/-/23934/adscripcion/cristina-lopez-rodriguez
https://www.upf.edu/web/biomed/entry/-/-/15818/adscripcion/jose-aramburu

Selected publications: Buxadé et al J Exp Med 2012; Ortells et al Nucleic Acids Res 2012; Berga-Bolaños et al 2013 Proc Natl Acad Sci USA; Aramburu et al 2014 Science Signaling; Tellechea et al. J Immunol 2017; Buxadé et al J Exp Med 2018.

Possible project: Characterization of gene regulatory mechanisms that confer macrophage population identity

Macrophages are immune sensors present in every tissue of the body that play central roles in homeostasis, pathogen elimination, and disease. Tissue resident macrophages have the ability to adapt to environmental changes through changes in the specific gene expression signature expressed. In this regard, activation of intracellular signaling pathways by factors present in a macrophage's microenvironment control enhancer elements for regulating gene transcription in a dynamic and plastic manner. The enhancer repertoire controls cellular identity of a given subset of resident macrophage population and their ability to dynamically alter gene expression programs in response to homeostatic and pathologic signals.

Transcription is a local and functional process at active enhancers, where enhancer RNAs, or eRNAs, are tightly correlated with transcription of protein-coding genes. Enhancers also establish physical contacts with key gene regulatory regions under their control, an association that despite being studied extensively using chromosome conformation capture analysis (3C), is still poorly understood at the molecular level.

We aim at understanding how these genomic elements control macrophage functions. We plan to study how enhancers in macrophages are formed and how they work, and also analyze their connection with the genes they control. This study will lead to a better understanding of human diseases as cancer, autoimmunity and obesity, which are driven by unbalanced macrophage responses.

The successful candidate will develop a master project working with molecular mechanisms of regulation of immune responses and will use technical approaches as single cell flow cytometry analysis, quantification of gene expression, analysis of chromatin modifications, and use mouse models of human diseases.

We value a clear motivation for research and a doctorate, as well as the ability to solve problems. We will also consider previous experience in immunology and laboratory training.

Interested candidates, please send your request to Dr. Cristina López-Rodríguez or Dr. Jose Aramburu: cristina.lopez-rodriguez@upf.edu or jose.aramburu@upf.edu, including your CV and the detailed academic transcript.

Project Title: Development of the mammalian cerebral cortex in physiological and pathological conditions

Project supervisor

Name**:** Mariona Arbonés

Title and Position: PhD. CSIC investigator. Group leader at the Instituto de Biología Molecular de Barcelona (IBMB)

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Summary of current research lines

One of the current challenges in developmental neurobiology is to understand the molecular mechanisms that regulate cell number and generate cell diversity in the brain. To approach this challenge our group is studying the development of the neocortex, the brain region responsible for cognitive function, sensory perception and consciousness. The many neuron types that form the mammalian neocortex are generated from a population of neural stem cells, also known as radial glial cells (RGC), or from RGC-derived progenitors with restricted neurogenic fate. The decision of a RGC to perform proliferative divisions, expanding the progenitor pool, or neurogenic divisions, giving rise to neurons with specific identities, is highly regulated in space and time by a combination of extrinsic signals and intracellular cues. Disturbances in the proliferation rates and type of division (proliferative or differenciative) of these progenitors may lead to alterations in brain size and are on the basis of developmental disorders such as autism and schizophrenia.

Current research lines of the group:

1. DYRK1A functions in neocortical development. DYRK1A is a protein kinase involved in Down syndrome and autism. We have previously shown that variations in the dosage of DYRK1A in the mouse lead to alterations in brain size, cortical neurogenesis and neuron survival. To better understand the role of DYRK1A in cortical development we are studying the regulation by DYRK1A of the activity of putative substrates and characterizing mutant mice with a conditional *Dyrk1a* deletion in neural progenitors.

2. Temporal regulation of gene expression in RGCs. During cortical neurogenesis the environment (extracellular cues) of RGCs suffers important changes. To provide insights on how the transcriptome of RGCs adapts to these changes we are analyzing RNA-seq data obtained from RGC samples isolated from mouse embryos at different developmental times.

Project Title:
Negative and positive regulation of the cell cycle by stress.

Project supervisor:
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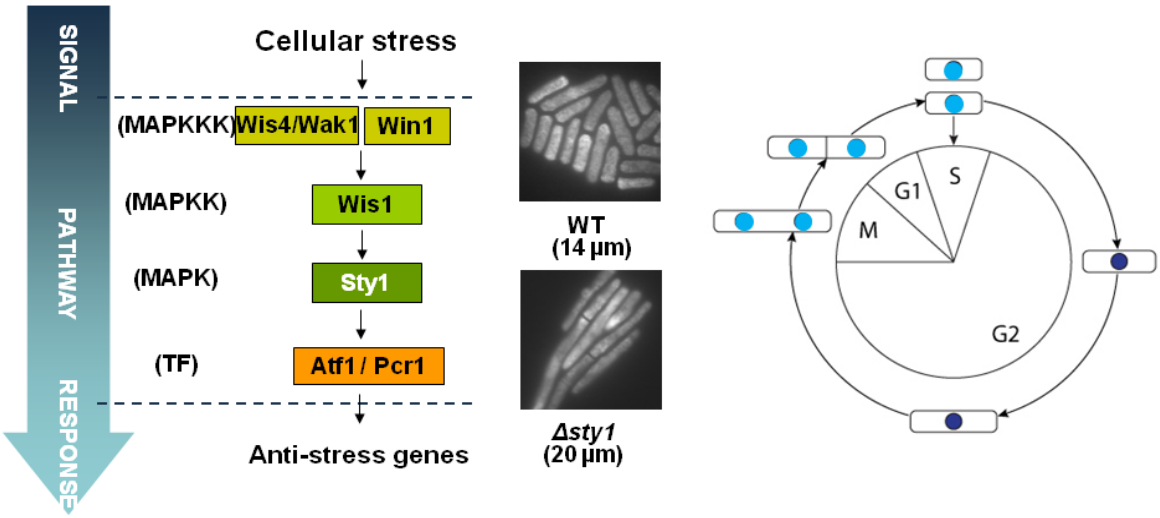
Summary of current research lines.
Our group is interested in studying the components and molecular mechanisms which regulate the responses to oxidative stress and the control of the cell cycle, using the fission yeast ***Schizosaccharomyces pombe*** as a model system. To obtain more information about the laboratory and about our research interests, please consult our group's web page (www.upf.edu/osccg). Some recent publications of the group include:

Domènech et al. 2018. BMC Biol. 16:61.
Boronat et al. 2017. PLoS Genet. 13:e1006858.
Alves-Rodrigues et al. 2016. Cell Reports 14:885.
Eckert et al. 2016. PLoS Genet. 12: e1005768.
García-Santamarina et al. 2014. Nature Protocols 9:1131.
Calvo, I.A. et al. 2013. Cell Reports 5:1413.
Ivanova, T. et al. 2013. Mol. Biol. Cell 24:3350.
Calvo, I.A. et al. 2012. Nucleic Acids Res. 40:4816.
Gómez-Escoda et al. 2011. EMBO Rep. 12:84.
Zuin, A. et al. 2010. EMBO J. 29:981.
Moldón et al. 2008. Nature 455:997.

The transitions to enter the S and M phases are tightly regulated upon nutritional and environmental clues. We pretend to characterize the participation of stress signaling cascades in the inhibition of the cycle upon stress imposition and of growth resumption once the stress in over.



Universitat Pompeu Fabra Barcelona

Project Title: UNDERLYING BIOLOGY IN LUNG TUMORIGENESIS OF PATIENTS WITH CHRONIC RESPIRATORY DISEASES.

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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Summary of project summary or current research lines (less than 300 words). Our research is based on the use of patients from clinical settings, animal models of disease, and in vitro primary cultures. We use all kinds of biochemical and molecular biology techniques (RT-PCR, immunoblotting, immunohistochemistry, 2-D electrophoresis, proteomics analysis, ELISA, activity assays, mitochondrial respiration, flow cytometry, etc.) in order to explore the target mechanisms of our research. In the last five years, we have also started a new avenue of research focusing on the underlying biology that accounts for the greater susceptibility of patients bearing chronic respiratory diseases (e.g. COPD) to develop lung tumors. The most relevant achievements of our research have been the following: the demonstration that oxidative and nitrosative stress, ubiquitin-proteasome system, NF-kB and FoxO signaling, alterations of epigenetic regulation, and loss of muscle-specific proteins are important players in chronic obstructive pulmonary disease (COPD)- and lung cancer-associated cachexia, whereas muscle inflammation does not participate in such a process. Moreover, we have also demonstrated that increased oxidative stress, inflammatory cytokines and disruption of epigenetic regulation are involved in the greater susceptibility of patients with COPD to develop lung cancer. In the last decade, my research group has published extensively (more than 200 publications including book chapters) in the field of the underlying biology of skeletal muscle dysfunction and loss in chronic respiratory conditions including lung cancer and acute diseases (sepsis). Recently, we have demonstrated the potential role of muscle regenerative potential in sarcopenia and models of disuse induced muscle atrophy. Ongoing research in my group will pursuit the identification of novel therapeutic strategies targeted to alleviate muscle mass loss and cachexia in patients with chronic disorders including lung cancer.

Barcelona, February 1st 2019

Project Title: Cognitive and cerebral correlates of behavioral deficits in the frontotemporal lobar degeneration spectrum

Project supervisor:

Dr. Alexandre Bejanin, PhD

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Servicio de Neurología - Hospital de la Santa Creu i Sant Pau

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Summary of project summary or current research lines:
Frontotemporal lobar degeneration (FTLD) defines a group of neurodegenerative brain disorders with predominant degeneration of the frontal and/or the temporal lobes of the brain. In patients younger than 65 years, FTLD is the second most common cause of neurodegenerative dementia after Alzheimer disease. Clinically, FTLD is heterogeneous and may present as a behavioral-dysexecutive disorder (behavioral variant frontotemporal dementia, bvFTD), one of the three clinically distinct language disorders (non-fluent/agrammatic variant primary progressive aphasia, nfvPPA; semantic variant, svPPA and, rarely, a logopenic variant, lvPPA) or as motor disorders such as corticobasal (CBS) or progressive supranuclear palsy (PSP) syndromes. Behavioral impairments predominate the clinical picture of bvFTD but are also present, to a different extent, in the others syndromes. While growing effort has been directed toward a better characterization of these behavioral impairments, it is still unclear how distinct behavioral deficits (e.g., apathy, disinhibition, irritability) can co-exist in FTLD patients. Furthermore, their relationships with cognitive functions (e.g., memory, executive functions, social cognition) and brain alterations remain to be explored. The aim of the current project is therefore to provide a better understanding of the behavioral deficits in FTLD syndromes. Specifically, the Master student will be using the behavioral data (>5 questionnaires) acquired in >200 cases of FTLD cases to establish i) how likely behavioral deficits tend to co-occur in FTLD patients and which are the ii) cognitive and iii) cerebral correlates of these deficits. This project offers a unique opportunity to learn more about FTLD in a high interdisciplinary atmosphere, and to get familiar with statistics (e.g., independent component analysis) and neuroimaging (structural MRI and/or FGD-PET) processing.

Project Title: Examiner versus relatives assessment of behavioral impairment in the frontotemporal lobar degeneration spectrum: two sides of the same coin?

Project supervisor:

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Summary of project summary or current research lines:
Frontotemporal lobar degeneration (FTLD) defines a group of neurodegenerative brain disorders with predominant degeneration of the frontal and/or the temporal lobes of the brain. In patients younger than 65 years, FTLD is the second most common cause of neurodegenerative dementia after Alzheimer disease. Clinically, FTLD is heterogeneous and may present as a behavioral-dysexecutive disorder (behavioral variant frontotemporal dementia, bvFTD), one of the three clinically distinct language disorders (non-fluent/agrammatic variant primary progressive aphasia, nfvPPA; semantic variant, svPPA and, rarely, a logopenic variant, lvPPA) or as motor disorders such as corticobasal (CBS) or progressive supranuclear palsy (PSP) syndromes. Behavioral impairments predominate the clinical picture of bvFTD but are also present, to a different extent, in the others syndromes. Currently, most behavioral evaluations rely on relatives (e.g., spouse) feedback. However, some behavioral disturbances might be subtle and not always noticed by a non-expert observer. In addition, some behavioral abnormalities may be more expressed in specific and formal contexts such as a medical interview. The aim of the present project is to determine the added value of an assessment of behavioral impairments by a clinician (neurologist/neuropsychologist) during his interview with FTLD patients (>200 cases). Specifically, the Master student will use data from the *Social Behavior Observer Checklist*, an examiner-facing questionnaire that measures socioemotional behavior via observed, spontaneous social behaviors enacted by the participant during the course of an evaluation. This data will be compared to standard behavioral assessment (i.e., filled by an informant) to determine the common versus specific information provided by these two types of evaluation. The relevance of clinician evaluation will be further assessed by testing associations with cognitive and imaging measurements. This project offers a unique opportunity to learn more about FTLD in a high interdisciplinary atmosphere and to get familiar with statistics and neuroimaging (structural MRI and/or FGD-PET) processing.

Project Title: Effect of bilingualism on the cognitive and neuroimaging features of Alzheimer's disease and behavioral-variant frontotemporal dementia

Project supervisor:

Dr. Alexandre Bejanin, PhD

Post-doctoral fellow in the Unidad de Memoria de Sant Pau

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Summary of project summary or current research lines:
Current research suggests that the clinical expression of dementia is modifiable by lifelong factors protecting against cognitive decline by enhancing the "cognitive reserve". Strong epidemiological evidence support that bilingualism may be one of these potential protective factors. For instance, older bilingual individuals manifest symptoms of Alzheimer's disease (AD) significantly later than comparable monolinguals. Recent evidence (Alladi et al., 2017, Neuropsychologia) showed that similar processes may exist in the behavioral-variant frontotemporal dementia (bvFTD), which is a clinical syndrome characterized by behavioral and executive impairments. However, the cognitive and cerebral mechanisms underlying these effects remained largely unexplored. Furthermore, it is unclear whether similar or distinct mechanisms sustained these effects in AD versus bvFTD. The aim of the current project is therefore to provide a further understanding of the effect of bilingualism on the cognitive and neuroimaging features of AD and bvFTD. Specifically, the master students will compare monolingual and bilingual patients and test whether there are common mechanisms of bilingualism in AD and bvFTD. This project offers a unique opportunity to learn more about neurodegenerative diseases in a high interdisciplinary atmosphere and to get familiar with statistics and neuroimaging (structural MRI and/or FGD-PET) processing.

Project Title: Effect of the APOE4 allele on the cognitive and neuroimaging features of Alzheimer's disease and behavioral-variant frontotemporal dementia

Project supervisor:

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Post-doctoral fellow in the Unidad de Memoria de Sant Pau

Servicio de Neurología - Hospital de la Santa Creu i Sant Pau

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Summary of project summary or current research lines:

The ε4 allele of the apolipoprotein E (ApoE) gene is the strongest known genetic risk factor for sporadic Alzheimer's disease (AD). It has notably a dose-dependent effect on the age of onset and the rate of cognitive decline. The mechanisms underlying these effects are still poorly understood but are thought to be related to the deposition and clearance of the amyloid β-protein. Yet, recent evidence suggested that the ApoE4 allele is also associated with other proteins involved in neurodegenerative disorders, such as tau or TDP-43. Furthermore, the ApoE4 allele was shown to have an effect on clinical and/or neuroimaging in a number of other neurological conditions including the behavioral-variant frontotemporal dementia (bvFTD). This latter is a clinical syndrome characterized by progressive behavioral and executive impairments underlined by the degeneration of the frontal and temporal lobes. Pathologically, bvFTD is heterogeneous but is mainly associated with tau and TDP-43 neuropathology. Whether ApoE4 is a genetic disease modifier in bvFTD remains controversial and poorly understood. The aim of the present project is therefore to investigate the influence of ApoE4 allele in a large cohort of patients with AD and bvFTD. Specifically, the Master student will compare carriers and non-carriers of the apoE4 allele in AD and bvFTD and test whether the apoE4 allele has common versus disease-specific effects on cognitive and neuroimaging measurements. This project offers a unique opportunity to learn more about neurodegenerative diseases in a high interdisciplinary atmosphere and to get familiar with statistics and neuroimaging (structural MRI and/or FGD-PET) processing.

Project Title: Interplay between structural (MRI) and functional (FDG-PET) cerebral changes associated with Alzheimer's disease and behavioral-variant frontotemporal dementia

Project supervisor:

Dr. Alexandre Bejanin, PhD

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Summary of project summary or current research lines:
The behavioral-variant frontotemporal dementia (bvFTD) is a clinical syndrome characterized by progressive behavioral and executive impairments underlined by the degeneration of the frontal and temporal lobes. This degeneration can be assessed by in vivo imaging techniques such as structural MRI and FDG-PET. While the pattern of gray matter atrophy (MRI) and glucose hypometabolism (FDG-PET) highly overlaps in bvFTD, previous evidence suggests that changes in metabolism may precede structural changes. Furthermore, part of the metabolic decline may result from a loss of input from connected brain regions. For instance, it has been shown in Alzheimer's disease (AD) that the hippocampal atrophy contributes, via the disruption of the cingulum bundle, to the glucose hypometabolism in medial parietal structures (Villain et al., 2010). Whether similar remote mechanisms may exist in bvFTD and influence the cognitive symptoms is still unknown. The aim of the present project is therefore to provide a better understanding of the interplay between structural MRI and FDG-PET in bvFTD and to compare these relationships to those observed in AD. Specifically, the Master student will assess local and distal relationships between gray matter atrophy and hypometabolism in both disorders to determine whether there are similar versus disease-specific associations. This project offers a unique opportunity to learn more about neurodegenerative diseases in a high interdisciplinary atmosphere and to get familiar with statistics and neuroimaging (structural MRI and FGD-PET) processing.

Project Title: Functional validation of adaptive variants in zinc transporter genes

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

Name: Elena Bosch, Ph D
Position: Professora Titular
Group: Evolutionary Population Genetics Lab
Institution: Universitat Pompeu Fabra
IBE, Institute of Evolutionary Biology (CSIC-UPF)
Postal address: CEXS-UPF-PRBB, Universitat Pompeu Fabra, C/Doctor Aiguader 88, 08003 Barcelona, Spain; Tel: + 34 93 316 0841
email: elena.bosch@upf.edu
web page: http://biologiaevolutiva.org/ebosch/

Summary of project summary or current research lines (less than 300 words).

Current research lines: Our group focus on investigating the genetic basis of human adaptations and on the experimental validation of adaptive variants. The search for genetic signatures of selection is pursued at different levels using comparative data but also exploring intraspecific diversity patterns among worldwide human populations. In those cases where the imprint of selection is confirmed, we then aim to determine the molecular bases of the functional adaptation.

Project summary: Zinc is an essential micronutrient involved in many different biological functions. In humans, zinc homeostasis is accomplished by the joint action of 24 zinc transporter genes (ZTGs) to ensure the molecular and cellular functions that depend on this micronutient. Until recently zinc intake in human populations directly correlated with the zinc content of the soil in which their crops were grown. Thus, zinc soil content may have been an important driver of local genetic adaptations. We have recently explored the complete set of 24 human ZTGs for signatures of adaptation by using sequencing data on 26 worldwide populations from 5 main geographical regions including zinc-deficient soils. Notably, at least three ZTGs showed significant signals for classical selective sweeps in Africa and/or East Asia. Additionally, we detected unusual concerted shifts in allele frequencies for the whole set of ZTGs, especially when comparing African to non-African populations. In that context, the main objective of this project will be to functionally validate differential potential molecular phenotypes for a predefined set of putative adaptive alleles behind the detected signatures of adaptation, including both nonsynonymous and non-coding regulatory variants. In particular, we will be using different in vitro experimental settings to explore their potential role on determining differences on the corresponding receptor surface protein expression, as well as on the basal intracellular levels of zinc and the zinc uptake they involve.

Project Title: Leukaemia and epigenetics: exploring the link between the histone variant macroH2A, chromatin architecture and cancer development.

Research group and project supervisor

Chromatin, Metabolism and Cell fate group
PI: Marcus Buschbeck (Team Leader)
Project supervisor: Marguerite-Marie Le Pannerer

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Group web page: http://tinyurl.com/buschbeck-group

Summary of project summary or current research lines (less than 300 words).

Myelodysplastic syndrome (MDS) is a hematopoietic disease due to the aberrant proliferation and ineffective differentiation of hematopoietic stem cells. This phenomenon leads to low numbers of functional blood cells and has a high risk of transformation to acute myeloid leukaemia.

Epigenetics is the study of element that are “on top” (*epi*) of the DNA (*genetics*). Epigenetics information is embedded how the genome is packaged as chromatin in the nucleus and its regulation comes in various forms: histone modifications, DNA methylation but also histone variants. Histone variants are proteins that can replace replication-coupled histone in the building block of chromatin. In our group we focus on the histone variant macroH2A which has primarily a tumor suppressive function (Hake and Buschbeck, 2017, Nature Reviews MCB). Recent results of the lab have shown that macroH2A links the three dimensional-organization of the genome to metabolism.

As we know that in 20% of MDS one of the genes encoding macroH2A is deleted, we explore the role and the mechanism of action of macroH2A proteins in the context of the disease. The Master project will embedded in the research line.

Litt.:

- The regulation and molecular function of histone variants (Buschbeck and Hake, 2017, Nature Reviews RM;
- Evidence linking macroH2A to 3D chromatin architecture (Douet et al, 2017, JCS, Kozlowski, Corujo et al., 2018, EMBO Rep).
- The link between metabolism and epigenetic regulation (Posavec Marianovic, Hurtado Bagès et al., 2017 Nature Structural Molecular Biology).

Contact

Highly motivated candidates are invited to submit their motivation letter and their CV including a summary of academic records to mlepannerer@carrerasresearch.org and mbuschbeck@carrerasresearch.org

Project Title: Understanding the functional relevance of citrullination in cancer.

Research group and project supervisor

Chromatin, Metabolism and Cell fate group
PI: Marcus Buschbeck (Team Leader)
Co-PI and project supervisor: Priyanka Sharma

Josep Carreras Leukaemia Research Institute
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How to find us: http://www.carrerasresearch.org/en/campus-ico-germans-trias-i-pujol_6210
Group web page: http://tinyurl.com/buschbeck-group

Project summary.

Epigenetics events focus on the study of mechanisms and chemical marks that influence gene activity, chromatin condensation and ultimately cell function. One of the chromatin associated post-translational modifications is the deimination of arginines to citrullines and catalysed by a family of enzymes called peptidyl arginine deiminases. Elevated levels of PADIs are associated with diverse pathological disorders including leukaemia and several other cancers, and autoimmune diseases. Arginine citrullination facilitates transcription of genes needed for cellular proliferation on cancer cells, suggesting one of the tumorigenic mechanisms (Sharma et al., 2019, Molecular cell https://doi.org/10.1016/j.molcel.2018.10.016). We are fascinated by the questions that how exactly these epigenetic events including citrullination operate on the molecular level to contribute to the disease progression and drug resistance.

Studying cancer cells we focus on molecular and functional aspects of epigenetic regulation and on the question whether we can translate this knowledge into diagnostic and therapeutic tools for the management of cancer. This 2019/2020 Master project will be embedded in our main research line with the objective:

- To study the role of citrullination events and key epigenetic changes in cancer cells as well as cells of the surrounding microenvironment.

Contact

Highly motivated candidates are invited to submit their motivation letter and their CV including a summary of academic records to: mbuschbeck@carrerasresearch.org

Project Title: Phylogeography of uniparental genomes in human populations

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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Summary of project summary or current research lines (less than 300 words).

mitochondrial DNA (mtDNA) and most of the Y chromosome, unlike the rest of the genome, do not experience recombination, which makes it extremely easy to construct phylogenies for their variation among humans, and allows also to use them to trace gene flow among human populations. New sequencing technologies have allowed to generate a large number of such sequences, both by targeting them, or as by-products of whole genome sequencing.

In our group, we use Y-chromosome and mtDNA sequences to address questions related to population history in several geographical areas:

* Catalonia and the Western Mediterranean
* Roma (Gypsies)
* SE Asia

Most of the analysis involves bioinformatic tools, although on occasion wet lab work may be required.

Project Title: **Unraveling the cell biology of the closest relatives of animals**

Project supervisors Elena Casacuberta, Iñaki Ruiz-Trillo

Institut de Biologia Evolutiva (CSIC-Universitat Pompeu Fabra)

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Summary:

Have you ever wondered how animals evolved from their unicellular ancestors? Have you ever wondered how are the protists that are most closely related to animals? Any idea how researchers develop new methodologies to convert an organism into a model organism?

In our labs we are working with different protists that are phylogenetically close to animals. For three of them, the icthyosporeans *Creolimax fragantisima* and *Abeoforma whisleri*; and the corallochytrian *Corallochytrium limacisporum,* we are developing genetic tools. These organisms have the potential to become important model to understand cell biology, because they have different life cycles and morphologies, from the coenocytic stage of Creolimax and Corallochrytrium to an incredible diversity of shapes and stages in Abeoforma (for pictures and videos of those taxa see:
"https://www.flickr.com/people/146564503@N06/"
"https://www.youtube.com/user/multicellgenomeLab")

A master student would join our project funded by the Moore Foundation to deeply study these emerging models in biology, by addressing questions about their cell cycle, their different life stages. We will also target with CrispR-Cas9 key genes to perform functional and evolutionary studies. The techniques involved in the project include basic molecular biology, cell culture, microbiology, and optical and fluorescent microscopy.

Project Title:

The regulation and function of mucosal antibody responses

Project Supervisor

Andrea Cerutti, MD, PhD

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Summary of project summary or current research lines (less than 300 words).

Project A. Pneumococcal vaccines induce immunity by stimulating systemic IgG responses, but the efficacy of these responses varies among vaccinated individuals. We hypothesize that IgA and IgM-coated gut commensal microbes contribute to this variability. In particular, we contend that the efficacy of pneumococcal vaccines depends on the configuration of the gut microbiota, which in turn relies on gut IgA and IgM production. We further argue that gut IgA and IgM responses enhance anti-pneumococcal IgG production by facilitating the activation of systemic pneumococcus-specific B cells.

Project B. Nasopharyngeal B cells mount IgD responses, but the function of such responses and the biology of IgD remain elusive. We hypothesize that secreted IgD promotes protective tolerance against aerodigestive antigens by linking B cells with both innate and adaptive arms of the immune system. We also argue that tandem-repeat galectins link secreted IgD with the receptor stabilizer CD44 and the endocytic receptor CD71. This IgD receptor complex would "arm" basophils, mast cells and phagocytes with an adaptive recognition system specific for aerodigestive antigens. Ligation of cell-bound IgD by these antigens would enhance Th2 cell-dependent B cell production of antigen-clearing IgG1 (in mice), IgG4 (in humans) and IgE antibodies. It would also stimulate tolerance by attenuating IgE-induced basophil and mast cell degranulation and by eliciting IL-10-mediated expansion of regulatory T cells.

References

1. Shan M, … , Cerutti A. Secreted IgD amplifies humoral T helper-2 responses by binding basophils via galectin-9 and CD44. ***Immunity*** 2018, 49:709-724.

2. Magri G, Comerma L, … Cerutti A. Human secretory IgM emerges from plasma cells clonally related to gut memory B cells and targets highly diverse commensals. ***Immunity*** 2017, 47:118-134.

Project Title: Epigenetic regulation of gene expression in malaria parasites

Project supervisor: Alfred Cortés
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Summary of project or current research lines (less than 300 words).

Two cells with identical genomes can have dramatically different phenotypes. If the differences are transmissible from one generation to the next, the differences are considered epigenetic. Our lab investigates how malaria parasites adapt to changes in their environment using spontaneous transcriptional variation controlled at the epigenetic level. Of the many genes regulated at the epigenetic level, our main focus at the moment is on clag3 genes, which are linked to solute transport and drug resistance, and pfap2-g, which is the master regulator of sexual conversion and transmission to mosquitoes. We investigate both the role of epigenetics in the regulation of these processes and the chromatin-based mechanisms regulating the expression of these genes. We also perform several studies at a genome-wide level. For our research we routinely use malaria parasite cultures, transcriptional analysis (usually by quantitative PCR), chromatin immunoprecipitation (ChIP), Illumina sequencing and generation of transgenic parasite lines using CRISPR/Cas9 technology.

Relevant recent publications from our group:

1. Bancells C, Llorà-Batlle O, Poran A, Nötzel C, Rovira-Graells N, Elemento O, Kafsack BFC, Cortés A, 2019, “Revisiting the initial steps of sexual development in the malaria parasite Plasmodium falciparum”, Nat. Microbiol. 4:144-154.
2. Mira-Martínez S, van Schuppen E, et al., Rosanas-Urgell A & Cortés A, 2017, “Expression of the Plasmodium falciparum Clonally Variant clag3 Genes in Human Infections”, J. Infect. Dis. 215:938-945.
3. Rovira-Graells, N., Crowley, V.M., Bancells, C., Mira-Martínez, S., Ribas de Pouplana, L. & Cortés, A., 2015 , “Deciphering the principles that govern mutually exclusive expression of Plasmodium falciparum clag3 genes”, Nucleic Acids Res. 438243-57.
4. Kafsack, B.F.C., Rovira-Graells, N., Clark, T.G., Bancells, C., Crowley, V.M., Campino, S.G., Williams, A.E., Drought, L.G., Kwiatkowski, D.P., Baker, D.A., Cortés, A. & Llinás, M., 2014, "A transcriptional switch underlies commitment to sexual development in malaria parasites", Nature 507:248-52.
5. Rovira-Graells, N., Gupta, A.P., Planet, E., Crowley, V.M., Mok, S., Ribas de Pouplana, L., Preiser, P.R., Bozdech, Z. & Cortés, A., 2012, “Transcriptional variation in the malaria parasite Plasmodium falciparum”, Genome Res., 22:925-38. Selected as a May 2012 highlight in Nature Reviews Genetics (Casci, T., 2012, “Adaptation: Malarial bet hedging”, Nat. Rev. Genet. 13:298-9).

Project Title: Understanding stress adaptation

Project supervisor: Eulàlia de Nadal

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Summary of project summary or current research lines

We aim to unravel how cells detect and respond to environmental changes. We focus our studies on the characterisation of stress signal transduction pathways, especially those regulated by MAP kinases of the Hog1/p38 family, also known as the stress-activated MAP kinases (SAPKs). Proper adaptation to stress involves the modulation of several basic aspects of cell biology, among them the cell cycle and gene expression. Using *S. cerevisiae* budding yeast as a model organism, as well as higher eukaryotic cells, we are dissecting the molecular mechanisms underlying cell response to changes in the extracellular environment and characterising the adaptive responses required for cell survival. Based on our knowledge of signal transduction and using synthetic biology, we also seek to modify cell behaviour to reprogram cell response to specific inputs/stimuli.

Research lines:

- SAPK signalling: Using quantitative data in single cells and mathematical modelling, together with mutational analyses, we study the basic signalling properties of stress-responsive MAP pathways and how to alter them.

- SAPK targets: Using proteomics, biochemistry and genetics, our main goal is to identify new targets for SAPKs and thus widen our understanding of cellular adaptation to stress. This information is expected to facilitate the characterisation of the bases of adaptation in eukaryotes.

- Cell cycle control: SAPKs act in several phases of the cell cycle to allow prompt response to extracellular stimuli and the maintenance of cell integrity. We are uncovering the mechanisms by which Hog1 and p38 SAPKs regulate the cell cycle.

- Regulation of mRNA biogenesis: SAPKs control critical steps of mRNA biogenesis and are thus key regulators of stress-responsive gene expression. Our main aim is to determine the contribution of multiple factors to overall gene expression in response to stress. We are also using genome-wide CRISPR screening to identify essential genes for stress adaptation.

Project Title: HYPOGLYCOSYLATION OF $Ca_V2.1$ AND PIEZO CHANNELS: NEW PATHOLOGICAL MECHANISMS AND THERAPEUTIC TARGETS FOR NEUROLOGICAL DISORDERS IN PHOSPHOMANNOMUTASE 2 DEFICIENCY

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Summary of project summary or current research lines

Phosphomannomutase Deficiency (PMM2-CDG), caused by deficiency in PMM2 enzymatic activity due to genetic mutations, is the most frequent congenital disorder of N-linked glycosylation (CDG). PMM2-CDG symptoms include severe neurological alterations. Progressive atrophy of the cerebellum is usually found in all PMM2-CDG patients, leading to the ataxia cerebellar syndrome, movement coordination disorders, abnormal eye movements, dysarthria and intellectual disability. Also, the stroke-like episode (SLE) is one of the unpredictable and serious neurological complications occurring in PMM2-CDG. Mechanisms underlying both SLE and cerebellar syndrome in PMM2-CDG are unknown and there are no guidelines for their prevention, detection and treatment. SLEs also complicate paroxysmal neurological diseases such as familial hemiplegic migraine (FHM), mostly caused by mutations in *CACNA1A* (encoding the neuronal pore-forming $Ca_V2.1$ channel α_{1A} subunit). We have recently reported similarity between clinical, neuroimaging and neurophysiological traits of PMM2-CDG patients and patients with *CACNA1A* mutations, including SLEs, ataxia, eye movement alterations and cerebellar atrophy. Accordingly, we found increased $Ca_V2.1$ activity (as occurs for FHM/ataxia CACNA1A mutations) due to deficient N-glycosylation, which may contribute to the development of both SLE and cerebellar syndrome in PMM2-CDG patients. Besides, we identified mild cranial trauma as a potential SLE trigger in PMM2-CDG patients. Mechanosensitive ion channels, including the Piezo family channel, have been suggested to underlie the transduction of different mechanical forces into a variety of neurological responses in the brain: i.e. neuronal excitability and neurotransmission; and YAP-related brain cell specification, neuropathic pain, and altered cerebellar development.
The overall objective of this proposal will be to study how hypoglycosylation affect the function of neuronal $Ca_V2.1$ and Piezo channels, and its relevance in SLEs and cerebral syndrome in PMM2-CDG, by using heterologous expression systems and cultured neurons endogenously expressing these channels (obtained from both wild-type and PMM2-CDG knock-in mice). Similar analysis will be performed in fibroblasts of patients with PMM2-CDG and healthy volunteers, and iPSC-derived neurons from those fibroblasts, to directly assess the degree of hypoglycosylation and dysfunction of $Ca_V2.1$ and Piezos in patients with distinct neurological phenotypes, and initiate a study of correlation with their clinical and genetic report.
Finally, in the context of an International Collaborative Project, we have identified novel selective $Ca_V2.1$ inhibitors as prospective hits to develop FHM therapeutic tools. As FHM/ataxia-linked $Ca_V2.1$ mutations and channel hypoglycosylation induce similar $Ca_V2.1$ gain-of-function, we will test the capability of these inhibitors to correct $Ca_V2.1$ hypoglycosylation effects, thus establishing a proof of concept to develop in the future a specific treatment for neurological events in PMM2-CDG.

Project Title: Engineering intracellular nanotools to image protein structures in vivo: resolving the mechanism of exocytosis

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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Summary of project summary or current research lines (less than 300 words).

Understanding the molecular mechanisms that drive life (and those that lead to death) requires structural characterization of the protein machinery sustaining the biology of the cell, both in a healthy and in a pathological situation. Historically, structural biology has been largely centered around *in vitro* approaches, as the only way to provide structures at the atomic scale. However, the degree of knowledge acquired to improve human health will be determined not only by the precision of the experimental measurements but also by their proximity to a physiological context. Therefore, to undertake future investigations relevant for biomedicine it will be necessary to implement structural biology in living cells.

Our group develops new methods of fluorescence microscopy that allow the study of macromolecular complexes directly in living cells. For instance, these methods can quantify protein-protein interactions and reconstruct the 3D architecture of protein complexes. We apply this new technology to study the molecular basis that control cell growth. The aim of the project is to develop new genetically-encoded nanotools to boost the power of quantitative fluorescence microscopy. In collaboration with the group of Alex De Marco, at the Monash University (Australia), we will also asses the implementation of these new nanotools in cryo-electron tomography. During the progression of the project the student will acquire a strong expertise in gene editing tools, advanced light microscopy and image analysis. Depending on the student's skills and interest, the project could also involve *in silico* integration of acquired data to model 3D structures of large protein complexes controlling exocytosis.

Project Title: Tumor stroma and cancer invasion during epithelial tumorigenesis

Project supervisor: **Antonio García de Herreros**, Programa de Recerca en Càncer, IMIM-Hospital del Mar, Parc de Recerca Biomèdica de Barcelona, Room 298.03, agarcia@imim.es, Tel 93 – 3160433.

Project summary or summary of current research lines:

Years ago we reported that Snail transcriptional factor down-regulated E-cadherin expression and induced an epithelial-mesenchymal transition (EMT) in tumor cells (Batlle et al Nature Cell. Biol. 2, 84-89, 2000). Our group has kept working on this transcriptional factor that is the main object of our research, not only as an E-cadherin repressor but also as an inductor of EMT. Therefore we have studied targets of Snail1 relevant for EMT and other effects of Snail1 expression in epithelial cells, such as the induction of invasiveness, resistance to apoptosis or stemness (for a recent article, Mazzolini et al, Nucl. Acid Res., 46, 146-158. 2018). We have also analyzed the mechanism of epithelial gene repression by Snail1 in genes directly inhibited by this factor, determining how Snail1 modifies epigenetic marks and also characterize the mechanism used to activate mesenchymal genes. We have also studied how Snail1 transcriptional activity is controlled. In the last years we have identified two new ubiquitin ligases modulated by several cellular stresses that down-reegulate Snail1 protein stability (Viñas-Castells et al, Nucl. Acids Res. 42, 1079, 2014). Moreover, we have recently characterized a new deubiquitinase, Usp27X that antagonizes the action of Snail1 E3 ligases and stabilizes Snail1 during EMT or fibroblast activation (Lambies et al, Cancer Res. 79, 33-46, 2019).

Although we are also interested in determining how Snail1 is upregulated in tumor cells by anti-neoplasic drugs, the most recent work of the group has been focused on the relevance of Snail1 expression in the tumoral stroma. We have described that Snail1 expression is detected in few cases in the epithelial component of the tumors, whereas is often observed in the stroma, more specifically in activated fibroblasts. Snail1 is necessary for the maintenance of the undifferentiated phenotype of mesenchymal stem cells a cellular entity very similar to cancer activated fibroblasts. Snail1 depletion causes the premature differentiation of these cells to adipocytes or osteoblasts (Batlle et al, Oncogene 32, 3381, 2013). Moreover, our results indicate that activation of mesenchymal stem cells or fibroblasts with TGF-β is impaired in Snail1 KO cells; Snail1 is required for a full transcriptional as well as functional response to this cytokine. Snail1 is also needed for the correct physiological function of activated fibroblasts, either in the pancreas (Loubat et al, Oncotarget, 7. 4468-4482, 2016) or during the process of wound-healing (Stanisavljevic et al, Cancer Res. 75, 284, 2015). We are currently characterizing the effect of Snail1 expression in fibroblasts on the coadjuvant effect of these cells on tumoral cell invasion and implantation. Our results indicate that the invasive capability of tumoral cells is markedly enhanced in the presence of fibroblasts, supporting the well-known effect of the stroma on tumor development. Snail1 expression in fibroblasts is required for this supportive effect (Lorena-Castellón et al, Cancer Res., 76, 6205-6217, 2016). The molecular basis of these effects is being investigated, both in in vitro assays (in cell culture) and in tumor animal models. Our group is also analyzing the role of Snail1 on other cells of the stroma, such as endothelial cells where it is required for tumor angiogenesis (Cabrerizo et al, in preparation). Finally we are also interested in the characterization of new drugs interfering with Snail1 expression and therefore enhancing the action of chemotherapeutic drugs on tumor cells.

Project Title:
Molecular mechanisms of endocytic traffic in health and disease

Project supervisor
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Summary of current research lines.

Our group is interested in understanding the molecular mechanisms underlying endocytic membrane traffic in eukaryotes and deciphering their relevance in human diseases. The endocytic pathway removes material from the cell surface in a highly regulated manner to either deliver it to the degradative compartments or to other cellular organelles or plasma membrane subdomains, thereby spatiotemporally controlling cell signalling, nutrient sensing and uptake, and cell reshaping. As a consequence, miss-function of the endocytic pathway has a major impact in neurological diseases and cancer. We use two experimental systems for the study of the endocytic pathway, the yeast *S. cerevisiae* and mammalian cultured cells, applying myriad of techniques including live-cell fluorescence microscopy of single endocytic events, quantitative electron microscopy and *in vivo* and *in vitro* membrane traffic assays. In *S. cerevisiae*, we investigate novel aspects of conserved molecular mechanisms. In this context, we have recently uncover an essential role in endocytosis of the yeast VAP (VAMP associated Protein) and ORP (Oxysterol Binding Protein Related Protein) homologues whose missfunction in humans leads to a moto-neuron disease (Encinar del Dedo (2017) Dev Cell). In mammalian cells, we focus in the study of genes not present in lower eukaryotes, which are likely to adapt the evolutionary conserved hard-core machinery to the complex physiological functions that endocytosis plays in multicellular organisms (Schmelzl (2002) EMBO Rep). In this context, we have identified a novel clathrin adaptor required for cell migration and cytokinesis, with a potential role in neurological diseases, dermatitis and cancer. The projects assigned to the students will be designed and developed in the context of one of these two research lines.

J. Encinar Del Dedo, F. Z. Idrissi, I. M. Fernandez-Golbano, P. Garcia, E. Rebollo, M. K. Krzyzanowski, H. Grötsch, M. I. Geli. “ORP-Mediated ER Contact with Endocytic Sites Facilitates Actin Polymerization” (2017) Dev Cell. 43:588-602.

I. M. Fernández-Golbano, F. Z. Idrissi, J. P. Giblin, B. L. Grosshans, V. Robles, H. Grötsch, M. M. Borrás and M. I. Geli*. “A cross-talk between PI(4,5)P_2 and CK2 modulates actin polymerization during endocytic uptake” (2014) Dev Cell. 30: 746-758.

F. Z. Idrissi, A. Blasco, A. Espinal and M. I. Geli. “Ultrastructural dynamics of proteins involved in endocytic budding” (2012) Proc Natl Acad Sci U S A. 109: E2587-94.

H. Grötsch, J. P. Giblin, F. Z. Idrissi, I. M. Fernández-Golbano, J. R. Collette, T. M. Newpher, V. Robles, S. K. Lemmon, M. I. Geli “Calmodulin dissociation regulates Myo5 recruitment and function at endocytic sites” EMBO J. (2010) 29: 2899-914.

F. Z. Idrissi, H. Grötsch, I. M. Fernández-Golbano, C. Presciatto-Baschong, H. Riezman and M. I. Geli (2008) “ Distinct acto/myosin-I structures associate with endocytic profiles at the plasma membrane” J. Cell Biol. 180: 1219-32.

B. Schmelzl, and M. I. Geli (2002) “An efficient genetic screen in mammalian cultured cells” EMBO Rep. 3, 683-87.

Project Title:
"EXPLORING MECHANISMS OF RESISTANCE IN ADULT AND PEDIATRIC T-ACUTE LYMPHOBLASTIC LEUKEMIA

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).
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Summary of project summary or current research lines (less than 300 words).
Despite recent improvements in T-cell acute lymphoblastic leukemia (T-ALL) therapy, approximately 20% of children and 50% of adult patients develop treatment-resistant disease. The power of new technologies such as whole genome/exome sequencing is rapidly changing the concept of leukemia evolution, as well as the possibility to predict patient outcome and response to particular treatments at early stages of the disease.

This project aims **to identify new mechanisms of resistance by using whole exome sequence (WXS) of matched DNA from adult T-ALL samples at diagnosis, remission and relapse**. We will use powerful in-house designed software (Oncodrive methods) to uncover **mutations driving tumor progression/maintenance, and those driving the process of resistance**, which will be functionally **validated in the appropriate genetic animal models and patient-derived xenografts**. In that context, we need to set-up conditions to *in vitro* culture leukemic cells. Part of the master student work will be focused on that.

Previous genomic data obtained from several leukemic/cancer models indicate that **mutations found at relapse were already present at diagnosis in variable frequencies**. In this context, increasing the sensibility of detection for driver and resistance-related mutations at the time of diagnosis is crucial for patient stratification and treatment protocol selection. With this objective, we will perform **high-depth sequencing of particular resistance-related mutations** identified in the first part of the project in all **diagnosis samples initially classified as negative**. We will use a minimum of 100 samples to increase the chance of **identifying rare pre-existing subclones and to obtaining enough statistic significance in terms of predicting relapse or therapy response.**

Project Title: Fighting the Resistance: Visible Light Photoswtichable Antibiotics

Project supervisor:
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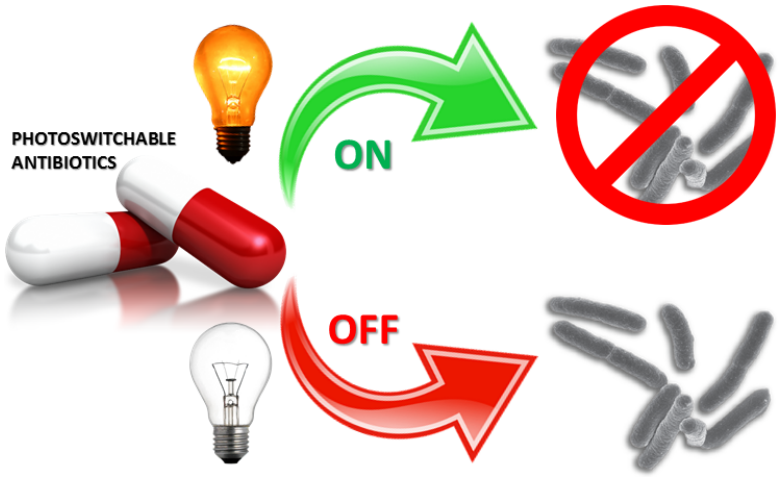
Summary of project summary or current research lines:
Antibiotic resistance is one of the major healthcare issues that humankind is facing at present and is becoming a growing concern as current therapies become inefficient against resistant strains. Discovering new classes of antibiotics that aim at new molecular targets can be helpful; however, these will eventually face the same fate as microbes become resistant to them due to their accumulation in the environment. Thus, ***a novel approach that changes the paradigm on how we fight against bacterial infections is on high demand.***

Photopharmacology has recently appeared as a unique way of turning drugs on and off using light. ***Switching antibiotics off after their therapeutic use will render them inactive to highly diminish the chances of resistance appearing as their accumulation in the environment does not increase the evolutionary pressure on bacteria.*** Most approaches to photoswitchable drugs rely on the use of azobenzenes, which require the use of harmful UV light for their activation. However, these can be modified to cause a red-shift that allows ***activation with visible light that does not harm tissues and can penetrate deeper than shorter wavelengths***.



The successful candidate will join a ***multidisciplinary project*** to work on ongoing research than covers most stages of drug design and development. This will combined with the use of state-of-the-art photoswitches currently being developed in the group, which can be used as a ***platform to develop several biomedical tools***.

Project Title:

Cloning, overexpression, purification and functional studies of proteins

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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Direct supervision at the bench will be carried out by an experienced member of the hosting lab.

Summary of project summary or current research lines (less than 300 words).

For biotechnological applications and assays of enzymes and other proteins it is indispensable to be able to produce sufficient amounts of pure material with which to perform biophysical, biochemical, functional and structural studies. The aim of the present module is to provide students of the BIOMED Master's Degree with the required practical skills to obtain large amounts (in the milligram range) of purified proteins as part of a wet-lab practicum in a biochemical laboratory dedicated to basic research. For this, the selected student will be introduced into key techniques aimed at cloning, recombinant overexpression, chromatographic purification of proteins, and functional assays under the guidance of an experienced researcher.

Thomas Graf lab

Project Title:

What determines a cell's reprogramming plasticity?

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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Summary of project summary or current research lines (less than 300 words).

Two of the most important questions in current stem cell research is how cells decide their fate and what makes already specialized cells plastic, capable to convert into another cell type? To study these questions, our laboratory has established two cell culture models that permit to convert B cells into another cell type, serving as models to investigate the mechanisms of mammalian cell fate decision. Starting from bone marrow derived pre-B cells, in the first model we induce their transdifferentiation into macrophages by the forced expression of the myeloid restricted transcription factor C/EBPa. In the second model we induce the cells' reprogramming into iPS cells, exposing them to a pulse of C/EBPa followed by the activation of the Yamanaka factors. In recent experiments in which we have analysed these two processes at the single cell level we made the surprising discovery that cells convert into the new cell type in an asynchronous way, that is, some cells do it rapidly and others more slowly. We were able to trace this back to a heterogeneity of the starting pre-B cells, finding that a subset of large pre-B cells can be reprogrammed at high frequencies but are more resistant to transdifferentiation while for a second target cell subset it is the other way around.

The project of the master student is to find out why these two types of closely related cells show such large differences in their reprogramming plasticity. For this she/he will perform cell sorting and cell reprogramming experiments as well as RNAseq, ChIPseq and ATACseq techniques. He/she will also learn how to apply bioinformatics tools to analyse the data.

Project Title

Gene-editing technology based therapeutics

Project supervisor

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Summary of project summary or current research lines

Our laboratory is focused on applied synthetic biology for therapeutic purposes. We have two lines of research, one in technology development for gene therapy, and one in skin microbiome engineering.

Advanced cell and gene therapies are gaining important impact in medicine. There are currently more than 2,500 on-going gene therapy trials on multiple diseases (cancer, genetic disease, infectious disease, etc…)[1] . However, multiple concerns have been raised on the safety of current technologies which prevent a wider deployment. Uncontrolled on-target[2], pro-cancer pathway activation[3], controversy on off-target[4], and lack of efficacy[5] still represent a major concern.

We are offering a master position in developing a new family of gene editing technologies that combines efficacy from viral vectors and precision of modern systems such as CRISPR/cas9. We will combine our system in a single unit called UNI-LARGE, to encapsulate tissue delivery and genome engineering.

Currently, we are deploying our technology to tackle congenital muscle dystrophies. We have initially focused in MDC1A (merosin-deficient congenital muscular dystrophy), which is a devastating disease caused my mutations in LAMA2 gene. However, we are planning to use our technology as a platform in further indications such as CAR-T therapy for cancer and others.

1- http://www.abedia.com/wiley/indications.php
2- Kosicki et al, Nat Biotech 2018
3- Haapaniemi et al, Nat Medicine 2018
4- Editorial comment: https://www.nature.com/articles/nmeth.4664
5- Mollanoori et al, Biotechnology letters 2018

Project Title:
Oxidative stress linked to toxicity and to signaling

Project supervisor:
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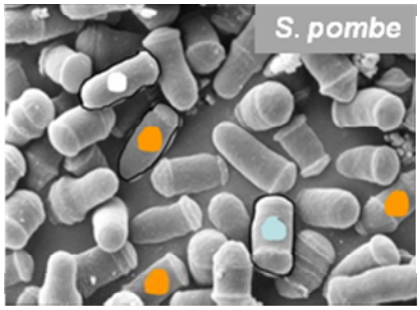
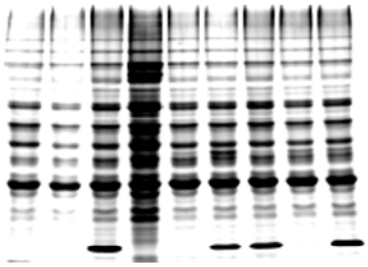
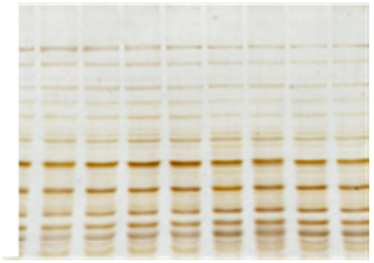
Summary of current research lines.
Our group is interested in studying the components and molecular mechanisms which regulate the responses to oxidative stress and the control of the cell cycle, using the fission yeast ***Schizosaccharomyces pombe*** as a model system. To obtain more information about the laboratory and about our research interests, please consult our group's web page (www.upf.edu/osccg). Some recent publications include:

Domènech et al. 2018. BMC Biol. 16:61.
Boronat et al. 2017. PLoS Genet. 13:e1006858.
Alves-Rodrigues et al. 2016. Cell Reports 14:885.
Encinar del Dedo et al 2015. PLoS Genet. 11:e1005106.
García-Santamarina et al. 2014. Nature Protocols 9:1131.
Calvo, I.A. et al. 2013. Cell Reports 5:1413.
Ivanova, T. et al. 2013. Mol. Biol. Cell 24:3350.
Calvo, I.A. et al. 2012. Nucleic Acids Res. 40:4816.
Gómez-Escoda et al. 2011. EMBO Rep. 12:84.
Zuin, A. et al. 2010. EMBO J. 29:981.
Moldón et al. 2008. Nature 455:997.

We have developed genetically-encoded fluorescent reporters to measure intracellular levels of hydrogen peroxide. The goal of this project will be to use these probes to measure oxidant fluctuations governing metabolic processes and cell cycle transitions.




Protein carbonyls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Universitat Pompeu Fabra Barcelona

Project Title: Evaluation of defects in social behavior in a new fish model of autism spectrum disorder

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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Summary of project summary or current research lines (less than 300 words).

Research in our lab is focused on understanding the roles that alternative splicing and other mechanisms of transcriptomic diversification play during vertebrate embryonic development and adulthood. In particular, we are very interested in learning how a special type of alternative exons, the microexons, contribute to the development and function of our brain. Microexons are highly conserved tiny exons (3-27nt) that are switched on during neuronal differentiation in vertebrates. Microexons impact proteins involved in various aspects of neuron physiology and differentiation, where they sculpt the surfaces of binding domains, often modulating protein-protein interactions in a neuron-specific manner.

Most microexons are specifically regulated by the neural splicing factor nSR100/SRRM4. Knockout mice for *Srrm4* show dramatic microexon misregulation and severe neurodevelopmental defects in both the central and peripheral nervous system, and most die soon after birth. Furthermore, microexon alterations have been associated with autism spectrum disorders (ASD) in humans. Interestingly, mice with reduced levels of Srrm4 expression recapitulate many hallmarks of ASD, including altered social behaviour. However, which specific microexons are responsible for these behavioural defects remains unknown.

To identify these microexons, we have developed a CRISPR-Cas9 KO screen in zebrafish, generating so far over 20 lines in which individual conserved neural microexons have been deleted. Among several other phenotypic analyses, our main goal is to test these mutants for defects in social behaviors. The proposed Master project will therefore involve working together with a PhD student that has set up in the lab a battery of experimental tests to analyze alterations in social interactions, locomotion, anxiety, stimulus-sensing response among others. The project will allow the candidate to learn how to work with zebrafish as a model organism (genetics and manipulation), how to perform different behavioral assays, and to analyze, interpret and discuss the data.

References
https://www.ncbi.nlm.nih.gov/pubmed/25525873
https://www.ncbi.nlm.nih.gov/pubmed/27984743
https://www.ncbi.nlm.nih.gov/pubmed/28193864

Project Title: DECIPHERING NOVEL MOLECULAR TARGETS FOR THERAPIES AIMED AT CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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Summary of project summary or current research lines (less than 300 words).

20% of children with acute lymphoblastic leukaemia (ALL), the most common paediatric cancer in developed societies, die within 5-years of diagnosis, highlighting the need to novel molecular targets for improving therapeutic strategies. Most of single nucleotide polymorphisms that confer susceptibility, as well as ALL-associated mutations and epimutations, lie in non-coding regions, frequently at regulatory regions, and could exert their functions by altering the regulation of the target genes that physically contact. Unfortunately, most of genes controlled by each regulatory element are unknown. Motivated by these findings, we are determined to significantly improve paediatric ALL clinical outcome by revealing novel genes associated with the development of this hematological disorder, which could be new therapeutic targets. For this aim, we propose to describe the three-dimensional genome architecture of hematopoietic stem cells and common progenitors, and to integrate this insight with ALL-associated genetic susceptibility, mutational and epimutational data. This project is based on the development of a new methodology to genome-wide detect the regulatory regions of the genome for all genes in rare cell types. In summary, this interdisciplinary project will provide unprecedented knowledge into our understanding of human haematopoiesis with a tremendous impact at regenerative medicine and blood malignancies.

Project Title: Unrevealing mechanism for p53-mediated tumour suppression

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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Summary of project summary or current research lines (less than 300 words).

Cancer is a disease that affects one of three of us at some point in our lives. The tumour suppressor gene p53 is mutated in more than half of the human cancers. Many pharma and biotech companies are working towards developing drugs to activate p53 in cancers with wild-type p53, or restoring wild-type p53 function in cancers driven by mutations in p53. However, there have been many difficulties in developing such strategies, and there is still extensive morbidity and mortality associated with cancers bearing p53 mutations. Given the obstacles to developing strategies for targeting wild-type or mutant, further understanding of basic p53 biology is required for successful clinical translation. Recent studies, including ours, have challenged the previously understood model of how the p53 gene is involved in tumour suppression. Our laboratory is focused on understanding the complexity of the p53 network in tumour suppression in different contexts. We use mouse models, genomic and biochemical approaches to investigate how p53 protects us from developing cancer. The Janic laboratory is part of Cell and Molecular Biology program at the Department of Experimental and Health Sciences (DCEXS) at University of Pompeu Fabra (https://www.upf.edu/web/cancer-biology/).

Project title Gene expression and cell signaling during Drosophila development

Project supervisor Gerardo Jiménez ICREA Research Professor

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https://www.icrea.cat/Web/ScientificStaff/gerardo-jimenez--canero-307

Summary of current research lines

Our research addresses the molecular mechanisms and pathways that control cell fate decisions during animal development. Most of our work uses the fruit fly, Drosophila, which allows us to combine classical genetic, cell biological and biochemical approaches with recently developed genome-editing technologies such as CRISPRCas9. One main line of research focuses on Ras-Erk signaling and its downstream effector Capicua (Cic), an evolutionarily conserved transcriptional repressor with key roles in normal development and human disorders. We are studying Cic function from different perspectives, including the analysis of its basic mechanism of action, its interaction with Erk signaling and other signal transduction pathways, and the functional significance of its two conserved isoforms, Short and Long. In addition, we have a long-term interest in transcriptional corepressors such as Groucho/TLE and Atrophin, which we are studying from a functional and mechanistic point of view. In the long term, our structural-functional studies are designed to characterize basic cell biological mechanisms that are relevant to human disease.

Cic controls anteroposterior body pattern formaton in the Drosophila embryo. In this system, Cic functions downstream of Ras-Erk signaling to regulate the tailless (tll) gene. In cic mutants, tll expression expands and this leads to repression of another patterning gene, knirps (kni). The cic mutation analyzed is equivalent to human cic mutations that cause oligodendroglioma and other tumors.

Recent publications

Papagianni et al. (2018) Proc. Natl. Acad Sci. USA 115, 1807-1812.

Simón-Carrasco et al. (2017)

Genes Dev. 31, 1456-1468. Forés et al. (2017)

PLoS Genetics 13, e1006622.

Yang et al. (2016) Proc. Natl. Acad Sci. USA 113, 10583-10588.

Forés et al. (2015) PLoS Genetics 11, e1004902.

Project Title:
Occupancy of histone H1 variants genome-wide and consequences of altering H1 levels on human chromatin organization.

Project supervisor

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Orientative project summary or summary of current research lines

We focus our research on the control of gene expression in human cells by chromatin organization, components and modifications. The degree of compaction of chromatin affecting a gene promoter dictates accessibility to transcription factors and RNA polymerase, and many chromatin modifying enzyme families act to overcome difficulties imposed by chromatin.

We investigate the role and specificity of histone H1 variants in chromatin organization and gene expression control. By RNA interference of the different human H1 variants we have found that they have different involvement in cellular processes such as cell cycle progression and gene expression. We have also described a differential role of H1 variants in pluripotency and differentiation. Currently, we are investigating the occupancy of H1 variants genome-wide by ChIP-seq (NGS) and the consequences of altering H1 levels on chromatin organization (ATAC-seq, DNA methylation, chromosome conformation-LADs, etc), with an extensive use of Genomics and Bioinformatics. Additionally, we are performing proteomics of H1 variant specific protein complexes in chromatin and nucleoplasm.

In a second line of research, we use an HIV promoter model to investigate the influence of chromatin organization at the integration site on HIV expression, with a focus on the role of heterochromatin and transcriptional interference on the establishment of viral latency.

References (on this subject):

- Izquierdo-Bouldstridge A*, Bustillos A*, Bonet-Costa C, Aribau P, Garcia D, Dabad M, Esteve-Codina A, Pascual L, Peiro S, Esteller M, Murtha M, Millán-Ariño LI, **Jordan A** (**2017**) Histone H1 depletion triggers an interferon response in cancer cells via activation of heterochromatic repeats. *Nucleic Acids Research* 45(20): 11622-42.
- Millán-Ariño LI, Izquierdo-Bouldstridge A, **Jordan A** (**2016**) Specificities and genomic distribution of somatic mammalian histone H1 subtypes. *BBA Gene Regulatory Mechanisms* 1859(3): 510-19.
- Mayor R*, Izquierdo-Bouldstridge A*, Millán-Ariño LI, Bustillos A, Sampaio C, Luque N, **Jordan A** (**2015**) Genome distribution of replication-independent histone H1 variants shows H1.0 associated with nucleolar domains and H1X associated with RNA polymerase II-enriched regions. *Journal of Biological Chemistry* 290(12):7474-91.
- Millán-Ariño LI, Islam A, Izquierdo-Bouldstridge A, Mayor R, Terme JM, Luque N, Sancho M, López-Bigas N, **Jordan A** (**2014**) Mapping of six somatic linker histone H1 variants in human breast cancer cells uncovers specific features of H1.2. *Nucleic Acids Research.* doi: 10.1093/nar/gku079
- Terme JM*, Sesé B*, Millán-Ariño L, Mayor R, Izpisua-Belmonte JC, Barrero MJ, **Jordan A** (2011) Histone H1 variants are differentially expressed and incorporated into chromatin during differentiation and reprogramming to pluripotency. *Journal of Biological Chemistry* 286(41):35347-57
- Sancho M, Diani E, Beato M, **Jordan A** (**2008**) Depletion of human histone H1 variants uncovers specific roles in gene expression and cell growth. *PLOS Genetics*- Oct;4(10):e1000227.

Project Title:

Cell fate choices during brain development and how these are linked to malformation.

Project supervisor:

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Summary of project summary or current research lines:

Our group studies the microtubule cytoskeleton and how defects in its organization are linked to diseases such as brain developmental disorders. Mutations in genes encoding components of the microtubule cytoskeleton can cause microcephaly and other brain malformations, which are frequently accompanied by intellectual disabilities. While the underlying mechanisms remain poorly understood, aberrant cell fate has emerged as an important determinant. During brain development microtubules are crucial during both proliferation and differentiation, assembling mitotic spindles in dividing neural progenitors and driving cell polarization including growth and branching of cellular extensions in differentiating neuronal cell types. Interfering with these functions can result in various cell fates including cell cycle exit, premature differentiation, or apoptosis, depending on the context. The student will participate in one of our on-going projects aimed at deciphering the cellular roles of proteins implicated in defective brain development, to learn about potential alterations in cell fate when their function is compromised by mutation. The work will involve culture and manipulation of cell lines, primary cells derived from mouse brain, or patient fibroblasts, cell-based assays, and analysis by immunofluorescence microscopy.

Project Title: Insulin signalling and RNAi in insects.

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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Summary of project summary or current research lines (less than 300 words).

At present in our group we are working on two related research lines:

1) We are studying the function of the insulin pathway in insects and its relationship with different processes, mainly reproduction and growth. To address this issue, different methodologies are used, among them interfering RNA (RNAi) techniques and the analysis of the phenotypes produced by this treatment, using quantitative real-time PCR to quantify mRNA levels or different microscopy techniques.

We are currently investigating the differential function of the various existing insulin receptors as well as the regulation of the expression of the different insulin-like peptides (ILPs).

2) We are interested in understanding how RNAi works in insects to produce the RNA depletion effect. This study involves the analysis of the characteristics of the dsRNA molecules for producing the maximum effect, how Dicer, R2D2 and Argonaute enzymes contribute to the knock down and which intermediate molecules (small interfering RNAs) are more likely to be produced. The methodologies used in this case include again RNAi and expression studies, but also analysis of RNASeq libraries obtained by Next Generation Sequencing.

We use as a model the cockroach *Blattella germanica*, a species with which we have been working for more than twenty years and in which RNAi works extraordinarily well.

Please, go to our website http://www.biologiaevolutiva.org/jmaestro/ for more information.

Ascertaining the role of selenium in pancreatic/bladder cancer aetiology according to genetic variations in the selenoprotein gene pathways

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Centro Nacional de Investigaciones Oncológicas / Spanish National Cancer Research Centre (CNIO)

Background: Pancreatic ductal adenocarcinoma (PDAC), accounting for 95% of all pancreatic cancer (PC) is the fifth leading cause of cancer-related death in Europe. The aggressive nature of PDAC and lack of early markers and effective treatment options result in one of the lowest relative five-year survival rates of all cancers (7%). Urothelial bladder cancer (UBC) is one of the most common cancer types among men worldwide, especially in developed countries. Few risk factors of both cancer types have been firmly established.
Evidence from animal models suggests that Selenium (Se), an essential trace micronutrient for human health, prevents carcinogenesis by combatting oxidative stress (OS). The biological activities and potential anti-carcinogenic properties of Se likely result from the incorporation of the amino acid selenocysteine in selenoproteins, which synthesis is influenced by both Se availability and genetic factors. Selenoproteins include the glutathione peroxidases (GPX), which protect cells from damaging oxidative radicals, and selenoprotein P (SEPP) which is also critical for Se transport. Functional single nucleotide polymorphism's (SNPs) in 3'-untranslated region (UTR) sequences needed for Selenocysteine incorporation, the promoter, and coding regions of selenoprotein genes GPX1, GPX3, GPX4, SEPP1 (gene coding for SEPP), SELS, TXNRD1 and SEP15, amongst others, can influence Se incorporation. Other essential nutrients, such as zinc (Zn), and copper (Cu) have shown to play vital roles in Se uptake, and the antioxidant network system plays another pivotal role in this regard.
The anti-cancer effects of Se have been evidenced by some in vivo and in vitro studies, but epidemiological studies assessing the association between Se and either PDAC or UBC risk are scarce and limited by sample size and an overly simplistic view of Se biology to come to any firm conclusion. None of the previous epidemiological studies, indeed, have accounted for the influence of particular selenoproteins genotypes on the association between Se status and risk for these cancers. Thus, Se is a major question in relation to susceptibility to develop PDAC/UBC in Europe, where Se status is known to be sub-optimal possibly due to the occurrence of particular selenoprotein genotypes in the population and low Se concentrations in soil.

Objective: After assessing determinants of Se status within the selenoprotein gene pathway (Aim 1), we aim to investigate the association between Se biomarker levels (in toenails) and risk of PDAC/UBC (Aim 2), within the PanGenEU study (an Europan multicentric case-control study on PDAC) and the Spanish Bladder Cancer/EPICURO Study, accounting for covariates and determinants of Se status (Se from dietary intake and supplements, biomarkers of other nutrients, genetic variants of selenoproteins functionality and signalling network loci, activity of the antioxidant network system and epigenetic markers) as potential effect modifiers of the association. The independent effect of these determinants on the abovementioned associations will be also assessed.

Research design: A case-control study (Ncases~2,500/Ncontrols~2,000 from PanGenEU regarding PDAC, or EPICURO regarding UBC) is proposed to analyse the association between dietary Se and PDAC/UBC risk. A second Se exposure indicator will be total Se measured in toenails by Inductively Coupled Plasma Mass Spectrometry (ICPMS). This technique will simultaneously measure several metals (Se, Zn, Ca, and others). Dietary intake of Se will be estimated by combining food frequency data collected at recruitment, country-specific portion sizes, and information from Se content in foods (food composition databases and literature review).
Single nucleotide polymorphism (SNP) data will come from genotyped data. Candidate genetic loci for Se uptake and function will be selected (SEP15, SELS, etc.) and signalling networks will be identified using bioinformatics tools based on integrative toxicogenomics database and known Se functionality loci (selenoproteins). Genetic variants of the antioxidant network system will be also identified. DNA methylome data is also available. CpGs that are differentially methylated with Se status will be identified with linear models of methylation levels at each probe as a function of Se status as well as dietary Se.

Project Title: GENETIC CONTROL OF SPINAL CORD MORPHOGENESIS AND GROWTH, A MODEL TO STUDY NEURODEVELOPMENTAL DISORDERS

Project supervisor: Elisa Martí

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Summary of project summary or current research lines

Our group aims to understand the mechanisms that control morphogenesis and growth in the vertebrate nervous system, with a particular focus in the spinal cord (the CNS region that controls body movement). To achieve this our group combines functional analysis in model organisms (zebrafish, chicken and mouse embryos) with data from high-throughput sequencing and proteomics and high resolution imaging, with the aim of building quantitative description of the growing spinal cord. This will as well as shed light on the origin of neurodevelopmental disorders.

Relevant recent papers from the lab

Le Dréau, et al., (2018) Elife. 2018 Aug 10;7. pii: e37267. doi: 10.7554/eLife.37267

Saade et al., (2017) Nature Cell Biology 19, 493–503 (2017) doi:10.1038/ncb3512

Rabadán et al., (2016) Development 143(12):2194-205. doi: 10.1242/dev.134981

Le Dréau, et al (2014) J Cell Biol. 204 (4) 591-605) doi: 10.1083/jcb.201307031

Saade, et al (2013) Cell Reports 4(3):492-503. doi: 10.1016/j.celrep.2013.06.038

Project Title: **"Epigenetic defects in intellectual disability: role of histone demethylase PHF8"**

Project supervisor:

Group: Signaling to chromatin, IBMB-CSIC, Parc Cientific

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Summary of project summary or current research lines (less than 300 words).

Student Project:

Intellectual disability (ID) is a highly diverse group of cognitive disorders with a high incidence in most populations. The causes underlying ID are extremely heterogeneous and include environmental factors, chromosomal aberrations and single mutation. Mutations in more than 300 genes have been shown to give rise to ID. Strikingly, a significant proportion of these genes are directly or indirectly involved in epigenetic regulation. Epigenetic mechanisms have a determinative impact on the regulation of gene expression through modulation of the chromatin structure. They are linked to normal neuronal function and to neurological disorders, in particular ID. Recently it has been shown that mutations in the histone demethylase PHF8 gene cause ID and autism. PHF8 removes mono- and dimethyl-lysine 9 on histone H3 (H3K9me2) and monomethyl-lysine 20 on histone H4 (H4K20me1). Mutations in and near the PHF8 JmjC (catalytic)-domain are associated with ID with cleft lip and/or a cleft palate (CL/P). Interestingly, many of these mutations impair its histone demethylase activity. How mutations on PHF8 lead to ID remains unclear. In the project the student will help to characterize PHF8 function during neural differentiation using mouse embryonic neural stem cells as a model.

Project Title: Targeting pregnant women for malaria surveillance: new tools and approaches for malaria elimination

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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Summary of project summary or current research lines (less than 300 words).

Antenatal clinics (ANC) can provide accessible information of theoretically healthy women, which might serve as a proxy of several health issues, mostly infections, at the community level. Malaria surveillance among pregnant women at ANCs, combined with other sources of surveillance data, can provide contemporary data on the level, and changes in levels, of malaria burden in the population for successful malaria control and elimination, while improving the management of malaria at first ANC contact as well as ANC performance. The overall aim of this project is to investigate multiple scales of P. falciparum dynamics (from genes to spatial-temporal patterns) in pregnant women at first antenatal visit with the ultimate goal of assessing their value to provide actionable information for malaria control and elimination. To achieve this goal, we will apply novel methods to characterize malaria exposure and infecting parasites at ANCs to derive precise metrics of transmission. We will also characterize the infecting parasites at the molecular level and the immune responses in pregnancy that reduce the adverse effects of malaria infections. The use of these tools in two districts from Southern Mozambique will allow us to compare malaria levels and trends at ANCs with patterns in the community and to develop methods to interpret ANC data in elimination settings. This research will advance the frontier of malaria epidemiology and physiopathology by shedding light on the importance of pregnant women as reservoirs of malaria transmission that may endanger elimination and ultimately of their value to sense malaria and provide data for direct action.

Project Title: Diagnosis and surveillance of vector-borne viruses and hemoparasites across the human-wildlife interface in the Amazon Basin.

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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https://www.isglobal.org/researcher?p_p_id=viewpersona_WAR_intranetportlet&p_p_lifecycle=0&p_p_col_id=column-3&p_p_col_count=1&_viewpersona_WAR_intranetportlet_struts_action=%2Fview%2FpersonaView&_viewpersona_WAR_intranetportlet_personaId=3300&_viewpersona_WAR_intranetportlet_typeOfPeople=researcher

Summary of project summary or current research lines (less than 300 words).

Vector-borne diseases are an important and re-emerging public health problem in Latin America, particularly in the highly biodiverse Amazon Basin. In highly biodiverse ecosystems, vector-borne pathogens, such as arbovirus and some malaria species, are maintained in a large variety of zoonotic cycles involving arthropod vectors and wildlife animal reservoirs. However, there are no sensitive diagnostic tools for the surveillance and diagnosis of zoonotic pathogens in the Amazonian wildlife, due to logistic and financial restrictions, as well its challenging, remote settings and complex multi-host ecosystems. We propose a monitoring system for vector-borne diseases in tropical regions based on the development of an innovative next generation sequencing diagnosis approach and a low-cost, multi-species collection strategy for wildlife biological samples. To achieve this, we will characterize the epidemiology of circulating pathogens in the Peruvian and Brazilian Amazon Basin by the evaluation of biological samples collected in FTA filter paper, which has been proven to be a cost-effective method for surveillance in remote tropical regions. This approach will address one of the main challenges faced in the disease surveillance in large tropical rainforest: the high cost of monitoring remote, isolated areas. This project will design a low-cost and appropriate monitoring system adapted to the difficult and isolated conditions of these remote Amazonian settings and reduces the need for cold chain during storage and transport in tropical settings that allows carrying out research and surveillance of emerging diseases. We will validate a novel diagnosis platform focused on a broad range of infectious pathogens, and elaborate an epidemiological framework that includes the interfaces of wildlife, vectors and humans in the same area from a synchronic and diachronic point of view.

Project Title:

Alzheimer's disease and insulin resistance: insulin signalling in hippocampus regarding regulation of amyloid beta-peptide production and neurotoxicity

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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Summary of project summary or current research lines (less than 300 words).

This project aims to elucidate the causes of sporadic Alzheimer's disease (AD) and to clarify the relevance of the basal forebrain cholinergic system (BFCS) and hippocampus in the etiopathology of the disease. The project has at least two main objectives:

i) To explore the function of the insulin receptor (IR) in the NGF-sensitive cholinergic neurons of the basal forebrain based on its selective localization and expression pattern.

ii) To clarify the role of IR signalling in BFCS and hippocampus to generate knowledge that may bring up new answers to the question of why these group of neurons degenerate early in AD. It means to establish a mechanistic link between diabetes mellitus, a known risk factor for AD, and the neurodegeneration of the BFCS and hippocampus observed in early stages of AD. Due to the role of IRS adaptor protein in the insulin intracellular signalling pathway, we will study a well-known insulin-resistance mechanism linked to diabetes, based on the JNK-dependent ser307 phosphorylation of IRS-1 and how this disturbs the intracellular signalling and the survival of this group of neurons by affecting the downstream activation of the Akt pathway and the upregulation of neuronal markers.

Project Title: Search of anti-*Trypanosoma cruzi* compounds in bird plasma.

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

Julio Alonso Padilla, PhD, Investigador Post-doctoral; julio.a.padilla@isglobal.org; T.: 932275400 – ext.: 4569; ISGlobal, Carrer Roselló 149, 08036 Barcelona.

Summary of project or current research lines (less than 300 words).

Chagas disease is a neglected disease caused by the parasite *Trypanosoma cruzi* (*T. cruzi*). Vectors that transmit the infection are endemic to America, where the disease has a huge social and economic impact. Migratory flows and vector-independent transmission routes have spread the disease to non-endemic areas like Europe. The World Health Organization estimates there are 7 million people infected worldwide. The vast majority of them are in Central and South American countries.

There are two drugs to treat the infection, benznidazole and nifurtimox. Despite they have a good efficacy against the acute phase of the disease, this is mostly asymptomatic, goes undiagnosed, and untreated. At the chronic symptomatic stage, when life-threatening disruption of heart and/or gut tissues occurs, the efficacy of the drugs is variable. Moreover, both drugs have frequent side effects associated. Thus, availability of safer and more efficient drugs for Chagas disease is an urgent clinical need.

We propose to search for new anti-*T. cruzi* compounds in bird plasma. Birds are refractory to the infection by *T. cruzi.* Historical studies have pointed out that such refractoriness is due to parasite lysis by bird plasma components. In order to identify the bird plasma components that lyse the parasite we will fractionate it by physicochemical methods into distinct fractions. We will test the fractions for their anti-*T. cruzi* activity in biological assays. Those fractions that lyse and/or inhibit the parasite growth will be further characterized.

Project Title: The use of *Trypanosoma cruzi* biologicals as a source of anticancer molecules.

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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Summary of project or current research lines (less than 300 words).

Background: discovery of anticancer therapies is a major challenge for medical science. Despite advancements in diagnosis and treatment, more potent and less toxic drugs are urgently needed. In their search, therapeutic use of pathogens and their biological material is being considered. This subject was pioneered by the protozoan parasite *Trypanosoma cruzi*, causative agent of Chagas disease. Although its antitumor application in animal and clinical studies yielded promising results, investigation was discontinued in late 1960´s. We propose to resume it with currently available biotechnological tools and updated knowledge on the biology of cancer disease and *T. cruzi*. Based upon them we will mine parasite derived biologicals for their anticancer properties. Fractions from extracts of *T. cruzi* mammalian infective stages (trypomastigotes and amastigotes) will be obtained, and their antitumor activity assessed in vitro on selected cancer cell lines from non-small cell lung and pancreatic cancers (respectively, NSCLC and PDAC).

Goal: identification of parasite derived products with antitumor activity in in vitro models of NSCLC and PDAC.

Expected outcome: the project might yield chemical departure points to further develop inhibitors against two cancer types that are in most need of more efficacious therapies. Notably, bearing in mind that the NSCLC and PDAC models to be used will be derived from patients´ primary tumors, and finely emulate tumor microenvironment upon implant, a prospective clinical translation of the results could be quickened and not be liaised to the current huge attrition rate.

Project Title: An epitope-based vaccine for Chagas disease.

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

Julio Alonso Padilla, PhD, Investigador Post-doctoral; julio.a.padilla@isglobal.org; T.: 932275400 – ext.: 4569; ISGlobal, Carrer Roselló 149, 08036 Barcelona.

Summary of project or current research lines (less than 300 words).

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There are two drugs to treat the infection, benznidazole and nifurtimox. Despite they have a good efficacy against the acute phase of the disease, this is mostly asymptomatic, goes undiagnosed, and untreated. At the chronic symptomatic stage, when life-threatening disruption of heart and/or gut tissues occurs, the efficacy of the drugs is variable. Moreover, both drugs have frequent side effects associated. Such features emphasize the need for a safe and effective vaccine. Nonetheless, vaccine development is hindered by the biological complexity of the parasite, as well as of its chronic interaction with the human host.

Vaccine approaches based on heat-killed or attenuated pathogens are far from ideal due to safety concerns. In contrast, synthetic vaccines could prove effective in treating and preventing Chagas disease. Based on the availability of *T. cruzi* genomic information, and recent advances in bioinformatics that provide a plethora of immunoinformatic tools we have identified a series of conserved B cell, CD8 T cell and CD4 T cell epitopes to ensemble a vaccine against the infection. We propose to test them and validate their use with that purpose by a series of biological assays in vitro. Those epitopes with the most promising characteristics will be considered for inclusion in a vaccine construct.

Project Title:

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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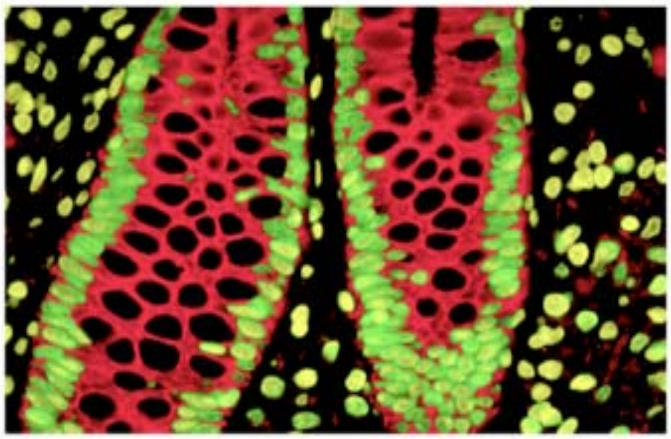
Summary of project summary or current research lines (less than 300 words).

My group's main research objective is focused on the characterization of chromatin dynamics and epigenetics in cancer and in epithelial-to-mesenchymal Transition (EMT). Our hypothesis is that during ***tumour progression*** and acquisition of malignant traits, ***global epigenetic changes*** together with ***high-order chromatin reorganization*** occurs to convert a non-invasive cell with the same DNA sequence in a more malignant and invasive cancer cell, which behaves completely different in the same biological environment. Large-scale mapping of genome-related parameters and their comparison is a logical and necessary next step in the exploration of genomes to understand how they are converted into malignant cells.

In the next few years, we aim to use very well-established EMT cellular *in vitro* models, together with patient–derived xerographs (PDXs) in different tumour stages (from low metastatic to high metastatic) to fully characterize the ***epigenetic changes*** together with ***high-order chromatin reorganization*** that are required in this process.

We will fully exploit the knowledge we will obtain about the epigenetic landscape and the 3D structure during this malignant process. First, we will use chromosome conformation–based techniques together with ChIP-seq, ATAC-seq and RNA-seq techniques; by combining the data obtained with excellent computational and statistical tools during the EMT process, a largely uncharted area with tremendous potential for ***early diagnosis***. Second, we will pioneer linking ***chromatin conformation changes*** within the acquisition of malignant traits. Third, we will evaluate the ***functional consequences*** of these changes in genes and pathways. Fourth, we will analyse ***how*** the movements take place at ***molecular level*** to identify putative drivers that can be targeted in the future. Finally, we will design a multi-genome PCR set of primes and FISH detection coupled with a ***complete bioinformatics analysis platform***. Thus, the project will ***translate research of chromatin conformation in cancer*** to the clinical setting.

Gene Regulation in Stem Cells, Cell Differentiation & Cancer



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Summary of project summary or current research lines

ZEB1 and ZEB2 are key regulators of stem cell phenotype, cell differentiation, and tumor initiation and progression. Our group is a pioneer and an international reference in the study of the ZEB transcription factors. The selected MSc student will have the opportunity to work in one of the hottest areas in cellular biology and/or molecular oncology. There are possibilities to develop an MSc project investigating the role of ZEB1 and ZEB2 in a number of different and timely projects involving cell differentiation (e.g., stemness, reprogramming) and oncology (cancer-tumor microenvironment crosstalk, metabolic reprogramming, cancer stem cells). In the area of cell differentiation, our group is focused on skeletal muscle and hematological and epithelial cells. In the area of cancer, we use colorectal and ovarian carcinomas and hematological neoplasias as the main models.

The project will make use a wide array of in vitro and in vivo approaches including transgenic mouse models unique to our group and high throughput techniques (RNAseq, metabolomics). The MSc student will also have the chance to participate in other projects currently ongoing in the group.

See https://www.icrea.cat/Web/ScientificStaff/antonio-postigo-379 for selected publications by the group

Requirements: Bachelor in Biology, Biotechnology or related biomedical-related discipline. Candidates with a strong academic record (higher than 2.8/4.0 or 8.7/10), previous lab experience and interested in pursuing later a PhD will receive special consideration in the selection process.

Recent Publications by the Group (as corresponding author): ***Nature Commun*** 10:1364 (Impact Factor 12.3); ***Nature Commun***. 9:2424 (IF 12.2); ***Nature Commun***. 4:2650 (IF 12.2); ***Nature Commun***. 5:5660 (IF 12.2); ***Nucleic Acids Res*** 46:10697 (IF: 11.6), ***EMBO J*** 36:3336 (IF 10.6); ***Gut*** 66:666 (IF 17.1); ***PNAS*** 108:19204 (IF 9.8); ***Clin Cancer Res*** 19:1071 (IF 10.2); ***Cell Death Differ*** 21:247 (IF 8.2); ***Oncogene*** 34:550 (IF 8.0)

Information. To obtain more information and to set up a visit to the laboratory, please send CV and the names and contact details of 2-3 persons familiar with the candidate's academic or research performance to **idibaps.postigo2@gmail.com** indicating "**Master UPF** " in the subject of the email.

Project Title:

Influences of pro-cognitive drugs on neural network dynamics in the mouse brain

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

Mª Victoria Puig Velasco, PhD (IMIM)
Principal investigator at IMIM (PRBB) in the Neurosciences Programme, group of "Recerca clínica en farmacologia humana i neurociències".
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Summary of project summary or current research lines (less than 300 words).

The Puig team at IMIM is looking for highly motivated and talented students willing to participate in a project related to the study of schizophrenia and cognition. More specifically, the project aims at better understanding the cellular mechanisms underlying the actions of pro-cognitive compounds in a mouse model of schizophrenia. We are currently investigating the influences of pro-cognitive drugs in neural network dynamics via chronic recordings of neural oscillatory activity in mice trained to perform several cognitive tasks. Data analyses focus on changes in the communication between different brain regions (alterations in synchrony of neural activity). This project combines several sophisticated techniques such as neuropharmacology, cognitive neuroscience, *in vivo* electrophysiology, and programming (Python).

We are a young laboratory that has recently launched at IMIM. The student will participate in this high impact project by helping in chronic recordings of neural network activity in mice and analysing neural data. The student should have enough knowledge of neuroscience to understand the goal of the project and the technical approaches used and be highly motivated to learn new tools in a scientific environment.

References:
Celada P, Puig MV, Artigas F. (2013) Serotonin modulation of cortical neurons and networks. Frontiers in Integrative Neuroscience; 7:25.
Puig MV, Miller EK (2012). The role of prefrontal dopamine D1 receptors in the neural mechanisms of associative learning. Neuron; 74(5): 874-886.
Puig MV, Gulledge AT (2011). Serotonin and prefrontal cortex function: neurons, networks, and circuits. Molecular Neurobiology; 44(3): 449-464.

Project Title: The synergistic effect of protein interaction on brain cortical structure. An MRI – PET study.

Project supervisor:

Dr. Eduard Vilaplana, PhD

Post-doctoral fellow in the Unidad de Memoria de Sant Pau

Servicio de Neurología - Hospital de la Santa Creu i Sant Pau

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Summary of project summary or current research lines:

Alzheimer's disease is the most common form of dementia and an increasing socio-economic problem as the world population ages. The pathophysiological alterations of Alzheimer's disease would start two decades before the clinical symptoms appear, which is called the pre-clinical phase. According to the amyloid cascade hypothesis, changes would begin with extracellular deposition in the brain of the protein amyloid-ß, followed by intracellular accumulation of hyperphosphorylated tau, hypometabolism and functional alterations, atrophy and finally cognitive decline. The effect of amyloid and tau on brain structure, however, remains controversial.

New imaging biomarkers and complex multimodal approaches could improve our understanding of Alzheimer's disease. An ongoing research project at the Alzheimer lab of the Memory Unit of Hospital de Sant Pau studies the effects of the proteins ß-amyloid and phosphorylated tau on the cortical structure, and two risk factors such as aging and the presence of ε4 apolipoprotein's allele. Possible interactions between biomarkers and these risk factors in the effect on brain structure remains uncertain. A more precise knowledge of this stage is essential for a better design of clinical trials in preclinical Alzheimer's disease, when the first clinical symptoms in the patient are not yet apparent.

The main objective of this multimodal study is to assess, through brain MRI and PET, the effect of amyloid and tau on brain structure and its potential synergistic effect. In this project, the master student will:

- Familiarize with Alzheimer's disease pathophysiology in a high interdisciplinary atmosphere.
- Learn to manage brain image processing tools
- Estimate cortical thickness using Freesurfer to study brain macrostructure taking advantage of high-resolution structural MRIs.
- Quantify the deposits of ß-amyloid and tau in the brain of Alzheimer's disease patients using PET
- Develop statistical approaches to study the local effect of protein deposition on brain structure

Project Title: Resting-state functional connectivity in preclinical Alzheimer's disease.

Project supervisor:

Dr. Eduard Vilaplana, PhD

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Summary of project summary or current research lines:

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New imaging biomarkers and complex multimodal approaches could improve our understanding of Alzheimer's disease. During the last decade there has been a growing interest in functional MRI, a technique that allows studying brain networks and cortical connectivity. It has been hypothesized that changes in brain connectivity could antedate structural brain changes and thus enable the study of Alzheimer's disease in a very early phase. Nevertheless, few works have studied the brain connectivity in the preclinical phase.

The main objective of this project is to study the brain connectivity in a multimodal fashion. The main hypothesis of this work is that brain connectivity is altered by aging and Alzheimer's.

In this project, the master student will:

- Familiarize with Alzheimer's disease pathophysiology in a high interdisciplinary atmosphere.
- Learn to manage brain image processing tools
- Process functional resting-state MRIs
- Study the effect of age and Alzheimer's disease on brain connectivity
- Learn concepts of graph theory and network analyses
- Develop statistical approaches to integrate the findings

Project Title: Cortical microstructure. Looking beyond atrophy: a diffusion-MRI study.

Project supervisor:

Dr. Eduard Vilaplana, PhD

Post-doctoral fellow in the Unidad de Memoria de Sant Pau

Servicio de Neurología - Hospital de la Santa Creu i Sant Pau

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Summary of project summary or current research lines:

Alzheimer's disease is the most common form of dementia and an increasing socio-economic problem as the world population ages. The pathophysiological alterations of Alzheimer's disease would start two decades before the clinical symptoms appear, which is called the pre-clinical phase. According to the amyloid cascade hypothesis, changes would begin with extracellular deposition in the brain of the protein amyloid-ß, followed by intracellular accumulation of hyperphosphorylated tau, hypometabolism and functional alterations, atrophy and finally cognitive decline.

New imaging biomarkers and complex multimodal approaches could improve our understanding of Alzheimer's disease. In this regard, there has been interest in diffusion MRI, a technique that allows to quantify the movement of water particles in the brain. It has been recently hypothesized that cortical diffusivity could be a sensitive biomarker to detect neurodegeneration in the brain but no study has assessed its value as a prognostic marker. The main objective of this project is to study cortical diffusivity in Alzheimer's disease.

In this project, the master student will:

- Familiarize with Alzheimer's disease pathophysiology in a high interdisciplinary atmosphere.
- Learn to manage brain image processing tools
- Process diffusion and structural MRIs
- Study the dynamics of cortical diffusivity in Alzheimer's disease cross-sectionally and longitudinally
- Familiarize with statistical approaches to integrate the findings

Project Title:
Deciphering how cell diversity is generated in the developing hindbrain

Project supervisor

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Summary of project summary or current research lines (less than 300 words).

The vast diversity of cells of the Central Nervous System is generated from a small, heterogeneous population of progenitors that undergo transcriptional changes during development to sequentially specify distinct cell fates. Guided by cell-intrinsic and -extrinsic cues, neural progenitors carefully regulate when and how many of each cell type is produced, enabling the formation of functional neural circuits. In Drosophila, regulation of neuroblast competence, and therefore expansion of neural diversity, is achieved by specifying distinct neuronal fates using combinatorial temporal patterning (Bayraktar and Doe, 2013). This has been proved the same in two mammalian neural structures such as the retina and the cortex.

Our goal is to unveil how spatiotemporally controlled cell specification (neurons and glia) and differentiation occur alongside morphogenesis. What we know up to date is that neurogenic capacity is spatiotemporally regionalized and restricted to the boundaries' flanking regions, in such a way that hindbrain boundaries and rhombomere centers remain devoid of neurogenesis. Thus, the main objective of the project will be to **understand how neuronal and glial progenitor capacities are spatiotemporally coordinated** within the embryonic hindbrain. To understand how this occurs, it is essential to **unveil the mechanisms for determining the neuronal/glial fate from early progenitors**. We have characterized the relationship between the different proneural gene expression domains and the putative neuronal subtypes arising from them [Belzunce et al, in preparation]. Moreover, we know that neurons and glial progenitors are spatially and mainly temporally segregated [C Belmonte, unpublished results].

Our model system is the zebrafish embryo because it permits to combine genome-editing tools such as CRISP/Cas9 with high resolution imaging approaches. The candidate will be involved in addressing whether neurogenic and gliogenic lineages derive from a common progenitor which fate is acquired by temporal specification, using a combination of functional experiments and cell tracing analyses.

Project Title: THE MOLECULAR PATHOGENESIS OF PANCREATIC AND BLADDER CANCER: FROM MICE TO MEN

Project supervisor

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Project to be conducted at the CNIO, Madrid

Summary of project summary or current research lines (less than 300 words).

Our laboratory works on pancreatic and bladder cancer and uses extensively genetic mouse models and organoids to understand the role of differentiation and inflammatory processes in cancer development. For this, we use a variety of strategies including genomic analyses and bioinformatics tools.

Pancreas cancer: We have shown that tissue-specific differentiation programs and inflammatory programs are coordinately regulated in epithelial cells. Disruption of these processes confer cancer susceptibiity in mice and probably in humans. We are trying to better understand the transcriptional networkds involved and to modulate pharmacologically or genetically their activity to suppress tumor development.

Bladder cancer: Using massive parallel sequencing (MPS) we have identified several novel genes involved in this tumor. We are focusing mainly on *STAG2* and *RBM10*. These genes are bladder cancer tumor suppressors and we are trying to identify the mechanisms involved. For this, we have generated conditional knockout models, organoids, and CRISPR-Cas9 knockout human cells. These studies are combined with the analysis of tissue samples from patients to also identify genes that cooperate with *STAG2* and *RBM10* to promote tumor development.

These are some of the questions we tackle:
1) *the genetics*: how prevalent are the mutations? where in the gene/protein do they occur? are they restricted to specific tumor subtypes discrete tumor progression pathways?
2) *the biology*: how do these genes contribute to cancer development/progression?;
3) *the clinical application*: can the gene mutations identify patients with distinct outcome? can they be applied to the detection of the tumor in urine?
4) *the therapy*: can these genes be targeted therapeutically? are there drugs available? can in vitro or in vivo models be used to assess the therapies?

If you want to contribute to answering these questions, you can work together with students and postdocs in the group to move the story forward!

Recent publications related to this project

- Balbás-Martínez C, et al. *Recurrent inactivation of STAG2 in bladder cancer is not associated with aneuploidy.* Nat Genet 2013; 45:1464-1469.
- Richart L, et al. *Bptf is required for c-Myc transcriptional activity and in vivo tumorigenesis*. Nat Comm 2016; 7:10153.
Martinelli P, et al. *GATA6 regulates EMT and tumor dissemination, and is a marker of response to adjuvant chemotherapy in pancreatic cance*r. Gut 2017; 66:1665-1676.
- Cobo I, et al. *Transcriptional regulation by NR5A2 links cell differentiation and inflammation in the pancreas*. Nature 2018; 554:533-537.

Project Title:

Role of intestinal microbiota in alcohol addiction/relapse in adolescent and adult mice.

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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Summary of project summary or current research lines (less than 300 words).

Excessive alcohol consumption induces addiction and dependence, two processes that have been associated with changes in multiple systems of neurotransmission in the central nervous system. These alterations may persist after detoxification and cause relapse, which represents a great burden on the public health system. Recently, the percentage of children under 17 years and young women who abuse large quantities of alcohol in a few hours ("binge drinking") has increased. This is preoccupying since this pattern of consumption can accelerate the addictive process. However, there are few treatments to prevent the development of excessive alcohol consumption, and addiction in more vulnerable populations such as adolescents and young women. Multiple studies have shown the relationship between the central nervous system and the intestinal microbiota via the "gut-brain axis". Recently different findings point to the influence of the microbiota on addictive behaviours. Several studies have shown that alcoholism and cocaine addiction induce changes in the composition of the intestinal microbiota, while others suggest that the intestinal microbiota could influence, to a certain extent, the initiation/development of addictive behaviours. However, it has not yet been demonstrated whether modifications of the microbiota induced by chronic alcohol consumption could contribute to the relapse process. Thus, in this research project we will study, on the one hand, whether the optimization of the gut microbiota with a pre/probiotic treatment starting at gestation prevents excessive alcohol consumption and relapse in adolescent mice. On the other hand, we will evaluate if the treatment with pre/probiotics prevents the relapse of adult mice that have already developed a pattern of excessive alcohol consumption. In both objectives, we will study the possible differences between males and females and correlate behavioural modifications with changes in neurotransmitter systems involved in these processes.

Project Title:

Encapsulation of microRNA in polymeric nanocapsules

Project supervisor

Anna Roig, PhD in Materials Science
Professor
Nanoparticles and Nanocomposites Group Leader
Institut de Ciència de Materials de Barcelona (ICMAB)
Consejo Superior de Investigaciones Científicas (CSIC)

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Summary of project summary or current research lines

One of Prof Roig research lines is to develop biocompatible nanoparticles as drug delivery vehicles and medical imaging contrast agents. This project will take advantage of nanotechnology to fabricate biodegradable nanocapsules to encapsulate microRNA with the long-term objective to treat acute infections such as sepsis.

The nanocapsules will be produced by an already optimized methodology in the group and the microRNA will be encapsulated simultaneously to their fabrication. Nanocapsules will be endowed with surface functionalities such as fluorescence or magnetic properties to be track by in-vitro and in-vivo imaging techniques.

The student will learn a synthetic methodology and will use various techniques to characterize the obtained materials such as electronic microscopy techniques (SEM and TEM); Zeta sizer Nano ZS to evaluated the nanocapsules sizes and Zeta-potential to gather information on their surface charge. Magnetic characterization and magnetic resonance-phantoms will be performed on the vesicles decorated with magnetic nanoparticles.

Time permitted, the student will also work on the determination of the microRNA encapsulation efficiency and the microRNAs release profile.

The student will have the opportunity to be part of a young international and multidisciplinary team and will be able to participate in the many training activities offered by our centre. Moreover, this project is a collaboration with biochemistry and clinical groups.

Project Title:
Investigating animal cell type diversity and regulation using single cell genomics and epigenomics approaches

Project supervisor
Arnau Sebe-Pedros - Group Leader
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Web: http://www.crg.eu/en/programmes-groups/single-cell-genomics-and-evolution

Summary of project or current research lines
Our group studies genome regulation from an evolutionary systems perspective. In particular, we are interested in deciphering the evolutionary dynamics of animal cell type programs and in reconstructing the emergence of genome regulatory mechanisms linked to cell type differentiation (from transcription factor binding through chromatin states to the physical architecture of the genome). To this end, we apply advanced single-cell genomics and chromatin experimental methods to molecularly dissect cell types and epigenomic landscapes in phylogenetically diverse organisms. We also develop computational tools to integrate these diverse data sources into models of cell type gene regulatory networks and we use phylogenetic methods to comparatively analyse these models. Our recent work has provided the first whole-organism cell type atlases in different species and mapped key regulatory genome features underlying these cellular programs. By sampling additional species and chromatin features at single-cell resolution, we now aim at dissecting the evolution of cell types and their underlying gene regulatory networks.

We are seeking a highly motivated student to join our team to work on an interdisciplinary project (experimental and computational) involving single-cell genomics and chromatin profiling in different systems. The research program for this position focuses on elucidating the origin and early evolution of animal genome regulation and cell type diversity (neurons, muscles, secretory cells, etc). To this end, the student will apply advanced functional genomics to characterize cell types and regulatory genome features in diverse systems.

References:
https://www.ncbi.nlm.nih.gov/pubmed/29856957
https://www.ncbi.nlm.nih.gov/pubmed/29942020
https://www.ncbi.nlm.nih.gov/pubmed/27114036

Project Title:

Mechanism of SGLT2 inhibition to prevent cardiorenal progression in type 2 diabetes.

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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Webpage: http://en.vhir.org/portal1/grup-equip.asp?t=nephrology&s=recerca&contentid=186797

Summary of project summary or current research lines (less than 300 words).

Diabetic kidney disease (DKD) progresses to end stage renal disease despite optimal current clinical management. Renin angiotensin system (RAS) blockade is known to delay the progression of renal damage. However, the proteinuria is reduced only in 30% and this treatment fails to prevent the progression to advanced DKD. Thus, new therapeutic approaches in early DN are needed. In NOD diabetic mice, with type 1 diabetes, paricalcitol (vitamin D analogue) modulates ACE2, ADAM17 and oxidative stress independently from the glycemic profile and albuminuria. Preliminary studies suggest that endothelin blockade modulated ACE2 in db/db mice. Recent studies demonstrated that sodium-dependent glucose cotransporter 2(SGLT2) inhibition on top of RAS blockade prevents cardiorenal progression in type 2 diabetic patients. We propose to perform “in vivo” and “in vitro” experimental studies to ascertain the cardiorenal functional, and molecular changes when RAS blockade is combined with an ETAR blockade and SGLT2 inhibition in the diabetic db/db mice and in the renal cells mainly involved in diabetic nephropathy development. For this purpose, we will study the effect of the administration of Ramipril (ACE inhibitor), atrasentan (endothelin A receptor antagonist), and empagliflozin (SGLT2 inhibitor) in the db/db mice as a model of type 2 diabetes. Renal-function studies, cardiac function studies, proteomic profiles, immunohistochemistry and gene expression will be performed. We will also study the effect of combined RAS and endothelin blockade on podocytes and proximal tubular cells. In addition, studies in tubular cells will be focused to assess the effect of this double blockade plus SGLT2 inhibition in oxidative stress, RAS gene expression and inflammatory pathways. Studying animal models developing early events of the diabetic nephropathy are mandatory to prevent DKD progression. In addition, the target altered pathways and protein involved will be subsequently assessed in kidney samples from DKD patients.

Project Title: Deciphering the role of HDAC11 in skeletal muscle differentiation, regeneration and growth.

Project supervisor

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Summary of project summary or current research lines

Histone deacetylases (HDACs) are essential epigenetic regulators of gene transcription. Histone deacetylase 11 (HDAC11) is the latest member identified of the HDAC family and it is the unique member of the class IV HDAC subfamily. Globally, its functions are unknown, and interestingly very recent published data relate HDAC11 with metabolic reprogramming. HDAC11 is highly expressed in skeletal muscle and its role in skeletal muscle physiology has never been addressed. Our laboratory has identified HDAC11 as a histone deacetylase highly expressed in quiescent muscle stem cells and differentiating myotubes, but not in proliferating myoblasts. We are addressing the role of HDAC11 in skeletal muscle differentiation, growth and muscle regeneration in primary muscle cell lines and in murine models. Our results suggest a role of HDAC11 regulating the transition between quiescence and cell proliferation state (cell cycle entry-exit). In addition, the examination of skeletal muscle tissue in Hdac11 wild type and knockout mice have showed that loss of HDAC11 has no obvious impact on skeletal muscle histology/structure and muscle growth. However, lack of HDAC11 promotes a switch in muscle fiber type, increasing the number of oxidative myofibers in skeletal tissue. Preliminary results suggest a role of HDAC11 regulating the metabolic state of skeletal muscle tissue and currently, we are performing experiments to better understand the contribution of HDAC11 in the skeletal muscle physiology, which is altered in chronic muscle pathologies and during aging.

The candidates should have some expertise in molecular biology and cell culture techniques and be very motivated students. Experience with mice handling will be well considered. We are interested in recruiting a PhD student, so the Master project can be continued with a PhD Thesis.

Contact to Mònica Suelves (msuelves@igtp.cat) sending a motivation letter, academic records and CV.

Project Title:

Intracellular signaling mediated by caspases and the ICAD~CAD endonuclease system in glioblastoma progression

Project supervisor (besides the name, title and position, please include the relevant contact information: e-mail, phone postal address, and webpage).

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Summary of project summary or current research lines (less than 300 words).

Although the ultimate goal of any antitumor treatment is the eradication of malignant cells with the highest possible selectivity, the type of cell death triggered during chemotherapy may be determinant to avoid or to promote tumor recurrences, generating new cells, even more resistant towards a cytotoxic challenge. In this sense, a sub-lethal activation of caspases, the key machinery of apoptosis, can lead to the appearance of aggressive phenotypes and has in the apoptotic endonuclease DFF40/CAD one of its main effectors. The DNA damage promoted by a partial activation of DFF40/CAD can be solved by the intracellular repair machinery that, being frequently altered in tumor cells, will introduce errors, leading to a new malignant phenotype, possibly resistant to the new extracellular environment. Glioblastoma (grade IV, according to W.H.O.) is a type of extremely aggressive brain tumor. The current treatment is based on a combined medical-surgical approach: surgery and radio-chemotherapy. Despite the potency of the treatment and the advances achieved in both basic and clinical research, glioblastoma remains an incurable tumor due to its high rate of relapse. In fact, almost all patients diagnosed with glioblastoma die, on average at 16 months, as a consequence of recurrences. Recent studies by our laboratory show that cells derived from human glioblastoma (commercial cell lines and cells isolated from patients) are deficient in DFF40/CAD expression. Our hypothesis is that the glioblastomatous cell has an inherent ability to activate low amounts of DFF40/CAD, avoiding massive DNA damage, but sufficient to promote genomic instability. Therefore, our main objective is to determine how these cells respond when challenged with different cytotoxic stimuli, exhibiting differential mechanistic peculiarities.

Ref.: Sánchez-Osuna M, *et al.*, *An intrinsic DFF40/CAD endonuclease deficiency impairs oligonucleosomal DNA hydrolysis during caspase-dependent cell death: a common trait in human glioblastoma cells.* Neuro Oncol. 2016 18(7):950-61.