Centre de Regulació Genòmica

1. Descripció del centre de recerca

El Centre de Regulació Genòmica (CRG) és un institut internacional de recerca biomèdica d'excel·lència, creat el juliol de l'any 2000. És una fundació sense ànim de lucre finançada pel Govern català a través del departament d'Empresa i de Coneixement i del departament de Salut, el Ministeri de Ciència i Innovació i la Fundació "la Caixa", i inclou la participació de la Universitat Pompeu Fabra.

La missió del CRG és descobrir i fer avançar el coneixement en benefici de la societat, la salut pública i la prosperitat econòmica. El CRG creu que la medicina del futur depèn de la ciència innovadora del present. Això requereix un equip científic interdisciplinari centrat en comprendre la complexitat de la vida, des del genoma fins a la cèl·lula i un organisme sencer, i la seva interacció amb l'entorn, oferint una visió integrada de les malalties genètiques.

- Adreça:

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2. Descripció del projecte

En el cas del CRG s'ofereixen 4 projectes diferents, en els següents grups de recerca:

a) Oocyte Biology & Cellular Dormancy.

- **Group leader:** Dr. Elvan Böke
- **Mentor:** Dr. Adriano Bolondi
- **Summary of the project:** Dormancy induction in embryonic and postnatal ovaries.

  Women face more challenges in becoming pregnant as they advance in age. Given that the initial childbearing age in Western countries is being pushed back (mean age of women at childbirth in the EU continues to rise from an average of 29.0 to 31.1 years between 2001 and 2022), infertility represents one of the biggest societal challenges of our time. The reduced fertility associated with advanced maternal age stems from many physiological causes, including changes in the ovulatory cycle, increased risk of pregnancy complications and miscarriage due to environmental toxin exposure, or the potential decline in uterine health. Nevertheless, poor oocyte quality represents the primary underlying cause of age-related female infertility.

Oocytes, the female germ cells that will become eggs, are remarkably specialized cells that ensure the continuity of our species by providing the female genome along with most of the housekeeping cellular machinery and nutrients to the early embryo upon fertilization. Oocytes arise during embryonic development in a conserved process called oogenesis, which culminates in the formation of "primordial" oocytes, which are consider "dormant" since they can persist within the ovary for decades, representing one of the longest-lived cells in the human body. Throughout the female reproductive lifespan, cohorts of primordial oocytes activate to grow and transition into primary and secondary follicles. At every fertile cycle, a subset of these follicles is recruited for final maturation and develops into fertilizable eggs.

Primordial oocytes cannot be maintained in culture, and no available protocol allows to culture them beyond few days. This limitation hampers our ability to study the biology of dormancy and to understand their susceptibility to environmental offences.

In this project, we are developing innovative culture conditions to preserve dormancy in primordial oocytes for weeks. We are combining state of the art in vivo and ex vivo ovary culture approaches with high-resolution wide-field and confocal microscopy to identify culture conditions that would preserve primordial oocyte dormancy. Moreover, we use biochemical and molecular biology readouts to benchmark our culture systems. Understanding the molecular and cellular basis of oocyte dormancy will therefore represent a major breakthrough and a revolutionary approach in reproductive biology research.

b) Computational Biology of RNA Processing.

- **Group leader:** Dr. Roderic Guigó
- **Mentor:** Tamara Perteghella
- **Summary of the project:** During library preparation for RNA sequencing, highly expressed genes usually dominate, making it difficult to detect and accurately quantify low-abundance or rare transcripts. This reduces the overall sensitivity of the experiment, especially when subtle changes or novel gene expression are being investigated. This can be further exacerbated by the PCR step, where most abundant transcripts will more likely be amplified, skewing the overall transcript representation. This poses several challenges for downstream analyses, increasing noise in differential expression or totally hampering the detection of lowly expressed transcripts, ultimately making the data harder to interpret. Commonly, capture arrays are used to enrich transcript diversity and target specific elements of interest, however that's not straightforward for poorly annotated species. Within the lab, we are trying to set up a protocol to overcome these limitations by depleting the most abundant genes via duplex-specific nuclease (DSN). This is particularly interesting in light of studies such as the Earth Biogenome Project.

We tested the use of DNS on HEK samples, followed by long-read Nanopore sequencing (one test and one control). The same conditions have been applied to human heart adult tissue (one test and one control), for which a further sample using a capture array is available for comparison. We therefore need to investigate the performances of DNS, between cell lines and complex tissues, as well with respect to capture arrays. We aim to do so by assessing general variation at quantification and specific detection of the most abundant genes, to finally select the most suitable protocol to propagate across the rest of the tissues and species.

c) Epigenetic Events in Cancer

- **Group leader:** Dr. Luciano Di Core
- **Mentor:** Andrea Barrera Conde
- **Summary of the project:** The maintenance of genome integrity is essential for the cell, yet it is constantly challenged by both exogenous and endogenous agents. To cope with this, cells have a complex response cascade that involves the coordination of multiple cellular pathways- which, as we now know, includes metabolic proteins. The aim of this project is to understand the molecular mechanism by which one of these metabolic proteins participates from the DNA Damage Response and explore the therapeutical implications of this mechanism.

d) Mechanics of Organelle Remodeling.

- **Group leader:** Dr. Adel Al Jord
- **Mentor:** Pierre Bercier
- **Summary of the project:** Our group is on a mission to uncover the mechanisms that cells use to functionally remodel their organelles in health and disease. One of our core research areas focuses on how mechanical forces regulate genetic messages essential for life. By understanding these mechanisms, we aim to develop innovative approaches to treat diseases related to altered cell mechanics, such as cancer and premature aging.

  The student will build an innovative biomimetic system to study how biophysical forces regulate RNA processing dynamics in isolated nuclei or synthetic nucleus-like structures. The student will:

  - Contribute to our understanding of the mechanobiology of nuclear compartmentalization and dynamics
  - Gain experience in advanced live microscopy, biophysical analyses, and synthetic biology
  - Develop skills in scientific reasoning, independent thinking, and communication.

3. Perfil específic

Estudiant de 3r o 4t de grau de ciències biomèdiques, bioquímica, biotecnologia, bioinformàtica, biologia, genètica, farmàcia, o altres relacionats. Cada grup de recerca ha especificat:

a) Oocyte Biology & Cellular Dormancy: We look for a highly motivated student to embark in this ambitious but highly rewarding project. The candidate would have previous laboratory experience. Mouse work, cell culture and image analysis expertise are a plus (even only one of these), but not required. Basic knowledge of mammalian developmental biology, oocyte biology and molecular biology techniques will also be preferred. The candidate will work at the interface between cell and tissue biology, learning a wide range of cutting edge technologies including ex vivo cultures, high resolution microscopy, quantitative image analysis, immunofluorescence, quantitative PCR and low-input biochemical assays. The trainee will be fully embedded within the lab environment for the duration of the internship, including participating in the weekly meetings and presenting their work at the end of the training. A training plan will be in place from the beginning of the fellowship to ensure the trainee's technical and professional growth. The candidate will have the unique opportunity to attend seminars and lectures within the PRBB, which hosts international renowned speakers on a weekly base, as well as access to interdisciplinary courses.

b) Computational Biology of RNA Processing: Ideally, the student should have a background in computational biology, and being familiar with the tools, the basic statistical concepts, and applications related to the field of transcriptomics. Theoretical knowledge of sequencing protocols and library prep, nanopore technology, as well as mapping and quantification tools will be evaluated positively. Good problem-solving skills and adaptability, as well as a will to autonomously stay abreast of developments in the field and to collaborate with a multidisciplinary team are also researched. Familiarity with bash basics and R scripting for data analysis and visualization is preferred. English proficiency (at least B2) is required.

c) Epigenetic Events in Cancer: The student is not expected to have prior wet lab experience, but rather a strong interest in the field of molecular biology. The student will be provided with relevant literature to understand the project and receive guidance throughout their stay. The research techniques the student will undertake include cell culture of embryonic stem cells and basic molecular biology techniques, e.g. western blot and RNA extraction. The student will be guided on how to properly interpret the data using the adequate softwares.

d) Mechanics of Organelle Remodeling: We are looking for motivated students with knowledge in cell and molecular biology. A background in bioinformatics would be a plus. Prior wet lab experience is appreciated. Basic knowledge of microscopy and image analysis would also be beneficial.