Master in Biomedical Research

2020-2021

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.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Antiprions: structural mutants against neurodegenerative diseases

Project supervisor:

Name: Martí Aldea
Mail: mambmc@ibmb.csic.es
Group name: Spatial control of cell cycle entry
Institution: Institut de Biologia Molecular de Barcelona, CSIC
Webpage of the group: www.ibmb.csic.es/groups/spatial-control-of-cell-cycle-entry

Main grant associated with this project:
Principal investigator: Martí Aldea
Agency: MICINN
Reference/ years: BIO2017-91613-EXP, 2019-2020

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

Prions and amyloid prion-like aggregates have been directly implicated in more than 20 human diseases, among them neurodegenerative pathologies such as Alzheimer's, Parkinson's, and Huntington's diseases. Prion proteins are self-propagating and transmissible protein isoforms that accumulate as large structure-driven aggregates, and it is generally accepted that prion accumulation in the human brain is a direct cause of neuronal degeneration. However, appropriate therapeutic approaches and effective treatments are largely lacking, and efforts to prevent or decrease the rate of prion aggregation with peptides have produced very limited results. Here we hypothesize that, similarly to the opposing twins Prometheus and Epimetheus, antiprions could originate from prion domains as quasi-twin structures that (1) still bind with high efficiency to prion aggregates but (2) do not transmit the pathological fold to newly recruited monomers, thus preventing prion aggregate growth. Giving support to this hypothesis, prion misfolding and aggregation takes place in successive steps of conformational change. However, the structural details of these transitions are largely unknown, making impossible the post hoc design of mutants based on predicted structural properties. For this reason, our proposal is grounded in a non-biased approach, and plans to use human prion sequences (Aβ42 and αSyn) as initials seeds to perform (1) an unprecedented, extensive and highly sensitive random-mutagenesis based screen designed to generate and test more than ten million independent mutant peptides as antiprion factors, and (2) a comprehensive functional survey of the isolated antiprion peptides by their ability to counteract aggregation of human prions and their concomitant pathological effects in neurons.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Understanding the role of kinase DYRK1A in cerebral cortex development

Project supervisor (principal investigator of the laboratory)

Name: Mariona Arbonés
Mail: marbmc@ibmb.csic.es
Group name: Proliferation and differentiation of the nervous system
Institution: Institut de Biologia Molecular de Barcelona, IBMB-CSIC
Webpage of the group: http://www.ibmb.csic.es/home/marbones/

Main grant associated with this project: Functions of DYRK1A kinase and microRNAs in the neurogenesis of the developing cerebral cortex
Principal investigator: Mariona Arbonés
Agency: Ministerio de Ciencia e Innovación
Reference/ years: SAF2016-77971-R. 2017-2019, extended until December 2020

Brief summary of the project or current research lines of the group

The neocortex is the brain region responsible for sensory perception and integration, sensory-motor transformation and learning and memory. Neocortical neurons are morphologically and functionally very heterogeneous. These neurons are generated at different developmental times from progenitors located in distinct proliferative domains of the embryo telencephalon. Shortly after mitosis, newborn neurons migrate from these domains to the future neocortex where they mature and ensemble into circuits. Alterations in the cellular and molecular mechanisms that regulate neuron production and differentiation could be pathogenic leading to intellectual disability and autism spectrum disorder.

One of the current research lines of the group aims to uncover the multifaceted functions of DYRK1A in cerebral cortex development and to identify which of these DYRK1A-mediated functions are sensitive to variations in the dosage of DYRK1A. DYRK1A kinase, encoded by a chromosome-21 gene, is involved in several aspect of Down syndrome. Loss-of function mutations in *DYRK1A* cause *DYRK1A*-related intellectual disability syndrome (DYRK1A syndrome for short), which is characterized by the presence of microcephaly, speech delay, learning problems, epilepsy and autistic traits. Studies by our group and others have shown that DYRK1A regulates neurogenesis, neuronal differentiation and developmental cell death. However, the knowledge of the distinct DYRK1A-mediated activities involved in these developmental processes is limited. To gain new insights in this direction we will use the *Dyrk1a*$^{+/-}$ mouse model, which recapitulates the main features of DYRK1A syndrome, and novel mouse *Dyrk1a* mutants with a conditional deletion of *Dyrk1a* in specific sets of neural progenitors or postmitotic neurons. In these mutants we will asses *in vivo*: i/ the proliferation and differentiation capacities of the progenitors that give rise to the distinct types of excitatory and inhibitory neocortical neurones and ii/ the stereotyped projections of the main excitatory neocortical neurons that connect the two brain hemispheres (callosal neurons). In addition we will perform a transcriptomic and proteomic analysis in neural progenitors isolated from conditional *Dyrk1a* mutant embryos. The comparison between the data obtained from homozygous (2 alleles) and heterozygous (1 allele) *Dyrk1a* mutants will give us information of the neurodevelopment activities/functions that are affected in DYRK1A syndrome.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Cell cycle control: elaborating an integrative map of DNA synthesis regulators and tumour progression

Project supervisor (principal investigator of the laboratory)
Name: Jose Ayté
Mail: jose.ayte@upf.edu
Group name: Oxidative Stress and Cell Cycle
Institution: Universitat Pompeu Fabra
Webpage of the group: https://www.upf.edu/web/osccg/

Main grant associated with this project:
Principal investigator: Jose Ayté
Agency: Ministerio de Ciencia, Innovación y Universidades
Reference/ years: 2019-2021

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

We are ultimately interested in deciphering the mechanisms that control cell cycle progression. Inactivation of the Retinoblastoma protein (RB) leads to unregulated cell cycle progression promoting cell growth, genomic instability and aneuploidy, hallmarks of tumor progression. RB activity is achieved through binding the E2F family of transcription factors. It is well known that a tumor process is very complex, accumulating secondary mutations that eliminate the brakes to the cell cycle. Even though many regulators of the RB-E2F are known, an integrative view of all the regulatory events controlling the G1/S transition is required to anticipate putative interventions able to block proliferative processes.
The candidate will characterize the regulation of the yeast MBF complex (functional homolog of human RB-E2F). The regulated activity of this complex is also essential for the G1/S transition since cells with hyperactive MBF have genomic instability. The candidate will perform 2 whole-genomic screens searching for global regulators of MBF. We have developed a reporter strain in the laboratory that measures MBF activity in vivo as an YFP/RFP output, either on FACS or on an automated fluorescence microscope platform. This reporter strain will be introduced in a commercial yeast KO deletion library. These screenings will allow the creation of a complete map with all the MBF regulators and, by extrapolation, will establish the nodes that regulate the RB pathway.
Required student background: A high motivation towards a scientific career in projects related to basic research, which is the research that is carried out in our group, is a must. Also, a solid background in Genetics, Cell Biology and Molecular Biology is a requirement to carry out this project. Since the project includes bar-code sequencing of pools of KO strains, previous experience with ultra-sequencing will be appreciated. Similarly, previous work with yeast and/or cell cycle will be a plus.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: *Epigenetic regulation of chromatin structure and function: the role of linker histones H1*

Project supervisor (principal investigator of the laboratory)

Name: Ferran Azorín/Jordi Bernués
Mail: fambmc@ibmb.csic.es/jbmbmc@ibmb.csic.es
Group name: Chromatin Structure and Function
Institution: IRB Barcelona and IBMB, CSIC
Webpage of the group:

Main grant associated with this project:
Principal investigator: Ferran Azorín
Agency: MCINN
Reference/ years: PGC2018-094538-B-I00/ (2019-2021)

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

Despite the fact that linker histones H1 are intrinsic components of chromatin, their contribution to the epigenetic regulation of chromatin structure and function remains poorly understood. Histones H1 are less well conserved than core histones and generally exist in multiple variants that play partially redundant functions. In this project, we aim to study the contribution of linker histones H1 to the regulation of chromatin structure and function. In particular, we will address the role of histones H1 in the formation of chromatin condensates and 3D folding. The project involves the extensive use of NGS technologies (ChIP-seq, ATAC-seq, MNase-seq, DRIP-seq, RNA-seq, HiC, Hi-ChIP).

Recent Publications in the field of the project

A. Carbonell, S. Pérez-Montero, P. Climent, O. Reina and **F. Azorín** (2017) "The germilne linker histone dBigH1 and the translational regulator Bam form a repressor loop essential for male germ stem cell differentiation" **Cell Rep**, 21, 3178-3189.

A. Bayona-Feliu, A. Casas-Lamesa, O. Reina, J. Bernués and **F. Azorín** (2017) "Linker histone H1 prevents R-loop accumulation and genome instability in heterochromatin". **Nature Commun**, 18, 283 (doi: 10.1038/s41467-017-00338-5).

A. Bayona-Feliu, A. Casas-Lamesa, A. Carbonell, P. Climent-Cantó, M. Tatarski, S. Pérez-Montero, **F. Azorín** and J. Bernués (2016) "Histone H1: lessons from *Drosophila*". **Biochim Biophys Acta-Gene Regul Mech**, 1859, 526-532.

S. Pérez-Montero, A. Carbonell and **F. Azorín** (2016) "Germline specific H1 variants: the “sexy” linker histones". **Chromosoma**, 125, 1-13.

S. Pérez-Montero, A. Carbonell, T. Morán, A. Vaquero and **F. Azorín** (2013) " The embryonic linker histone H1 variant of *Drosophila*, dBigH1, regulates zygotic genome activation" **Dev Cell**, 26, 578-590.

Bonet-Costa C, Vilaseca M, Diema C, Vujatovic O, Vaquero A, Omeñaca N, Castejón L, Bernués J, Giralt E, **Azorín F.** (2012) “Combined bottom-up and top-down mass spectrometry analyses of the pattern of post-translational modifications of *Drosophila melanogaster* linker histone H1” **J Proteomics**, 75, 4124-4138.

O. Vujatovic, K. Zaragoza, A. Vaquero, O. Reina, J. Bernués and **F. Azorín** (2012) “*Drosophila melanogaster* linker histone dH1 is required for transposon silencing and to preserve genome integrity” **Nucleic Acids Res**, 40, 5402-5414.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: *Centromere assembly and function: the coordination of mitotic events*

Project supervisor (principal investigator of the laboratory)

Name: Ferran Azorín/Mònica Torras
Mail: fambmc@ibmb.csic.es/mtlbmc@ibmb.csic.es
Group name: Chromatin Structure and Function
Institution: IRB Barcelona and IBMB, CSIC
Webpage of the group: https://www.irbbarcelona.org/en/research/chromatin-structure-and-function

Main grant associated with this project:
Principal investigator: Ferran Azorín
Agency: MCINN
Reference/ years: PGC2018-094538-B-I00/ (2019-2021)

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

Cell division requires the precise coordination of crucial mitotic events that involve extensive architectural rearrangements. Metazoans generally undergo open mitosis, which implies that the nuclear envelope (NE) disassembles at prometaphase and reassembles after chromosome segregation. How these processes are ultimately coordinated is not understood. We have identified that BAF, a factor that plays an essential role in post-mitotic NE assembly, associates with centromeres throughout the cell cycle and interacts with CENP-C, being required for centromere function. In this project we will study the role of centromeric BAF (cenBAF) in the co-ordination of chromosome segregation and NE dis-assembly/re-assembly in mitosis. The project involves extensive use of high-resolution microscopy techniques and gene modification methodologies.

Publications in the field of the project

O. Moreno-Moreno, M. Torras-Llort and **F. Azorín** (2019) “The E3-ligases SCF^{Ppa} and APC/C^{Cdh1} co-operate to regulate CENP-A^{CID} expression across the cell cycle” **Nucleic Acids Res**, 47, 3395-3406

O. Moreno-Moreno, M. Torras-Llort and **F. Azorín** (2017) "Variations on a nucleosome theme: the structural bases of centromere function" **BioEssays**, 39 (doi: 10.1002/bies.201600241).

O. Moreno-Moreno, S. Medina-Giró, M. Torras-Llort and **F. Azorín** (2011) “The F-box protein partner-of-paired (Ppa) regulates stability of *Drosophila* centromeric histone H3, CenH3^{CID}” **Curr Biol,** 21, 1488-1493.

M. Torras-Llort, S. Medina-Giró, O. Moreno-Moreno and **F. Azorín** (2010) “A conserved arginine-rich motif within the hypervariable N-domain of *Drosophila* centromeric histone H3 (CenH3^{CID}) mediates BubR1 recruitment” **PloS ONE**, 5, e13747.

M. Torras-Llort, O. Moreno-Moreno and **F. Azorín** (2009) “Focus on the centre: the role of chromatin on the regulation of centromere identity and function” **EMBO J**, 28, 2337–2348.

O. Moreno-Moreno, M. Torras-Llort and **F. Azorín** (2006) “Proteolysis restricts localization of CID, the centromere-specific histone H3 variant of *Drosophila*, to centromeres” **Nucleic Acids Res** 34, 6247-55.

Project Title: MUSCLE REGENERATIVE POTENTIAL IN MODELS OF SARCOPENIA AND CACHEXIA: FROM THE MOLECULE TO THE PATIENT

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

Dr Esther Barreiro, MD, PhD
Staff physician, IMIM-Hospital del Mar
Visiting professor, Universitat Pompeu Fabra
URMAR, IMIM, PRBB, Dr. Aiguader, 88, 08003 Barcelona
ebarreiro@imim.es
Phone: 93 316 0400/0385
Web page: www.imim.es

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 (180 publications including 16 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, January 27th 2020

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title:

Project supervisor (principal investigator of the laboratory)

Name: Arnau Busquets Garcia
Mail: abusquets@imim.es
Group name: Cell-type mechanisms in normal and pathological behavior
Institution: Institut Hospital del Mar d'Investigacions Mèdiques (IMIM)
Webpage of the group: https://www.imim.cat/programesrecerca/neurociencies/grfh/cell-type_mechanisms_in_normal_and_pathological_behavior/index.htm

Main grant associated with this project:
Principal investigator: Arnau Busquets Garcia
Agency: Mineco (Retos)
Reference/ years: RTI2018-093667-A-100 (2019-2021)

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

Alzheimer's disease (AD) is a devastating age-dependent neurodegenerative process distinct from normal aging. AD pathology is accompanied by severe molecular and behavioral alterations, including brain bioenergetic deficits and cognitive dysfunctions. In this sense, the pathogenesis of several brain diseases involves mitochondrial dysfunctions. However, very little is known on which specific mechanisms are affected by malfunctioning mitochondria to generate brain diseases (and vice versa). In this sense, the study of **mitochondrial cannabinoid CB1 receptors** (mtCB1) in the brain represents an opportunity to better understand these mechanisms. For instance, ATP levels modulation, calcium control or regulation of the redox state are all potential links between cannabinoid-dependent mitochondrial dysfunctions and AD pathophysiology. Therefore, that brain mtCB1 receptor signalling might be centrally involved in the molecular, bioenergetic and behavioral effects found in APP/PS1 mice. To address this idea, we will use genetic, molecular and pharmacological approaches.

This project will benefit from the creation of a new transgenic **APP/PS1 mice lacking CB1 receptors specifically in the mitochondria**. We will cross the APP/PS1 mice with a recently developed mouse mutant line specifically lacking mitochondrial localization of CB1 receptors ("no-mtCB1", available in the group of Dr. Marsicano, see Hebert-Catelain et al. 2015) for molecular details of the approach. These mice ($APP/PS1^{/no\text{-}mtCB1}$) and their control littermates ($WT^{/WT}$, $WT^{/no\text{-}mtCB1}$ and $APP/PS1^{/WT}$) will undergo biochemical and behavioral investigations at different time points (2, 4 or 6 months) in order to investigate the involvement of mtCB1 in AD pathology.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title:

Towards CRISPR 2.0: *Caenorhabditis elegans* as model for next generation genome editing

Project supervisor (principal investigator of the laboratory)

Name: **Julián Cerón Madrigal**
Mail: jceron@idibell.cat
Group name: Modeling human diseases in *C. elegans*
Institution: Bellvitge Biomedical Research Institute (IDIBELL)

Webpage of the group: www.ceronlab.com and www.idibell.cat

Main grant associated with this project:

Principal investigator: Julián Cerón Madrigal
Agency: Ministerio de Ciencia e Innovación
Reference/ years: PID2019-105729GB-I00 /2020-2023

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

Our lab uses the powerful genetic model *C. elegans* to investigate human diseases: rare diseases (*Kukhtar et al, 2020*) or cancer (*Serrat et al, 2019*). We have broad expertise on CRISPR technologies that are being applied to model human diseases (ex. by introducing human mutations in *C. elegans*). Moreover, we have an active research line on optimizing CRISPR genome editing by using distinct Cas9 systems to increase efficiency and the capacity of inserting long DNA fragments in the genome site of interest (*Vicencio et al, 2019*). Thus, a Master research project in our lab would include training in molecular biology, CRISPR and genetics.

Recent publications:

Mimicking of splicing-related retinitis pigmentosa mutations in C. elegans allow drug screens and identification of disease modifiers. Kukhtar D, Rubio-Peña K, Serrat X, Cerón J.
Human Molecular Genetics 2020 Jan 10. pii: ddz315. doi: 10.1093/hmg/ddz315.

CRISPR editing of sftb-1/SF3B1 in Caenorhabditis elegans allows the identification of synthetic interactions with cancer-related mutations and the chemical inhibition of splicing. Serrat X, Kukhtar D, Cornes E, Esteve-Codina A, Benlloch H, Cecere G, Cerón J.
PLoS Genetics. 2019 Oct 21;15(10):e1008464. doi: 10.1371/journal.pgen.1008464

Efficient Generation of Endogenous Fluorescent Reporters by Nested CRISPR in Caenorhabditis elegans. Vicencio J, Martínez-Fernández C, Serrat X, Cerón J.
Genetics. 2019 Apr;211(4):1143-1154. doi: 10.1534/genetics.119.301965

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Transcriptome analysis in human brain tissue of patients with amyotrophic lateral sclerosis and frontotemporal dementia to discover novel biomarkers.

Project supervisor (principal investigator of the laboratory)

Name: Jordi Clarimón Echavarria and Oriol Dols Icardo
Mail: jclarimon@santpau.cat and odols@santpau.cat
Group name: Genetics of Neurodegenerative Disorders Unit
Institution: Sant Pau Biomedical Research Institute
Webpage of the group: http://santpaumemoryunit.com

Main grant associated with this project: PI18/00326
Principal investigator: Jordi Clarimón
Agency: Instituto de Salud Carlos III
Reference/ years: 3

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

A histopathological hallmark of some neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) is the aggregation of TAR DNA-binding protein 43 (TDP43) in the cytosol of affected neurons. TDP43 is an RNA-binding protein (RBP) involved in transcription regulation, alternative splicing and RNA stability. The fact that other RBPs have been implicated in these disorders reinforces the idea that aberrant RNA metabolism is a major contributor to their pathophysiology. Recent advances in high-throughput sequencing technologies have revealed that most of the genome is transcribed and unexpectedly large numbers of non-coding RNAs (ncRNAs) and circular RNAs are now considered fundamental constituents of the human transcriptome. We will perform a global transcriptome analysis of postmortem brain tissue of affected subjects (both ALS and FTD) to disclose, through state-of-the-art bioinformatic tools, differential gene expression, transcript usage, circular RNA expression and gene co-expression modules resulting from defective transcription machinery. Furthermore, cell-type deconvolution using human single-nucleus RNAseq data will be applied to disentangle cellular heterogeneity. Finally, these candidate RNA alterations will be evaluated in the cerebrospinal fluid and/or blood of living patients to assess their role as possible biomarkers for disease diagnosis and prognosis.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Epigenetic regulation of gene expression in malaria parasites

Project supervisor (principal investigator of the laboratory)
Name: Alfred Cortés, ICREA Research Professor
Mail: alfred.cortes@isglobal.org
Group name: Malaria Epigenetics Lab
Institution: Barcelona Institute for Global Health (ISGlobal)
Webpage of the group: http://www.icrea.cat/Web/ScientificStaff/Alfred-Cortes-Closas-375

Main grant associated with this project: Dissecting the initial molecular events that trigger sexual conversion and transmission in malaria parasites
Principal investigator: Alfred Cortés
Agency: La Caixa Health Research
Reference/ years: HR18-00267 (2019-2022)

Brief summary of the project or current research lines of the group

The team. Our team investigates transcriptional processes, including chromatin-based epigenetic regulation, in the malaria parasite *Plasmodium falciparum*. We study the transcriptional changes underlying parasite adaptation to the conditions of their environment, with a special focus on sexual conversion, the heat-shock response and solute permeability.

The project. The transmission of malaria from one human host to another occurs via mosquito vectors. In the human blood, the majority of parasites multiply asexually, but the only forms that can infect a mosquito are the sexual forms termed gametocytes. Hence, the conversion of some asexually-growing parasites into sexual gametocytes is essential for malaria transmission. Some important regulators of this developmental switch were recently identified by us and by others, including the master regulator PfAP2-G. Of note, the gene encoding PfAP2-G is regulated by euchromatin-heterochromatin transitions. Here we will investigate the very first events that trigger sexual conversion, with a special focus on the role of heterochromatin.

Techniques. For our research we routinely use *P. falciparum* cultures, transcriptional analysis (using qPCR and microarrays), chromatin immunoprecipitation (ChIP-qPCR and ChIP-seq), flow cytometry, and genome editing using CRISPR/Cas9 technology.

Most relevant publications from the team:

Portugaliza HP, Llorà-Batlle O, Rosanas-Urgell A & Cortés A, 2019, "Reporter lines based on the *gexp02* promoter enable early quantification of sexual conversion rates in the malaria parasite *Plasmodium falciparum*", ***Sci. Rep.*** 9:14595.

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*", ***Nature Microbiol.*** 4:144-154.

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.*** 43:8243-57.

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.

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.

Integration of Experimental and Computational Technologies to Explore "Primed" Signaling in Cancer

Pau Creixell
Postdoctoral Fellow in Michael B. Yaffe's lab
Koch Institute for Integrative Cancer Research
Massachusetts Institute of Technology (MIT)
500 Main Street, Cambridge 02139
Massachusetts, USA.
e-mail: creixell@mit.edu

Project summary

The over-arching goal of the Yaffe lab's research is to understand how signaling pathways are integrated at the molecular and systems level to control cellular responses, and how they are misregulated in cancer progression and response to therapy. In our multi-disciplinary lab, we use a broad range of technologies to decode how protein kinases work and cell-signaling pathways are "wired" into functional networks. By phosphorylating key substrates involved in virtually every cellular process, protein kinases are critical regulators of cell fate. It is therefore not surprising that aberrant kinase activity contributes to multiple human pathologies, in particular to cancer, or that kinases are major targets for anti-cancer therapeutics (Lee et al., 2012, Cell 149, 780–794; Creixell et al., 2012, Nat Biotechnol, 30, 842–848; Fleuren et al., 2016, 16, 83–98).

To understand their role in healthy and cancer cells, it is essential to identify the specific substrates that a kinase phosphorylates. Kinases select their specific target sites from a large collection of serine, threonine and tyrosine residues. This specificity is largely achieved through recognition of a consensus motif; the amino acid sequence that surrounds the phospho-acceptor site and fits into the active site of the kinase in a key-lock principle (Creixell et al., 2015, Cell 163, 187–201; Creixell et al., 2015, Cell 163, 202–217). Our most recent preliminary data suggests that a large number of kinases use previously phosphorylated residues (a process also known as 'priming') to recognize their substrates, similarly as previously shown for EGFR (Begley et al. 2015, Nat Struct Mol Biol, 22, 983–990). In this project, we will further characterize 'priming' signaling, explore the molecular mechanisms behind it and define cellular phenotypes associated with it.

Techniques: The student may use or get trained in techniques including molecular cloning, site-directed mutagenesis, cell culture, transfection, protein purification, crystallography, SDS-PAGE, western blotting, *in vitro* kinase assays and bioinformatics. Candidates must feel comfortable using (low amounts of) radioactive ^{33}P.

Special consideration for candidates who: Can commit for longer than six months (ideally for a full year), have a strong academic record and previous research experience.

Additional information: As a result of their hard work, previous students have contributed valuable data, become authors in our articles and successfully transitioned to competitive PhD programs in Europe and the US. Exact location of the research may change depending on ongoing lab relocation.

To apply: Please send **CV**, **transcripts**, **cover letter** and contact details for **2 referees**.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Understanding the molecular basis of Down syndrome myeloid leukaemia

Project supervisor (principal investigator of the laboratory)

Name: Sergi Cuartero
Mail: scuartero@carrerasresearch.org
Group name: Transcriptional Dynamics in Leukemia
Institution: Josep Carreras Leukaemia Research Institute
Webpage of the group: http://www.carrerasresearch.org/en/transcriptional-dynamics-in-leukemia_129664

Main grant associated with this project:
Principal investigator: Sergi Cuartero
Agency: Jerome Lejeune Foundation
Reference/ years: 2 years

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

The *Transcriptional Dynamics in Leukemia* lab is a recently-established team focused on understanding the molecular events that lead to leukaemia. We are located in the brand-new building of the Josep Carreras Leukaemia Research Institute (IJC) in the Can Ruti Campus, surrounded by a multitude of high-profile research teams and state-of-the-art research facilities and equipment. We investigate how mutations in epigenetic modifiers and transcription factors contribute to leukaemia development.
Down syndrome children have a 500-fold increased risk of developing acute megakaryoblastic leukaemia, a rare type of myeloid leukaemia. Currently, the main treatment option is standard chemotherapy. Nonetheless, a substantial number of patients are refractory to it, or relapse and have a poor prognosis. Therefore, there is an unmet clinical need for new treatment options. Down syndrome-associated acute megakaryoblastic leukaemia is characterized by an exceptionally high frequency of mutations in the transcription factor GATA1 and in the cohesin complex. Our understanding of the role of cohesin in gene regulation and genome folding has greatly increased in recent years. However, the role of cohesin in the pathogenesis of Down syndrome leukaemia has largely been overlooked. Based on our recent findings linking cohesin to key hematopoietic signalling pathways, here we propose to study the molecular basis of GATA1 and cohesin mutations in Down syndrome leukaemia with the goal of uncovering new therapeutic opportunities.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

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

Project supervisor (principal investigator of the laboratory)
Name: Oriol Gallego
Mail: oriol.gallego@upf.edu
Group name: Live-cell structural biology
Institution: Department of Experimental and health Sciences, UPF
Webpage of the group: www.gallegolab.org

Main grant associated with this project:
Principal investigator: Oriol Gallego
Agency: MINECO-Spain
Reference/ years: PGC2018-095745-B-I00, 2019-2021

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

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 microenvironment and cancer invasion during epithelial tumorigenesis

Project supervisor: **Antonio García de Herreros**, Programa de Recerca en Càncer, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Parc de Recerca Biomèdica de Barcelona, Room 298.03, agarcia@imim.es, Tel 93 – 3160433.

Main grant associated with this project:
Principal investigator: Antonio García de Herreros; Plan Nacional de Salud, (SAF2016-76461-R) 2017-2020.

Brief summary of the project or current research lines of the group:

Our group has a long staining interest in the study of the process of epithelial tumor invasion and it relation with epithelial-to-mesenchymal transition (EMT). Snail1 is transcriptional factor required for EMT that has been the topic of our research for many years. Besides controlling tumor invasion, Snail1 expression is also required for the acquisition of resistance to apoptosis or cancer stem properties. We have analyzed molecular targets of Snail1 involved in these two properties; for a recent article, see, Mazzolini et al, Nucl. Acid Res., 46, 146-158. 2018). In the last years we have studied how Snail1 expression is controlled, focusing in the transcriptional control by Wnt ligands (Villarroel et al, Cell Mol Life Sci.. doi: 10.1007/s00018-019-03221-2. Epub ahead of print) and also in the role of ubiquitin ligases and deubiquitinases in the modulation of the protein half-life. We have recently characterized a new deubiquitinase, Usp27X that antagonizes the action of Snail1 E3 ligases and stabilizes Snail1 during EMT (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 tumor microenvironment. 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 activation of cancer-associated fibroblasts (CAFs) by TGFβ or other cytokines derived from the tumor cells. We have investigated 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 CAFs, supporting the well-known effect of the microenvironment cells 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 tumor microenviroment, such as endothelial cells where it is required for tumor angiogenesis (Cabrerizo et al, in preparation). We also plan to assess the role of other cancer micronvironment cells in the activation of CAFs and in the invasive properties of tumor cells. 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. .

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Spatiotemporal organization of the microbiome at the single-cell level

Project supervisor
Name: **Jordi Garcia Ojalvo**
Mail: Jordi.g.ojalvo@upf.edu
Group name: Dynamical Systems Biology
Institution: Universitat Pompeu Fabra
Webpage of the group: https://www.upf.edu/web/dsb

Main grant associated with this project:
Principal investigator: Jordi Garcia Ojalvo
Agency: Agencia Estatal de Investigación
Reference/ years: PGC2018-101251-B-I00 (2019-2021)

Brief summary of the project

The goal of the project is to explore the mechanisms underlying the regulation of the human microbiome in space and time, at the single-cell level. The student will use techniques such as time-lapse fluorescence microscopy, flow cytometry, and spectrophotometry to monitor the response of gut bacteria, both in planktonic and biofilm conditions, to different types of time-dependent inputs (such as nutrients, antibiotics, temperature and inorganic ions). The interactions between different bacterial species will be especially examined.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: **Use of Next Generation Sequencing (NGS) as a unique genomic technique to use to improve diagnosis, prognosis and treatment of T-cell Acute Lymphoblastic Leukemia patients**

Project supervisor (principal investigator of the laboratory)

Eulàlia Genescà-PhD
ALL Research Group
Josep Carreras Leukaemia Research Institute (IJC)
Carretera de Canyet s/n, camí de les escoles. Edifici IMPPC
08916, Badalona (Barcelona), SPAIN.
Tel: +(34) 93 557 28 08/ + (34) 93557 28 07
egenesca@carrerasresearch.org
http://www.carrerasresearch.org/ca/acute-lymphoblastic-leukemia-all-_3726

Main grant associated with this project:
Principal investigator: Eulàlia Genescà
Agency: ISCIII-FIS
Reference/ years:

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

ALL is characterized by a multistep oncogenic process leading to maturation arrest and malignant transformation of lymphoid hematopoietic precursors. T-ALL is the less common and the most complex and heterogeneous at the genetic level. Genetics plays a key role in the development of T-ALL and also has prognostic value. However, until now in the diagnosis only cytogenetic data have been considered. Nowadays, genomics allows obtaining a large amount of genetic data that can help to improve the stratification of these patients and design new specific therapeutic alternatives. However, we are still far from applying it routinely in the diagnosis of patients. To do this we must simplify the analysis of genomic data and apply the minimum number of possible genomic techniques, obtaining the maximum information, in order to reduce the cost involved in the extensive use of these techniques. Here we propose to design, analyze and validate a customized NGS panel to detect structural alterations, point mutations and *indels* in order to stratify patients with T-ALL according to the potential treatment to apply. We also want to use the panel as a predictive tool for relapse. In this way, we believe that we will accelerate the implementation of genomics at the healthcare level, a fact that will undoubtedly help improve the survival of patients with this neoplasm.

Goals

The main goal of this project is to test and validate a NGS panel that will allow us to integrate all the necessary genomic information in a single technique to improve the stratification of patients with T-ALL and predict their relapse.

Project Title: ***Molecular analysis of peptidases and their inhibitors of biomedical or biotechnological interest***.

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

F. Xavier Gomis-Rüth
Proteolysis Lab
Department of Structural Biology
Barcelona Science Parc, Helix Building
C/ Baldiri Reixac,15-21
08028 Barcelona
Tel. 934020186 / Fax. 934034979 / e-mail. xgrcri@ibmb.csic.es /
https://www.sbu.csic.es/research-groups/proteolysis-lab

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

The research group is centered on the study of proteins involved in host-microbiome interactions, including microbial virulence factors and antibiotic resistance determinants, as well as potential therapeutic targets. Such molecules include (metallo)proteases of mammals, protozoans and prokaryotes, as well as their inhibitors and interacting partners. We also work with integral-membrane metalloproteases. The student would participate in the cloning, overexpression and purification of such protein targets under the supervision of an experienced member of the lab. In addition or alternatively, she/he could participate in the biochemical, biophysical, functional, and structural characterization. The candidate should have strong marks and a very hard-working capacity, dedication and lab skills. This work could be continued within the frame of a Ph.D. thesis.

Selected recent publications:

J.L. Arolas, C. Broder, T. Jefferson, T. Guevara, E.E. Sterchi, W. Bode, W. Stöcker, C. Becker-Pauly & F.X. Gomis-Rüth (2012). Structural basis for the sheddase function of human meprin β metalloproteinase at the plasma membrane. *Proc. Natl. Acad. Sci. USA*, 109, 16131-16136.

S. Trillo-Muyo, S. Martínez-Rodríguez, J.L. Arolas & F.X. Gomis-Rüth (2013). Mechanism of action of a Janus-faced single-domain protein inhibitor simultaneously targeting two peptidase classes. *Chem. Sci.*, 4, 791-797.

M. López-Pelegrín, N. Cerdà-Costa, A. Cintas-Pedrola, F. Herranz-Trillo, P. Bernadó, J.R. Peinado, J.L. Arolas & F.X. Gomis-Rüth (2014). Multiple stable conformations account for reversible concentration-depedent oligomerization and autoinhibition of a metamorphic metallopeptidase. *Angew. Chem. Int. Ed.*, 53, 10624-10630 (chosen for the frontispiece of the section on communications).

P.F. Huesgen, P.F. Lange, L.D. Rogers, N. Solis, U. Eckhard, O. Kleifeld, T. Goulas, F.X. Gomis-Rüth & C.M. Overall (2015). LysargiNase mirrors trypsin for identification of protein C-termini and methylation sites. *Nat. Meth.*, 12, 55-58 (the enzyme lysargiNase was discovered by Ulrich Baumann in the laboratory of F.X. Gomis-Rüth, where it is currently produced and commercialized worldwide in collaboration with the laboratory of C.M. Overall. A license agreement currently allows distribution through EMD Millipore Corp., see http://www.merckmillipore.com/ES/es/product/LysargiNase,MM_NF-EMS0008).

I. Garcia-Ferrer, P. Arêde, J. Gómez-Blanco, D. Luque, S. Duquerroy, J.R. Castón, T. Goulas & F.X. Gomis-Rüth (2015). Structural and functional insights into *Escherichia coli* α_2-macroglobulin endopeptidase snap-trap inhibition. *Proc. Natl. Acad. Sci. USA*, 112, 8290-8295 (highlighted by the Spanish Biophysical Society as one of four Papers of the Month by SBE Members in July; Bio*física* Magazine, issue #2, May-August 2015, http://www.sbe.es/ph2015-07.asp; selected by the Spanish Society of Biochemistry and Molecular Biology as The Article of the Month, January 2016, http://www.sebbm.es/web/en/science-for-society/article-of-the-month).

J.L. Arolas, T. Goulas, A. Cuppari & F.X. Gomis-Rüth (2018). Multiple architectures and mechanisms of latency in metallopeptidase zymogens. *Chem. Rev.*, 118, 5581-5597.

A. Cuppari, H. Körschgen, D. Fahrenkamp, C. Schmitz, T. Guevara, K. Karmilin, M. Kuske, M. Olf, E. Ditzel, I. Yiallouros, D. de Sanctis, T. Goulas, R. Weiskirchen, W. Jahnen-Dechent, J. Floehr, W. Stöcker, L. Jovine & F.X. Gomis-Rüth (2019). Structure of mammalian plasma fetuin-B and its mechanism of selective metallopeptidase inhibition. *IUCrJ*, 6, 317-330.

T. Guevara, A. Rodríguez-Banqueri, M. Ksiazek, J. Potempa & F.X. Gomis-Rüth (2020). Structure-based mechanism of cysteine-switch latency and of catalysis by pappalysin-family metallopeptidases. *IUCrJ*, 7, 18-29 (scientific commentary in the same issue: E.S. Radisky (2020). Mirolysin structures open a window on gum diseases. *IUCrJ*, 7, 3-4).

Project Title

Gene-editing technology-based therapeutics

Project supervisor

Marc Güell
Tenure Track Professor
Pompeu Fabra University

Web: https://www.upf.edu/en/web/synbio
Mail: marc.guell@upf.edu
Address:
PRBB – Room 704
C/. Dr. Aiguader 88
08003 - Barcelona

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

Skin microbiome engineering

Project supervisor

Marc Güell
Tenure Track Professor
Pompeu Fabra University

Web: https://www.upf.edu/en/web/synbio
Mail: marc.guell@upf.edu
Address:
PRBB – Room 704
C/. Dr. Aiguader 88
08003 - Barcelona

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.

The skin is populated by numerous microorganisms which profoundly affect host health. We aim to develop precise genetic methodologies to modulate skin microbiome population and behaviour to enable novel therapeutic strategies for skin disease and wellbeing.

We are offering a master position in developing skin probiotics with advanced functionalities. Specifically, we are equipping skin microbes with sensing circuits and therapeutic circuits to create novel advanced therapeutics.

Project Title:
Oxidative stress linked to toxicity and to signaling

Project supervisor:
Elena Hidalgo
Universitat Pompeu Fabra
C/ Dr.Aiguader 88
08003 Barcelona
Tel. 34-93-316-0848
Fax. 34-93-316-0901
elena.hidalgo@upf.edu

Summary of current research lines.
Our group is interested in studying the components and molecular mechanisms controlling cellular fitness, both after stress conditions and during aging. Thus,our projects are related to:
(i) study cellular adaptation responses to oxidative stress;
(ii) characterization of the protein quality control system.
We use 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:
Cabrera et al. 2020. Cell Rep. (in press)
Carmona et al. 2019. Nat. Commun. 10:4526.
Boronat et al. 2017. PLoS Genet. 13:e1006858.
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.
Calvo, I.A. et al. 2012. Nucleic Acids Res. 40:4816.
Zuin, A. et al. 2010. EMBO J. 29:981.
Our current goal is to characterize the thermo-sensitive proteome of *S. pombe,*that is, the collection of unstable proteins which may contribute to cell aging.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Probing *Plasmodium falciparum* glycosylation to devise new tools against Malaria

Project supervisor (principal investigator of the laboratory)

Name: Luis Izquierdo
Mail: luis.izquierdo@isglobal.org
Group name: *Plasmodium* glycobiology
Institution: Barcelona Institute for Global Health (ISGlobal)
Webpage of the group: https://izquierdolab.wordpress.com

Main grant associated with this project:
Principal investigator: Luis Izquierdo
Agency: Spanish Ministry of Science and Innovation
Reference/years: SAF2016-76080-R (2017-2020)

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

The cell surfaces and endosomal/lysosomal systems of protozoan parasites are rich in glycoconjugates that play essential roles in their survival, infectivity or virulence. In the last decade, several works have outlined fundamental aspects of the glycobiology of the malaria parasite, posing new questions about the relevance and extent of glycosylation in *Plasmodium* and uncovering novel opportunities to tackle the disease. Thus, an immune response against anti-α-galactose-containing glycans is related to malaria protection in humans, although the nature and structure of the purported *P. falciparum* α-galactose glycoconjugates remain completely unknown. Likewise, short non-complex glycans (*O*-fucose, which can be further substituted with a hexose; and *C*-mannose) modify CSP and TRAP, essential adhesive proteins and major vaccine targets against malaria. However, we do not know how these glycosylations influence the immune response against these proteins, and there are still certain controversies concerning their biological function. Furthermore, despite *P. falciparum* conserves a complete *N*-glycosylation machinery and synthesizes very short *N*-linked glycans, this process -critical for cell viability in eukaryotes- has not been unequivocally demonstrated in the parasite. The aforementioned issues are important for *P. falciparum* biology and their thorough description will unlock new opportunities to devise new tools against malaria.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Deciphering novel molecular targets for therapies aimed at childhood acute lymphoblastic leukemia

Project supervisor (principal investigator of the laboratory)
Name: Biola M. Javierre
Mail: bmjavierre@carrerasresearch.org
Group name: 3D Chromatin Organization
Institution: Josep Carreras Leukaemia Research Institute
Webpage of the group: http://www.carrerasresearch.org

Main grant associated with this project: Programa Estatal de I+D+i Orientada a los Retos de la Sociedad (RTI2018-094788-A-I00)
Principal investigator: Biola M. Javierre
Agency: (Spanish Ministry of
Science, Innovation and University)
Reference/ years: 2019-2022

ABSTRACT OF THE PROJECT:

20% of children with acute lymphoblastic leukemia (ALL), the most common pediatric 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 pediatric 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 experimental and computational 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 hematopoiesis with a tremendous impact at regenerative medicine and blood malignancies.

BIG PICTURE OF THE GROUP:

Every cell in our body has about 2 meters of linear DNA containing the genes that shape our being. This DNA, which is the same in every cell, is not-randomly packed into the nucleus of a few microns diameter, and the manner in which it is wrapped plays a fundamental role in regulating genome function. In some cases it does this by putting regulatory elements, such as enhancer, and target gene promoters into physical contact. In fact, this can partially explain how cells encoding the same genetic information are phenotypically and functionally different. It has been estimated that the genome harbors around one million regulatory elements, some of these are cell-type specific, but the vast majority of interactions between these elements and the corresponding regulated gene are uncharted, constituting a major missing link in understanding genome control.

Chromatin interactions are crucial for cellular health due to their main role in genome expression regulation and errors in these interactions give rise to the development of a broad range of diseases including blood cancer. The investigation of these altered 3D structures can help us to improve our knowledge of the tumour process, providing new opportunities for the development of novel treatment approaches and diagnostic strategies.

Additionally, genetic studies have identified thousands of single nucleotide polymorphisms and mutations associated with blood cancer, but most of them expand non-coding regions, which makes them difficult to interpret. Interestingly these non-coding genetic variants cluster on DNA hypersensitivity sites, which are the hallmark of a regulatory element, pointing to a potential role for these genetic variants in the deregulation of target genes. By studying the physical interactions between gene promoter and regulatory elements we are able to connect blood cancer genetic alterations to putative target genes, prioritizing new disease-candidate genes and pathways, and revealing insights into genomic regulatory mechanisms underlying cancer. The interpretation of non-coding variation will also help us to improve the prediction of patient outcome as well as allowing us to design better and more personalized treatments.

The main research goals of our lab are:

- Defining the cell type-specific 3D chromatin organization in human hematopoietic cells
- Identifying the altered DNA topology in blood cancer
- Prioritizing new candidate genes and pathways related to blood cancer

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Unrevealing mechanism for p53-mediated tumour suppression

Project supervisor (principal investigator of the laboratory)

Name: Ana Janic
Mail: ana.janic@upf.edu
Group name: Cancer Biology
Institution: Department of Experimental and Health Sciences
Webpage of the group: https://www.upf.edu/web/cancer-biology/

Main grant associated with this project:
Principal investigator: Ana Janic
Agency: Retos- Plan Estatal
Reference/ years: 2019-2021

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

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/).

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Molecular analysis of Capicua, a conserved Ras-MAPK signaling sensor
Project supervisor (principal investigator of the laboratory)

Name: Gerardo Jiménez
Mail: gjcbmc@ibmb.csic.es
Group name: Gene expression and signaling
Institution: Institut de Biologia Molecular de Barcelona (CSIC), ICREA
Webpage of the group:
http://www.ibmb.csic.es/groups/gene-expression-and-signaling

Main grant associated with this project:
Principal investigator: G. Jiménez
Agency: Ministerio de Ciencia e Innovación
Reference/ years: BFU2017-87244-P (2018-2020)

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

The Ras-MAPK pathway controls numerous cellular and developmental processes and is the main signaling pathway mutated in cancer. Therefore, studying how MAPK signaling drives appropriate cellular responses is a very active area of research. We are addressing this topic by focusing on Capicua (Cic), an evolutionarily conserved transcriptional repressor that functions downstream of MAPK signaling in many biological contexts. In general, Cic is phosphorylated and inactivated (for example, degraded) by MAPK, thereby relieving Cic-mediated repression and permitting expression of Cic targets when signaling is active. In humans, Cic acts as tumor and metastasis suppressor and is also implicated in SCA1 neurodegeneration, although how Cic functions at the molecular level remains incompletely understood. We are exploring Cic activity and regulation by combining genetic, biochemical, imaging and genome-engineering approaches such as CRISPR/Cas9. Most of our work uses the fruit fly *Drosophila*, a powerful experimental system where Cic was originally discovered.

Project Title:

Role of human histone H1 variants in cell proliferation, gene expression and cancer progression

Project supervisor

Albert Jordan, PhD, Científic Titular CSIC, Group leader
Institut de Biologia Molecular Barcelona IBMB-CSIC, Dept. Molecular Genomics
Parc Científic de Barcelona, Baldiri i Reixac, 4, 08028 Barcelona
Tel. + 34 93 402 0487 e-mail: albert.jordan@ibmb.csic.es
http://www.ibmb.csic.es/groups/chromatin-regulation-of-human-and-viral-gene-expression

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. DNA repeats and satellites immersed in heterochromatin are also regulated by these factors.

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.

More recently we have found that depletion of multiple H1 variants in breast cancer cells induce the interferon response as a consequence of derepression of ERVs and satellites. We will investigate whether this also occurs in melanoma cells and this could help immunotherapy to fight cancer cells.

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.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Insulin signalling and RNAi in insects.

Project supervisor (principal investigator of the laboratory)
Name: José Luis Maestro
Mail: joseluis.maestro@ibe.upf-csic.es
Group name: Nutritional signals in insects
Institution: Institute of Evolutionary Biology (CSIC-UPF)
Webpage of the group: http://www.biologiaevolutiva.org/jmaestro/

Main grant associated with this project:
Principal investigator: José L. Maestro
Agency: Plan Nacional, Ministerio de Ciencia e Innovación
Reference/ years: Present: CGL2016-76011-R: 2017-2020
Under revision: PID2019-104483GB-I00: 2020-2023

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

In our group we are studying the function of the insulin pathway in insects and its relationship with different processes, including reproduction, metamorphosis and embryogenesis. Insects have two insulin receptors (InR1 and InR2), produced by an old duplication of an ancestral gene. However, it has been recently discovered that in the lineage that gave rise to cockroaches and termites, there was a duplication of InR1 that yielded InR3. The objective of our project is to reconstruct the sequence of duplications that led to the three InRs in cockroaches: InR1, InR2 and InR3, and to study of their respective functions. The model used will be the cockroach, *Blattella germanica*, about which a great deal of information (its genome has been sequenced with contributions of our group), and tools (we have found that it is very sensitive to the RNAi, which is extremely useful for functional genomics studies), are available.

We will perform RNAi against each of the InR and, looking at the obtained phenotypes, we will determine the processes to which each of the InR is devoted. In addition, we plan to perform transcriptomic analysis of each treatment for analyzing the genes that are affected by the RNAi-triggered depletion of each InR.

The conclusions of the present project will be to identify the role and functional molecular mechanism of the InR of cockroaches and to determine the outcome of the InR duplications in insects and cockroaches: non-functionalization, subfunctionalization or neofunctionalization.

Project Title: ***GENETIC CONTROL OF SPINAL CORD DEVELOPMENT, A MODEL TO UNDERSTAND NEURODEVELOPMENTAL DISORDERS***

Project supervisor: **Elisa Martí**
emgbmc@ibmb.csic.es
Instituto de Biologia Molecular de Barcelona (IBMB-CSIC)
http://www.ibmb.csic.es/groups/morphogenesis-of-the-vertebrate-nervous-system
Main Grant: BFU2016-77498-P

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

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

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

Project supervisor (principal investigator of the laboratory)

Name: Máriam Martínez-Balbás
Mail: mmbbmc@ibmb.csic.es
Group name: Molecular signaling and chromatin
Institution: IBMB, CSIC
Webpage of the group: http://www.ibmb.csic.es/groups/molecular-signaling-and-chromatin

Main grant associated with this project:
Principal investigator: Máriam Martínez-Balbás
Agency: Ministerio de Ciencia y Tecnología
Reference/ years: PGC2018-096082-B-I00. Years: 2019-2021

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

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.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Understanding stress adaptation

Project supervisor (principal investigator of the laboratory)
Name: Eulàlia de Nadal
Mail: eulalia.nadal@irbbarcelona.org; eulalia.nadal@upf.edu

Group name: Cell Signaling Group
Institution: IRB Barcelona
Webpage of the group: https://www.irbbarcelona.org/en/research/cell-signaling

Main grant associated with this project:
Principal investigator: Eulàlia de Nadal
Agency: Spanish Government
Reference/ years: BFU2017-85152-P / 2017-20

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

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.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Neuronal calcium intracellular signalling in Alzheimer's disease

Project supervisor (principal investigator of the laboratory)
Name: Francisco José Muñoz López
Mail: paco.munoz@upf.edu
Group name: Ageing Brain Research Group
Institution: UPF
Webpage of the group:

Main grant associated with this project:
Principal investigator: Francisco José Muñoz López
Agency: SAF- Ministerio de Ciencia, Innovación
Reference/ years: SAF 2017-83372-R

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

Alzheimer's disease (AD) is the most common cause of dementia affecting more than 47 million people worldwide, being a major public health problem with a high economic impact. Due to the progressive increase in life expectancy, it has been proposed that its prevalence will triple in the next 30 years.

EA is characterized by the accumulation of amyloid ß-peptide (Aß) which aggregates into ß-sheets forming neurotoxic oligomers and fibers. The fibers accumulate in the senile plaques of the cerebral parenchyma while the oligomers initiate the damage producing synaptotoxicity that will eventually produce neuronal death. Therefore the production and toxicity of Aß aggregates are determinants in the onset and progression of AD.

There are many experimental evidences that calcium dysregulation is related to the pathophysiology of the disease affecting to synaptic transmission, neuronal death and even increasing Aß production. Our group has recently screened 5,154 mutants of S. cerevisiae that overexpress Aβ, identifying a large number of genes involved in amyloid pathology. Of these we have selected 9 genes that regulate homeostasis and calcium signaling that have not been related to AD at the present time.

HYPOTHESIS: Based on previous studies by our group and other laboratories, we propose the study of the importance of calcium regulation in the pathophysiology of AD by characterizing new genes, not previously related to AD, that play key role in Aß neurotoxicity and production.

OBJECTIVES:

1. Characterization of the new molecular mechanisms mediated by calcium that affect Aß-induced toxicity. The mammalian orthologs of yeast genes that affect Aβ-induced toxicity will be studied in human neuroblastoma cells (SH-SY5Y) and in primary cultures of mouse hippocampal neurons to study their pathophysiological role in neurons. In this study we will focus on the SURF4 protein because of its possible direct relationship with the Ca2 + Store-Operated (SOC).
2. Study of the effect of calcium signaling on Aß production. Characterization of the role of SPCA1 in the production of amyloid through the study of intracellular trafficking of APP, beta- and gamma-secretases and Aß itself.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: The Integrated Stress Response as a modulator of cancer survival and interactions with the immune system

Project supervisor (principal investigator of the laboratory)
Name: Cristina Muñoz Pinedo
Mail: cmunoz@idibell.cat
Group name: Cell death and metabolism
Institution: IDIBELL
Webpage of the group:

Main grant associated with this project:

"Regulation of cell death and cytokine secretion by the Integrated Stress Response. Involvement in lung cancer progression (APOMETALUNG)"
Principal investigator: Cristina Muñoz Pinedo
Agency: Ministerio de Ciencia e Innovación (pending resolution)
Reference/ years: 2020-2023

"Targeting the metabolism-immune system connections in Cancer"
Principal investigator: Cristina Muñoz Pinedo
Agency: European Commission – Excellent Science Department, Marie Sklodowska-Curie Innovative Training Networks.
Reference/ years: Ref. 766214. H2020-MSCA-ITN-2017-2021

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

Lung cancer requires new therapeutic approaches and improvement of existing ones. The cells that form these tumors are frequently stressed due to their high metabolic needs and their exhaustion of nutrients. It has been found that in most tumors, including Non Small Cell Lung Carcinoma (NSCLC), cells display metabolic rewiring. At least one subtype of NSCLC has also been shown to be adapted to deal with stress via constitutive activation of the Integrated Stress Response, which shares one of the pathways of response to endoplasmic reticulum stress, the UPR. This response is mediated by phosphorylation of eIF2alpha and induction of the transcription factor ATF4 and provides the tumor the capacity to adapt to nutrient shortage and other stressful situations, and it allows metabolic rewiring and also secretion of cytokines that may contribute to permanent inflammation and immunosuppression. However, the same response can also turn to cell death.

As NSCLC are very dependent on glucose, we aim to characterize here the starvation response to glucose in these cells by analyzing their transcriptome but more especially their translatome, via polysome profiling. We will examine whether the starvation and/or ISR-sustained translatome is required for survival of NSCLC in vitro to challenges like nutrient deprivation or chemotherapy. We will characterize the precise mechanism of induction of the cell death/cell survival related proteins. We will also analyze cell-cell responses mediated by the translated proteins.

As preliminary results, published and unpublished, we and other groups have previously characterized a number of secreted proteins, cytokines and chemokines including IL-8 and cytokines of the IL-6 family, that are required for NSCLC progression and whose secretion is mediated by increases in their translation or through ATF4. We will characterize the pathways involved in secretion of these cytokines and the paracrine roles of the less studied ones, including effects on cell death of the tumor, the vasculature and the immune system. This will also be applied to newly discovered secreted proteins in the translatome.

Finally, we will address the role of the TRAIL death receptor pathway in secretion of these cytokines, as these proteins have both cell death promoting and also paracrine effects in NSCLC.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Epigenetic Characterization of Cholangiocarcinomas

Project supervisor (principal investigator of the laboratory)
Name: Sandra Peiró
Mail: speiro@vhio.net
Group name: Chromatin Dynamics in Cancer
Institution: Vall d'Hebron Institut d'Oncologia (VHIO)
Webpage of the group: https://www.vhio.net/ca/chromatin-dynamics-in-cancer-group/

Main grant associated with this project:
Principal investigator: Sandra Peiró
Agency: Fundació La Marató TV3
Reference/ years: 2020/2023

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

Cholangiocarcinoma (CCA) is a rare type of cancer and the second most common hepatobiliary malignancy, accounting for 10 to 20% of primary liver cancers. In the recent years, different groups have published data on the molecular biology of CCA, describing a complex pathogenesis, involving various molecular pathways, some of them potential therapeutic targets, such as mutations in IDH1, IDH2, BRAF, PI3K, MET, or translocations in FGFR2. Among them, IDH1/2 mutation represents 20% of patients with CCA. This IDH-mutant generates an "oncolometabolite", D-(R)-2HG (D2HG), responsible for many, if not all, biological effects of cancer-associated IDH mutations. D2HG competitively inhibits a large family of α-KG-dependent enzymes (TET, JmJC) which results in a global increase of DNA and histone methylation. A comprehensive understanding of how IDH1 mutation alters chromatin states is lacking in CCA and needs to be stablished. Here we will analyse the epigenome of CCA_PDXs and cholangiocarcinoma cell lines in terms of histone methylation patterns, DNA accessibility, DNA methylation and transcriptome profiling of both protein coding and lncRNAs in IDH1 wild- type and mutant population. Therefore, we propose to combine the latest high-throughput epigenome and transcriptome profiling techniques together with cutting-edge computational analyses to analyse a unique set of CCA patient derived models. The goal of this project is to perform an integrative analysis to characterize CCA molecularly and epigenetically and shed light on the relation between the genetic and epigenetic architecture of the disease. We also plan to test different inhibitors in IDH1 CCA_PDXs models and to study the biology behind this activity to identify potential biomarkers.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title:
How stem cell capacity is regulated in the developing brain ?

Project supervisor (principal investigator of the laboratory)
Cristina Pujades, PhD
Associate Professor, Department of Experimental and Health Sciences
Universitat Pompeu Fabra
PRBB, Dr Aiguader 88
08003 Barcelona

cristina.pujades@upf.edu
@CristinaPujades
https://www.upf.edu/web/pujadeslab

Main grant associated with this project:
Unveiling the coordination between progenitor dynamics and tissue morphogenesis during neural development: towards a 4D-perspective
MICIU, 2019-21 PGC2018-095663-B-I00

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

The Central Nervous System is initially subdivided into regions with distinct identity that underlies the generation of a specific set of cell types, each of which must arise at the right time and place and in the correct proportions for normal brain development and function. We focus our studies on the embryonic development of the hindbrain, as a model to study how cellular compartments operate during brain development, and how cell diversity is generated. Our goals are to unveil when and how brain progenitors commit to a given fate, how they behave once committed, and how cell fate decisions are regulated to generate the distinct cell lineages.

The main aim of the project is to study **how cell diversity is generated in the developing hindbrain.** We want to understand how the neurogenic capacity is allocated to specific regions of the hindbrain, and the role that Notch-pathway plays. We combine functional experiments with high-resolution *in vivo* imaging and gene transcriptional activation signature analyses.

Our model system is the zebrafish embryo because it permits to combine genetic tools with high resolution imaging approaches. The candidate will be involved in the analysis of different transgenic lines, and in clonal and cell lineage studies.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

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

Project supervisor (principal investigator of the laboratory)

Francisco X. Real
Professor of Cell Biology, Universitat Pompeu Fabra, Barcelona
Senior Group Leader, Epithelial Carcinogenesis Group
Centro Nacional de Investigaciones Oncológicas, Madrid
28029-Madrid (Spain)
Phone +34 917328000 ext 3660
E-mail preal@cnio.es
https://www.cnio.es/investigacion-e-innovacion/programas-cientificos/programa-de-oncologia-molecular/grupo-de-carcinogenesis-epitelial/

Main grant associated with this project:
Principal investigator: Francisco X Real
Agency: MICIN, Asociación Española Contra el Cáncer
Reference/ years: 2019-2021; 2014-2020

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

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.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Encapsulation of microRNA in polymeric nanovesicles as a potential treatment for sepsis

Project supervisor (principal investigator of the laboratory)
Name: ANNA ROIG
Mail: roig@icmab.es
Group name: Nanoparticles and Nanocomposites
Institution: Institut de Ciència de Materials de Barcelona (ICMAB-CSIC)
Webpage of the group: www.icmab.es/nn

Main grant associated with this project:
Synthetic nanovesicles as new treatment for sepsis
Principal investigator: ANNA ROIG
Agency: Fundación Ramón Areces
Reference/ years: SPRINT-4-SPESIS Oct 2019-Sept 2022

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

Sepsis is a life-threatening illness and among the most common causes of death in the intensive care unit's patients. Each year, more than 30 million people develop sepsis and nearly 7 to 9 million die as a result. Sepsis does not have a specific treatment targeting the dysregulated inflammation and the recovery of the acute lung injury. It has been shown that mesenchymal stem cells (MSCs) can be therapeutic for this illness by modulating the deregulated inflammatory response. Other research works have shown that the variety of miRNAs and proteins contained in the extracellular vesicles (EVs) released by the MSCS can also have a regenerative effect in the lungs. SPRINT-4-SEPSIS aims to identify the relevant therapeutic agents inside the EVs released by MSCs activated in different sepsis models. With this information, few active agents will be encapsulated in synthetic biocompatible nanovesicles (NVs). Synthetic NVs can be used to administer sensitive, insoluble or multi-components drugs by protecting the encapsulated therapeutic molecules from inactivation or degradation, as well as by reducing potential toxicity, increasing blood circulation time and tissue specificity. Hence, these NVs will then mimic the MSCs action in the repair and restoration of lung injury in a sepsis model. The ICMAB Group is responsible to engineered the synthetic nanovesicles and encapsulated therapeutic microRNA.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title:

- **Toxico-metabolomics study of silk in *Caenorhabditis elegans***

Project supervisor (principal investigator of the laboratory)

Name: Amanda Muños and Anna Laromaine (**IP of the group: Anna Roig**)
Mail: amunoz@icmab.es, alaromaine@icmab.es
Group name: Nanoparticles and Nanocomposites group
Institution: ICMAB-CSIC
Webpage of the group: www.icmab.es/nn

Main grant associated with this project: Expanding the possibilities of cellulose
Principal investigator: Anna Laromaine
Agency: MINECO
Reference/ years:2019-2021

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

Currently a large variety of nanomaterials (NMs) exist potentially useful in medicine, food industry and cosmetics. Although mechanisms to design, produce and characterise NMs are efficient and quick, it takes 11-15 years and € 350-550 million for a product to arrive to the market. Therefore, reliable and fast models to screen potential drugs, food and cosmetic additives to save money and time are in need.
For this purpose we use the 1 mm-long nematode *Caenorhabditis elegans* as an animal model to test the toxicity of the materials we design. Between 60-80% of the *C. elegans* genome has human homologous genes and most of the metabolic pathways are also conserved. Transparency, short life cycle and minimal maintenance and growth requirements stand out among all the advantages of using this worm. The use of simple non-mammalian model organisms minimise the cost associated with *in vivo* experiments in the early stages of discovery and yields highly informative results such as survival rate, growth effects, reproduction toxicity and changes in the metabolism. Moreover, we can study how NMs are transformed by characterising them after their pass through the organism.

Polymers synthesised by living organisms, biopolymers, are used for drug and food complementation without any evidence of being toxic but, its size´s decrease at the nanoscale can affect the toxicity and their properties. Additionally it has been observed that the oral administration of biopolymers produced changes in the motility, absorption and metabolism of the intestine, key for treating gastrointestinal diseases.

This project will evaluate silk as biopolymer in this tiny worm. The project will consist on: A) Production and characterisation of silk biopolymer B) Evaluation of silk *in vivo using C. elegans* as an animal model. The survival rate, growth effect and reproduction will be the primary endpoints that will be studied. C) Identification of metabolic changes produced by silk. Specific strains and stainings to study lipid and protein metabolism will be evaluated.

The student will have the opportunity to get experience in an international research environment. We, the group of Nanoparticles and Nanocomposite group at ICMAB, are chemists, physics and biotechnologists from all over the world focused on the rational synthesis of functional nanomaterials. The student will learn about a broad range of techniques of synthesis and characterization techniques. We are looking for a highly motivated student, matured and with interest to work in an interdisciplinary field.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Novel roles of the protein kinase Nek9 in the control of chromosome segregation

Project supervisor (principal investigator of the laboratory)
Name: Joan Roig Amorós
Mail: joan.roig@ibmb.csic.es
Group name: Cell Cycle and Signaling
Institution: Institut de Biologia Molecular de Barcelona IBMB-CSIC
Webpage of the group: http://www.ibmb.csic.es/groups/cell-cycle-and-signaling

Main grant associated with this project:
Principal investigator: Joan Roig
Agency: Plan Nacional de I+D, Ministerio de Ciencia, Innovación y Universidades, Spain.
Reference/ years: PGC2018-096307-B-I00 (2019-2021)

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

Our group is interested in understanding how mitosis is controlled, and more specifically how centrosomes and the microtubule cytoskeleton are regulated both in time and space in order to organize the mitotic spindle and allow for proper chromosome segregation. We focus our research on the roles of different protein kinases, and specially Plk1 and its downstream partners, the related Nek9, Nek6 and Nek7. These three NIMA-family kinases form a signalling module activated at the centrosomes that we have shown has a central role controlling the separation and maturation of these organelles during mitotic entry (Bertran *et al.* (2011) EMBO J. **30**: 2634-2647; Sdelci *et al.* (2012) Curr. Biol. **22**: 1516-1523; Eibes *et al.* (2018) Curr. Biol. **28**: 121-129.e4).

Failure to properly separate or mature the centrosomes results in abnormal mitosis, frequently leading to abnormal chromosome segregation and aneuploidy -one of the major hallmarks of cancer cells. Our group has engineered different animal models that will allow us to study in detail the different functions of Nek9/6/7. Using these models plus genetically modified cell lines produced through CRISPR-Cas9 technology, the project will involve characterizing the consequences of Nek9 malfunction at the cellular level, especially in relationship to the control of the centrosome cycle and chromosome segregation, the onset of aneuploidy, and its relationship to cell transformation and the apparition of cancer.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: **UNDERSTAINDING THE MOLECULAR MECHANISMS UNDERLYING ZIKA VIRUS ASSOCIATED NEUROPATHY**

Project supervisor (principal investigator of the laboratory)

Name: Murielle Saade
Mail: msabmc@ibmb.csic.es
Group name: Cilia Signalling in Neural Development
Institution: Instituto de Biologia Molecular de Barcelona IBMB-CSIC
Webpage of the group: http://www.ibmb.csic.es/groups/morphogenesis-of-the-vertebrate-nervous-system

Main grant associated with this project:
Principal investigator: Murielle Saade
Agency: Ministerio de Ciencia, Innovación y Universidades
Reference/ years: RYC2018-025379-I, 01/01/2020-31/12/2024

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

Zika virus (ZIKV) infection, an Aedes mosquito-borne flavivirus, is declared a global threat for public health due to its association with congenital neurodevelopmental birth defects. Despite the enormous basic and clinical research efforts, no specific therapy has yet been approved for the treatment or prevention of ZIKV infection, thus a better understanding of its pathogenesis is an urgent need. ZIKV specifically affects neural progenitor cells (NPCs) evolving multiple mechanisms to restrict proliferation and enhance cell death, although the underlying cellular events involved remain unclear. Our recent studies of the effect of ZIKV non-structural (NS) -proteins on NPCs proliferation, show that the ZIKV-NS5 protein interacts with host proteins at the base of the primary cilia, causing an atypical non-genetic ciliopathy and premature neuron delamination. Furthermore, in human microcephalic fetal brain tissue, we showed that ZIKV-NS5 persists at the base of the motile cilia in ependymal cells, which also exhibit a severe ciliopathy. This research proposal is the natural continuation of these previous finding, in which we seek to provide high resolution pictures of the ZIKV-NS5-cilia base proteins interactions, shedding new light into the mechanisms by which ZIKV-NS5 interferes with the molecular machinery of primary cilia formation and highlighting new potential targets for therapeutic intervention. To that end, we propose three specific aims; the first aim is to establish the first human embryonic stem cells derived neural tube (NT) organoids and validate it as a valuable platform for the next phase of ZIKV-related research (**Aim 1**). The ability to engineer NT organoids will help us studying the potential role of the ubiquitin ligase 3 HUWE1 in coordinating local degradation of centrosomal proteins, allowing ZIKV-NS5 to achieve stringent control of ciliogenesis (**Aim 2**). Finally, we will also unravel structural-interactome studies and will provide the first snapshot of ZIKV-NS5-host protein interactions toward the discovery of the critical residues responsible of ZIKV-NS5 associated ciliopathy (**Aim 3**). Mutations in the ZIKV-NS5-host protein interacting surfaces will be validated in NT organoids paving the way for a promising starting point towards the design of new pharmacologically targets for antiviral therapeutic intervention.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Genome-wide profiling of mRNA methylation during myeloid cell differentiation.

Project supervisor (principal investigator of the laboratory)

Name: José Luis Sardina Ortega
Mail: jsardina@carrerrasresearch.org
Group name: Epigenetic Control of Haematopoiesis
Institution: Josep Carreras Leukaemia Research Institute
Webpage of the group: http://www.carrerasresearch.org/en/epigenetic-control-of-haematopoiesis_129594

Main grant associated with this project:

Principal investigator: José Luis Sardina Ortega
Agency: Josep Carreras Leukaemia Research Institute
Reference/ years: Core funding (2019-2025)

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

Research in the Epigenetic Control of Haematopoiesis group is aimed to uncover the molecular mechanisms governing haematopoietic cell fate decisions, with a special interest in those leading to the onset and development of blood malignancies

Cell fate decisions, such as blood cell differentiation, are typically initiated by transcription factors that regulate gene expression in concert with epigenetic modifications, which typically include histone and DNA modifications. DNA methylation related genes including *DNMT3A* or *TET2* are among the most frequently mutated genes in blood malignancies. Traditionally, studies aimed at understanding the effect of aberrant DNA methylation in cancer patients have focused on gene promoters and gene bodies. However, we and others have recently described that the most DNA methylation-dynamic regions are located distally from the genes (at enhancer elements), coinciding with their preferential binding by DNMT3A and TET2. Therefore, how aberrant DNA methylation dynamics impact on the chromatin structure at distal regulatory regions during blood cancer onset and progression remains to be fully elucidated.

Of note, chemical modifications (including methylation) not only occur in the DNA but are also extremely abundant and diverse in the RNA. Among them, N6-methyladenosine (m6A) is the most prevalent internal modification of the messenger RNA (mRNA). Despite its existence being reported 40 years ago, the biological function and significance of m6A have only recently entered the research spotlight. Interestingly, the lately discovered enzymes controlling the deposition (METTL3-METTL14 complex) and removal (FTO and/or ALKBH5) of m6A are tightly expressed at discrete cell stages of the myeloid differentiation process. Thus, highlighting the potential involvement of a mRNA methylation-mediated post-transcriptional mechanism in the transition from hematopoietic stem cells into mature myeloid cells. Remarkably, MTLL3 protein has been recently reported as a pro-tumorigenic factor in the context of acute myeloid leukaemia.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Transcriptome-wide profiling of mRNA methylation during myeloid cell differentiation.

Project supervisor (principal investigator of the laboratory)

Name: José Luis Sardina Ortega
Mail: jsardina@carrerrasresearch.org
Group name: Epigenetic Control of Haematopoiesis
Institution: Josep Carreras Leukaemia Research Institute
Webpage of the group: http://www.carrerasresearch.org/en/epigenetic-control-of-haematopoiesis_129594

Main grant associated with this project:
Principal investigator: José Luis Sardina Ortega
Agency: Josep Carreras Leukaemia Research Institute
Reference/ years: Core funding (2019-2025)

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

Research in the Epigenetic Control of Haematopoiesis group is aimed to uncover the molecular mechanisms governing haematopoietic cell fate decisions, with a special interest in those leading to the onset and development of blood malignancies

Cell fate decisions, such as blood cell differentiation, are typically initiated by transcription factors that regulate gene expression in concert with epigenetic modifications, which typically include histone and DNA modifications. DNA methylation related genes including *DNMT3A* or *TET2* are among the most frequently mutated genes in blood malignancies. Traditionally, studies aimed at understanding the effect of aberrant DNA methylation in cancer patients have focused on gene promoters and gene bodies. However, we and others have recently described that the most DNA methylation-dynamic regions are located distally from the genes (at enhancer elements), coinciding with their preferential binding by DNMT3A and TET2. Therefore, how aberrant DNA methylation dynamics impact on the chromatin structure at distal regulatory regions during blood cancer onset and progression remains to be fully elucidated.

Of note, chemical modifications (including methylation) not only occur in the DNA but are also extremely abundant and diverse in the RNA. Among them, N6-methyladenosine (m6A) is the most prevalent internal modification of the messenger RNA (mRNA). Despite its existence being reported 40 years ago, the biological function and significance of m6A have only recently entered the research spotlight. Interestingly, the lately discovered enzymes controlling the deposition (METTL3-METTL14 complex) and removal (FTO and/or ALKBH5) of m6A are tightly expressed at discrete cell stages of the myeloid differentiation process. Thus, highlighting the potential involvement of a mRNA methylation-mediated post-transcriptional mechanism in the transition from hematopoietic stem cells into mature myeloid cells. Remarkably, MTLL3 protein has been recently reported as a pro-tumorigenic factor in the context of acute myeloid leukaemia.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

Project Title: Molecular mechanisms of plant immune cell death

Project supervisor (principal investigator of the laboratory)

Name: Núria Sánchez Coll
Mail: nuria.sanchez-coll@cragenomica.es
Group name: Bacterial Plant Pathogens and Plant Cell Death
Institution: Centre for Research in Agricultural Genomics
Webpage of the group:
https://www.cragenomica.es/research-groups/bacterial-plant-diseases-and-plant-cell-death

Main grant associated with this project:
Principal investigator: Núria Sánchez Coll, Marc Valls
Agency: Minesterio de Economía y Competitividad
Reference/ years: AGL2016-78002-R / 2017-2020. Period 2020-2022: grant requested, evaluation pending.

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

The main goal of our team is to decipher the mechanisms that lead to resistance against pathogens in plants. To detect potential invaders and respond appropriately, plants have evolved a complex and fine-tuned immune system. Pathogen recognition often leads to a form of highly regulated cell death known as the hypersensitive response. The hypersensitive response has two main functions: limiting pathogen spread and alerting surrounding cells of the upcoming attack. The molecular mechanisms regulating this type of cell death remain vastly unknown, despite its agronomical interest and the fact that it bears interesting resemblances with inflammatory cell death in mammals. One of our research lines focuses on understanding how a family of proteases, known as metacaspases –distant relatives of animal caspases- regulate this pathogen-triggered cell death phenomenon. In particular, the student will contribute to the functional characterization of several metacaspase-interacting proteins that have been previously identified by immunoaffinity purification of metacaspases. This project will allow the student using a broad array of techniques, including in vitro culture, plant pathogenicity tests, western blot analyses and plant genetic modification.

Call for project proposals, master in Biomedical Research practicum, 2021, UPF

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

Project supervisor (principal investigator of the laboratory)

Name: María José Soler Romeo
Mail: m.soler@vhebron.net
Group name: Nephrology Group
Institution: Vall d´Hebron Research Institute
Webpage: http://es.vhir.org/portal1/grup-equip.asp?t=nefrologia&s=recerca&contentid=186797

Main grant associated with this project:
Principal investigator: María José Soler Romeo
Agency: Instituto Carlos III
Reference/ years: PI17/00257 (2018-2020, will be extended until the end of 2021)

Brief summary of the project or current research lines of the group (please do not include pictures or logos)

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 Supervisor:
Name: Josep Vilardell
Group: pre-mRNA splicing
Institution: IBMB
email: josep.vilardell@ibmb.csic.es
web page: http://www.ibmb.csic.es/vilardell
http://www.ibmb.csic.es/groups/molecular-mechanisms-of-pre-mrna-splicing

Project Title: Molecular Strategies for pre-mRNA Recognition

Summary: With very few exceptions, during their synthesis all human pre-mRNAs become substrate of the spliceosome to get their introns removed and the remaining exons spliced together into mRNAs. In fact, exons could be seen as an oddity in many pre-mRNAs. Most of them are short segments <200-nt long, surrounded by introns that can be hundreds of kilobases long. Yet, a splicing error of a single base could be lethal.
The notion that there must be a mechanism to properly identify exons in pre-mRNAs and that it is regulated is clearly supported by data. However, we know little on the spliceosomal interactions that take place, and we lack a good experimental model to analyze them. It is believed that cross-exonic interactions require additional factors, because the spliceosome 'core', in charge of identifying and processing the intron, does not recognize exons. This is view is consistent with what we know from yeast, a great working model to study the properties of the core spliceosome. Yeast has a relatively simple transcriptome, with most genes lacking introns. Accordingly, the yeast spliceosome machinery is reduced to the basic components, and it appears to just recognize introns. Work from others and us has helped to decipher to a great extent the code of this intronic recognition.
However, a refined Bioinformatics analysis of the yeast genome and transcriptome suggested that even the core spliceosome can “sense” some exons. That is, some exons may influence the recognition of their surrounding introns. This, if confirmed, would support the possibility that the core spliceosome is capable of at least some exon-definition interactions. These would have then expanded during evolution to the complexity of mammalian splicing.
With this motivation we have developed a synthetic gene that appears to be processed in yeast following the exon-definition model. We have done an extensive mutagenesis of the cassette exon (as in Julien et al 2016) and we are analyzing the data.
Specifically, the tasks would be (1) identify exonic parameters that determine how the spliceosome identifies its substrate, (2) suggest spliceosomal components that may be involved in exonic recognition, (3) biological relevance (mechanisms of exon definition in human cells).

References:

* Yan C, Hang J, Wan R, Huang M, Wong CC, Shi Y. "Structure of a yeast spliceosome at 3.6-angstrom resolution." (2015) Science. 349(6253):1182-91.
* Devillers H, Morin N, Neuvéglise C. "Enhancing Structural Annotation of Yeast Genomes with RNA-Seq Data."(2016) Methods Mol Biol.;1361:41-56.
* Julien P, Miñana B, Baeza-Centurion P, Valcárcel J, Lehner B. The complete local genotype-phenotype landscape for the alternative splicing of a human exon" (2916) Nat Commun. 7:11558.
* Meyer M, Plass M, Pérez-Valle J, Eyras E, Vilardell J. "Deciphering 3'ss selection in the yeast genome reveals an RNA thermosensor that mediates alternative splicing." (2011) Mol Cell. 43(6):1033-9.
* Bitton, D. A., et al. (2014). "LaSSO, a strategy for genome-wide mapping of intronic lariats and branch points using RNA-seq." Genome Res 24(7): 1169-1179..
* Kawashima T et al (2014) Widespread use of non-productive alternative splice sites in Saccharo-myces cerevisiae. PLoS Genet. 2014 Apr 10;10(4):e1004249.
* Plass, M., et al. (2012). "RNA secondary structure mediates alternative 3'ss selection in Saccha-romyces cerevisiae." RNA 18(6): 1103-1115.

Project Supervisor:
Name: Josep Vilardell
Group: pre-mRNA splicing
Institution: IBMB
email: josep.vilardell@ibmb.csic.es
web page: http://www.ibmb.csic.es/vilardell
http://www.ibmb.csic.es/groups/molecular-mechanisms-of-pre-mrna-splicing

Project Title: Epigenetics and control of pre-mRNA splicing. (Do the nucleosome and the spliceosome talk?)

Summary: The majority of our pre-mRNAs are subjected to pre-mRNA splicing, greatly expanding the genetic and coding capabilities of our genome. Interestingly, while it is becoming increasingly clear that epigenetic marks such as histone-tail modifications can modulate splicing of the nascent pre-mRNA, how this is happening at molecular level is not understood yet.
Recent results from our work on the splicing of the *RPL30* transcript indicate that this connection between the spliceosome and the nucleosome is present in the yeast model system. Since we can monitor how chromatin marks impact spliceosome assembly on that transcript, we have an excellent an opportunity to investigate the link between chromatin and regulated splicing.
Specifically, the aims of this project are (1) Determine which histone marks have a greater impact on the regulation of spliceosome assembly on the *RPL30* transcript. For this we will take advantage of the collection of yeast histone mutants. (2) Suggest possible spliceosomal factors sensitive to histone modifications, which would point to possible mechanisms. (3) Investigate the biological significance of any finding by asking whether it can be reproduced in human cells.

Further Reading:
1- Regulation of alternative splicing by local histone modifications: potential roles for RNA-guided mechanisms. Zhou HL, Luo G, Wise JA, Lou H.
Nucleic Acids Res. 2014 Jan;42(2):701-13. doi: 10.1093/nar/gkt875 PMID: 24081581
2- Regulation of alternative splicing through coupling with transcription and chromatin structure. Naftelberg S, Schor IE, Ast G, Kornblihtt AR.
Annu Rev Biochem. 2015;84:165-98. doi: 10.1146/annurev-biochem-060614-034242. PMID:26034889
3- L30 binds the nascent RPL30 transcript to repress U2 snRNP recruitment. Macías S, Bragulat M, Tardiff DF, Vilardell J.
Mol Cell. 2008 Jun 20;30(6):732-42. doi: 10.1016/j.molcel.2008.05.002. PMID:18570876