Job offer

A 4-year predoctoral contract is offered (PIF2024 predoctoral researcher training grant, formerly FPI) to carry out a training plan (see below) in the Functional and Comparative Multiomics lab at the Spanish National Center for Biotechnology (CNB). The contract is associated with the project "*Repair or remove: study of the molecular strategies in primates to promote tumor suppression, longevity, and bigger bodies*", (PID2023-148831NA-I00).

Eligibility Requirements

We are searching for a highly motivated candidate interested in pursuing a PhD in the context of Comparative Multi-omics, Cancer Research, and Primate Evolution with the following profile:

- Bachelor's and Master's degrees in Biomedicine, Biochemistry, Biotechnology, Biology, or related sciences are required.

- Fluent oral and written English is required.

- Previous experience in cell culture, genomics, epigenomics, and transcriptomics techniques and/or in computational biology and bioinformatics will be positively valued.

- The candidate is expected to be committed to acquiring and applying both experimental and computational skills to contribute to the different stages of the project.

Project

Repair or remove: study of the molecular strategies in primates to promote tumor suppression, longevity, and bigger bodies

Cancer, a significant health challenge, stems mostly from DNA mutations causing uncontrolled cell growth and tumoral traits. It's largely a random process, with mutations building up from imperfectly repaired DNA in cells that avoid apoptosis and senescence. The likelihood of cancer increases with an individual's size (as cell count increases) and age6 (allowing more time for mutations). Contradictorily, larger and long-lived species don't have a higher incidence of cancer, an enigma known as Peto's paradox.

The primary goal of this project is to discover the main differences in the DNA Damage Response of a panel of primate species to uncover the molecular drivers of Peto's paradox, disentangling the molecular strategies associated with the evolution of different body sizes, longevities, and cancer prevalences. DDR outcomes can be summarized into (i) repaired damage (first barrier), (ii) cell removal by senescence or apoptosis (second barrier), or (iii) unsolved potentially dangerous damage.

We propose that specific changes in the DDR can explain Peto's paradox:

1.- Increased DNA repair effectiveness shields long-lived and non-renewable cells, extending lifespans and detaching cancer rates from longevity.

2.- Enhanced apoptosis and senescence prevent excessive mutational loads associated to bigger cell numbers, allowing for bigger body sizes without affecting lifespan and disassociating cancer occurrence from body mass.

3.- Distinct species will exhibit Peto's paradox uniquely, reflecting their particular trade-offs between lifespan and body size.

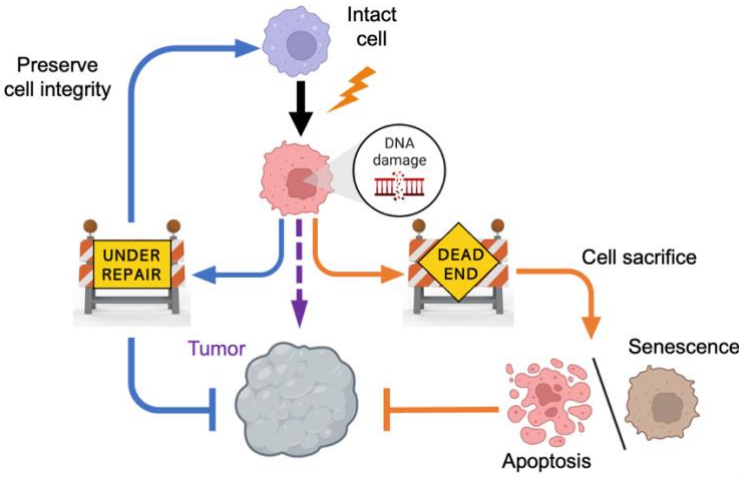

Figure 2. The two barriers of the DNA Damage Response to the accumulation of somatic mutations.

Previous studies support this hypothesis showing that the longevous human species presents a reduced apoptotic response in fibroblasts compared to chimpanzees and macaques, and higher resistance and better DNA repair efficacy to UV-C light mutagenesis than mouse lemurs.

To pinpoint molecular adaptations underlying these and others still to discover differences in DDR across the primate phylogeny, we will examine DDR triggered by three different mutagens selected to activate different repair mechanisms across nine Non-Human Primates. We will investigate differences in the DNA repair efficiency and cellular apoptosis/senescence activity throughout the phylogenetic tree uncovering the underlying genetic and regulatory changes.

For this, we will perform:

1.- Real-time health cell assays after each treatment to characterize the cellular response of each species.

2.- RNA-seq and ATAC-seq experiments to perform a comparative study of the regulatory response to a selected mutagen in primates.

3.- Nanoseq experiments for every species after treatment to quantify the mutations accumulated after DNA damage response to the mutagen. The results will allow us to determine to what extent cancer prevalence can be explained by changes in DDR leading to differences in mutation accumulation.

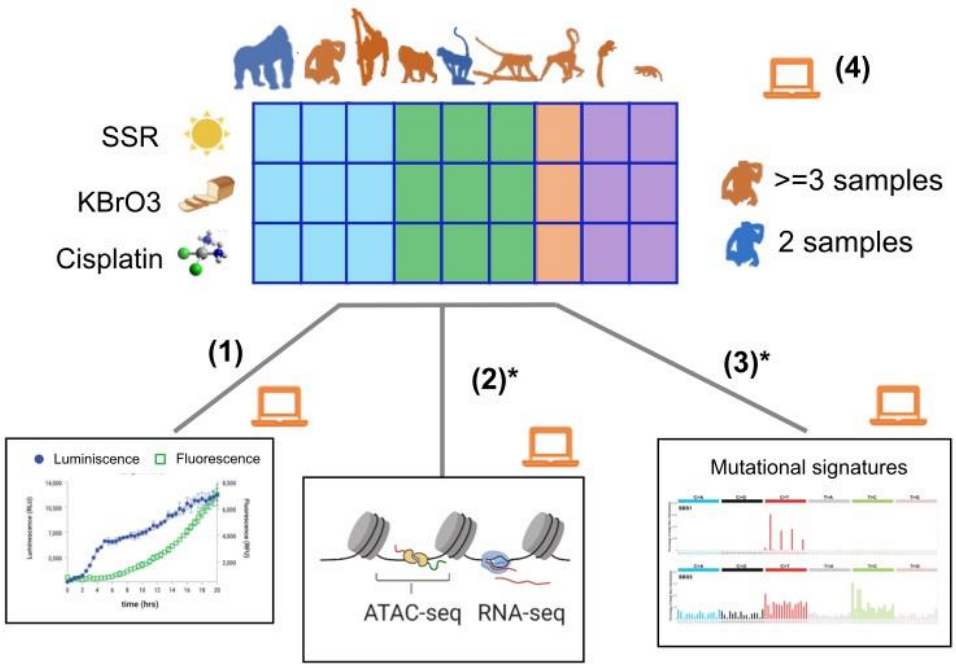

Figure 2. Schema of the project. We will study three mutagen exposures for 9 species with 3 replicates for primary fibroblasts. Experimental grids are colored according to body mass. Silhouette colors indicate the number of individuals already available for that species. Proposed experiments are represented below. *Only for a selected treatment

In parallel, we create a pipeline to analyze each of the types of data generated and integrate them. We will apply this pipeline to analyze cell health, RNA-seq, ATAC-seq, and Nanoseq separately and to integrate them and recover genetic and regulatory elements associated with the evolution of DDR.

The functional and therapeutic implications of the results will be further investigated in the context of available knowledge at the moment and prioritized to pursue further experimental work in other cell types and organoids. In summary, this comparative study aims to uncover the molecular foundations behind the evolutionary strategies that have led to healthier, longer-living humans and other primates. It addresses a significant scientific question, providing necessary insights for the development of specific and safer therapeutic approaches and interventions.

Functional and Comparative Multiomics lab

Principal Researcher: David Juan (**publication record**)

Our conceptual framework:

For over 500 million years, evolution has shaped animal species, resulting in a vast array of unique traits and molecular configurations. Studying these configurations helps us better understand how different species respond to common survival challenges, such as infectious diseases, genetic disorders, aging, and extreme environmental conditions. Our team integrates cutting-edge “omics” technologies with computational methods to explore evolutionary changes in different animal lineages, focusing on genomic, epigenomic, transcriptomic, and proteomic layers. By building this molecular framework, we aim to guide the development of better strategies for promoting human, animal, and biodiversity health.

Main Research Lines:

Cancer Evolution and Peto's Paradox in Primates. Cancer is primarily caused by specific mutations that accumulate in somatic cells over a lifetime. As individuals live longer or have more cells, their risk of developing cancer increases. Surprisingly, inter-species differences in longevity and size do always not directly influence cancer prevalence—this phenomenon is known as Peto's paradox. The mechanisms behind Peto's paradox remain unclear, but the DNA damage response (DDR) plays a crucial role in controlling the accumulation of somatic mutations, and changes in DDR are widespread in species with low cancer prevalence. To investigate its role in Peto's paradox, we study DDR across different cell types in humans and a panel of nonhuman primates with varying sizes and lifespans. We assess inter-species differences in cell-type-specific responses to mutagens using a combination of computational approaches, cell health assays, and genomic, epigenomic, and transcriptomic profiling. We aim to identify mutations and regulatory changes that control DNA damage and cancer prevalence in species closely related to humans, paving the way for new cancer and aging therapies.

Genetic Determinants of Primate and Mammal Phenome Evolution. The phenome represents the complete set of healthy traits in a species, whether at the level of individuals, tissues, cells, or molecules. These traits arise from molecular processes encoded in the genome and regulated through various mechanisms. Over time, evolution selects phenomes that enhance survival, leaving behind genetic traces in present-day genomes. In collaboration with the Evolutionary Genomics Lab at the Institute of Evolutionary Biology (IBE-CSIC), we conduct comparative studies across species to uncover genetic differences associated with phenotypic variations that have evolved over time. We gather data on hundreds of physical, ecological, and life-history traits from primates and other mammals with high-quality genome sequences. Using advanced computational tools, such as phylogenetic comparative methods, we identify genomic changes that may have influenced key traits in species closely related to humans. These candidate changes are further validated in the lab to confirm their role in shaping observed traits. Our goal is to leverage evolutionary insights to better understand healthy mammalian and primate genomes and phenomes. This knowledge can help inform new treatments for conditions like cancer, aging, neurodegenerative diseases, and rare disorders.

Monitoring Rainforest Biodiversity. Protecting ecosystems that are vital for stabilizing the global climate and preserving biodiversity is more urgent than ever. Rainforests, which play a key role in the planet's carbon dioxide-oxygen cycle, are home to over 50% of the world's biodiversity. However, the rapid loss of these still poorly understood tropical forests is pushing many species toward extinction. Our efforts to protect these ecosystems are limited by the lack of effective tools to monitor wildlife at the scale and speed required to prevent further degradation. We are collaborating with the Providence+ team (https://providenceplus.upc.edu/) in the context of the XPRIZE Rainforest challenge (https://www.xprize.org/prizes/rainforest) to develop a scalable solution for monitoring rainforest biodiversity using in situ environmental DNA metabarcoding. In partnership with the Comparative Genomics Lab at the Institute of Evolutionary Biology (IBE-CSIC), the

Laboratory of Applied Bioacoustics at the Technical University of Catalonia (UPC), and the Instituto de Desenvolvimento Sustentável Mamirauá (Brazil), we are creating a computational and experimental framework capable of rapidly profiling species in monitored areas through autonomous sampling. This system integrates other biomonitoring technologies used by Providence+, such as bioacoustics and satellite image analysis, to assess the ecological status of these regions. Our framework aims to improve our understanding of rainforest ecological dynamics and empower local communities and governments to manage their natural resources more effectively, supporting conservation and sustainability efforts.

Recent Publications (full publication record at David Juan's scholar profile)

1. D. Juan, G. Santpere, J. L. Kelley, O. E. Cornejo, T. Marques-Bonet, Current advances in primate genomics: novel approaches for understanding evolution and disease. Nat. Rev. Genet. (2023).
2. L. Ferrández-Peral, X. Zhan, M. Alvarez-Estape, C. Chiva, P. Esteller-Cucala, R. García-Pérez, E. Julià, E. Lizano, Ò. Fornas, E. Sabidó, Q. Li, T. Marquès-Bonet, D. Juan, G. Zhang, Transcriptome innovations in primates revealed by single-molecule long-read sequencing. Genome Res. (2022).
3. R. García-Pérez, P. Esteller-Cucala, G. Mas, I. Lobón, V. Di Carlo, M. Riera, M. Kuhlwilm, A. Navarro, A. Blancher, L. Di Croce, J. L. Gómez-Skarmeta, D. Juan, T. Marquès-Bonet, Epigenomic profiling of primate lymphoblastoid cell lines reveals the evolutionary patterns of epigenetic activities in gene regulatory architectures. Nat. Commun. 12, 3116 (2021).

A. Serres-Armero, B. W. Davis, I. S. Povolotskaya, C. Morcillo-Suarez, J. Plassais, D. Juan, E. A. Ostrander, T. Marques-Bonet, Copy number variation underlies complex phenotypes in domestic dog breeds and other canids. Genome Res. 31, 762–774 (2021).

4. J. M. Heredia-Genestar, T. Marquès-Bonet, D. Juan, A. Navarro, Extreme differences between human germline and tumor mutation densities are driven by ancestral human-specific deviations. Nat. Commun. 11, 2512 (2020).

The environment

CNB, is a flagship multidisciplinary research center of the CSIC, with 71 research groups and 489 personnel, the institute published 262 articles in 2022. CNB is committed to providing adequate laboratory space and access to highly specialized shared equipment and technological core facilities. These facilities encompass cutting-edge technologies, including microscopy, crystallography, bioinformatics, proteomics, and flow cytometry. Close to CNB, the Severo Ochoa Molecular Biology Centre (CBMSO), another flagship CSIC center, presents comparable dimensions, productivity, and training capabilities. It provides further possibilities for scientific collaboration, training initiatives, and access to research facilities. Crucially, CBMSO's Genomics and Massive Sequencing service reinforces the array of experimental techniques.

The CNB conducts both basic and applied research programs, offering infrastructure support to 158 PhD students in 2022. The institute has established a robust PhD training program, with committees organizing annual activities such as predoctoral scientific workshops, welcome events for new PhD students, and courses covering public presentation skills, scientific paper writing, and research ethics. The CNB Training Program is coordinated by a

Training Advisory Board and a Junior Committee formed by predoctoral researchers' representatives.

With a program featuring over 170 seminars, conferences, workshops, and courses in 2022, PhD students and researchers gain valuable opportunities to learn the latest advances in biotechnology, molecular biology, and bioinformatics. The CNB actively promotes gender equality, implementing CSIC's equality plan and organizing initiatives like the "Visibles-CNB" research talks and practical training workshops on gender equality, that all members of our lab will attend as part of our basic training. Additionally, predoctoral researchers actively engage in weekly lab and monthly department seminars, participating in journal club meetings and progress report series to present and discuss their research results.

Our training program

Our group is committed to pioneering research in comparative functional genomics, maintaining a balance between experimental and computational approaches. Over the past decade, it has become apparent that addressing key questions in molecular biology often requires well-designed experiments using high-throughput techniques, coupled with dedicated computational analyses to unravel the complexities of the generated data. Comparative functional multi-omics stands at the forefront of this global trend. Consequently, we firmly believe that new researchers equipped with the background and skills to leverage this experimental-computational duality will shape the future of research. Predoctoral research trainees in our group will undergo training based on this conviction.

The CNB Training Program will provide training on essential research skills, including scientific and critical reasoning, research ethics, experiment design, statistics, public presentation skills, scientific paper writing and illustration, and time and stress management. CNB's Training Program will also complement lab work and doctoral program, with courses on experimental and computational techniques such as R/Python/C++ programming, the Linux environment, machine learning, online resources and repositories, biosecurity, next-generation sequencing analysis, lab safety, cell culture techniques, and more. Based on PI´s experience as a teacher and Ph.D. supervisor, we will supplement these courses with internal training. The predoctoral research trainee will have access to all necessary resources for his/her training, including state-of-the-art technologies and supporting facilities associated with bioinformatics. cell culture and genomics.

The predoctoral researcher will be required to enroll in the master's and doctoral programs of Molecular Biosciences at the Universidad Autónoma de Madrid, within the same campus as CNB, at the start of her/his grants, aiming to obtain the academic accreditation necessary for his/her Ph.D. S/he will work under David Juan's supervision, receiving guidance in her/his daily tasks at the lab. First, s/he will acquire basic technical and scientific skills through training courses provided in our environment. Then, S/he will gradually be introduced to the group's research lines through supervised short training practical projects of increasing complexity and responsibility, contributing to various research collaborations. By the beginning of the second year, the predoctoral researcher is expected to contribute to the development of the proposal, participating in specific subtasks combining experimental and computational work.

In the third year, the predoctoral researcher will take on a more substantial role in the development of the proposal's computational framework. By the project's conclusion, the predoctoral researcher is expected to have made significant contributions to the proposal and various collaborations, resulting in a strong publication record with several publications (at least two first-author authorships in high-profile journals).

Additionally, we plan to send the candidate to visit national and international groups with whom we collaborate, enhancing her/his training and it is expected that the predoctoral researcher will participate in at least 3 conferences (two national and one international to communicate his/her results and work on her/his communication and networking skills.

Our training experience

Drawing on David Juan's experience as a PhD co-supervisor (6 finished and 2 ongoing PhDs), as a teacher in several Master´s programs (over 20 years) and in the Bioengineering Degree by UPF (5 years), and on his extensive worldwide network of collaborations, including large consortia like Zoonomia or the Primate Genomes Project, we aim to nurture outstanding researchers, equipping them with the skills, capabilities, and collaborative networks for international success and recognition.

Completed supervised PhDs:

1. **Raquel García Pérez**. "Evolutionary interplay between epigenetic and gene expression dynamics in human and other primates". Universidad Pompeu Fabra (UPF), 29/01/2019. Publications: 1st author: *Nat. Comm.*; other: *Science*, *Nat. ecol. & evol.*, *Genome res.*, *Nat. comm.*, *Gigascience*.
2. **José María Heredia Genestar**. "The good, the bad, and the hairy: Comparative genomics of great apes from the point of view of human cancer". UPF, 28/01/2020. Publications: 1st author: *Nat. Comm.*; other: *Science, Nature, Genome Biol. & Evol., PLOS Genetics*.
3. **Aitor Serres Armero**. "Understanding dog breed copy number differences in the framework of gray wolf copy number variation". UPF, 03/02/2020. Publications: 1st author: *Genome Res. BMC Genom*.; other: *Science*, *Cell*, *Genome Res.*, (2) *Current Biol., Nat. Comm., Gigascience*
4. **Luis Ferrández Peral**. "Evolution of the transcriptomic regulation in the primate lineage". UPF, 08/06/2022. Publications: 1st author: *Genome Res*.; other: *Science*, *Comm. Biol.*
5. **Paula Esteller Cucala**. "Evolutionary insights into primate gene regulation and development of methods to study DNA modifications". Publications: 1st author: *Nat. Comm.*, *Curr Opin Genet Dev*, *Scientific. Rep., Comm. Biol.*; other: *Science*, *Nat. ecol. & evol., Genome Res.*, *Front Aging*.
6. **Alejandro Valenzuela Seba.** "Phylogenomic Genome-Phenome Analysis in Primates". UPF, 02/07/2024. Publications: 1st author: *In Prep*; other: (4) *Science, Nature, Bioinformatics, American Journal of Primatology*

On-going PhD theses:

1. **Maria Torralvo Márquez.** "Evolution of DNA methylation in the primate lineage". UPF. Publications: 1st author: -; other –
2. **Miguel Ramón Alonso**, "Molecular convergence in the evolution of cancer prevalence in primates and other mammals". UPF. Publications: 1st author: -; other –

Scientific or professional development of our graduate doctors.

1. **Raquel García Pérez**. Data Scientist at Asserta Global Healthcare Solutions. Sant Quirze del Vallès. Spain. Publications: 1st author: *Cell Genom.*; other: *Nat. Comm.*
2. **José María Heredia Genestar**. Postdoctoral researcher at Erasmus MC. Rotterdam. Netherlands. Publications: 1st author: -; other: *Aging Cell*, *EMBO Mol. Med., Front. Syst. Neurosci.*
3. **Aitor Serres Armero**. Postdoctoral fellow at National Human Genome Research Institute (NHGRI). Bethesda. USA. 1st author: -; other: (2) *Science, PNAS, Comm. Biol., Scientific Data*
4. **Luis Ferrández Peral.** Postdoctoral researcher at Biozentrum/University of Basel. Basel. Switzerland. 1st author: -; other: *Nat. Comm, Nat. Methods*
5. **Paula Esteller Cucala**. Postdoctoral researcher at Sant Joan de Déu Institut de Reserca. Barcelona. Spain. 1st author: -; other: -
6. **Alejandro Valenzuela Seba**. Postdoctoral researcher at the Institute of Evolutionary Biology (IBE, UPF/CSIC). Barcelona. Spain. 1st author: -; other: -