

Fictitious Research Projects

(Available on the website of the Doctoral School as from Friday, June 21 2024)

To give equal opportunity to all candidates irrespective of their home university, candidates will present a "fictitious" research project, independent of the actual thesis subjects proposed by the Doctoral School. Each project is accompanied by bibliographical references that serve as a framework for the project.

The candidate is not required to prove to be a specialist of the proposed project but, given his / her research training, to demonstrate his or her ability to think and to be autonomous. The candidate should elaborate on this project an introduction, the methods to be implemented, the expected results and their interest. The project should be feasible in three years. This should not be an article analysis nor a review of the literature. Nor should it be a major laboratory project.

Each candidate can freely choose from the list of proposed "fictitious" projects the one he wishes to present, whatever the real thesis topic he is interested in.

The classification of proposed themes is purely indicative, the candidate can take any subject whatever the category indicated.

The duration of the presentation of the project is of the order of 10 min (the total oral presentation curriculum + project must not exceed 15 min).

Note: All the referenced articles can be downloaded from [the graduate research school website](#) in PDF and from [this link](#) in zip file.

1. Biochemistry

A. Structural biochemistry

Ref :

Norrpa AJ. et al., Nucleic Acids Research 2024, 52(7):4037-4052. doi: 10.1093/nar/gkae070.

Pre-mRNA splicing stands as a pivotal stage in eukaryotic gene expression, involving the intricate process of excising introns and joining exons. Within mammals, two distinct intron types exist: the prevalent U2-introns (comprising 99%) processed by the major spliceosome, and the less common U12-

introns (constituting 1%) managed by the minor spliceosome. While atomic-level structures of major spliceosome intermediates are well-documented, insights into minor spliceosome intermediates are gradually emerging in the literature. Both spliceosomes undergo a stepwise assembly, with the identification of intronic cis RNA elements representing the limiting step. In the major spliceosome, the

5'-splice site is recognized by U1 snRNP, while U2 snRNP binds the branch point, culminating in the formation of the A complex. Conversely, in the minor spliceosome, U11 and U12 snRNPs coalesce into a unified entity, concurrently engaging the 5'-splice site and the branch point within U12 introns. The proposed linkage between U11 and U12 involves the U11-65K protein and the 3' stem loop of U12 snRNA. Recent findings have elucidated that post-splicing, the RNA binding protein RBM41 replace U1165k at the 3' stem loop of U12 snRNA. Given the association between aberrant splicing patterns and human diseases, deciphering the atomic intricacies of minor spliceosome functionality stands as a major challenge.

Expected: The candidate should develop a PhD project to understand at atomic level the role of U12 snRNA 3' stem loop during U12-intron excision. The candidate will build a strategy to characterize the protein-RNA interactions involving the U12 snRNA 3' stem loop during minor intron splicing. Validation of the structures in a cellular environment could also be performed.

B. Cellular and metabolic biochemistry

Ref :

Jones SA, Ruprecht JJ, Crichton PG, Kunji ERS. Structural mechanisms of mitochondrial uncoupling protein 1 regulation in thermogenesis. Trends Biochem Sci. 2024 Apr 1:S0968-0004(24)00071-9. doi: 10.1016/j.tibs.2024.03.005. Epub ahead of print. PMID: 38565497.

Bertholet AM, Kirichok Y. UCP1: A transporter for H⁺ and fatty acid anions. Biochimie. 2017 Mar;134:28-34. doi: 10.1016/j.biochi.2016.10.013. Epub 2016 Oct 27. PMID: 27984203; PMCID: PMC5461058.

Ost M, Keipert S, Klaus S. Targeted mitochondrial uncoupling beyond UCP1 - The fine line between death and metabolic health. Biochimie. 2017 Mar;134:77-85. doi: 10.1016/j.biochi.2016.11.013. Epub 2016 Dec 2. PMID: 27916644.

The uncoupling protein UCP1 is a member of the mitochondrial transporter family. Its function is to dissipate the proton-motive force in the mitochondria of brown adipose tissue. This process short-circuits ATP synthesis and generates heat.

The regulation of UCP1 is complex, involving nucleotides and fatty acids in particular, and the mechanisms leading to uncoupling remain elusive. Article 1 reviews recent structural data obtained by cryoEM, shedding light on the effect of nucleotides on UCP1 conformation, identifying the residues involved, and discusses models proposed to explain the activation of proton transport by fatty acids.

The "Outstanding questions" listed in the review may help you in building your project. Article 2 describes bioenergetic approaches for measuring UCP1 activity. Article 3 opens up the pathophysiological perspectives of UCP1 studies.

You will propose a research project to be carried out within 3 years, aimed at gaining a better understanding of the mechanisms and regulation of UCP1. You may use structural biology and/or functional biochemistry (structure/function) approaches coupled with bioenergetics and/or metabolic measurements.

2. Cell Biology

Ref :

Mechanobiology of organelles: illuminating their roles in mechanosensing and mechanotransduction

Reference: S. Phuyal, P. Romani, S. Dupont and H. Farhan. Trends in Cell Biology. 2023, Vol. 33, No. 12.

Mechanical Forces in Nuclear Organization

Reference: Y. Miroshnikova and S. Wickström. N Cold Spring Harb Perspect Biol 2022;14:a039685

Mechanobiology studies the mechanisms by which cells detect and respond to the mechanical forces and physical properties of their environment. In this context, you will propose an original fictional thesis project, achievable in 3 years, to explore how mechanical forces regulate the biological functions of intracellular organelles. Based on the two reviews above, you may choose one or more of the organelles described (endoplasmic reticulum (ER), Golgi apparatus, endo-lysosomal system, mitochondria or cell nucleus).

3. Cancer biology

A. Cell cancer biology

Ref :

Tumor Innervation: Cancer Has Some Nerve, Hunter D. Reavis,1,2,3 H. Isaac Chen,4,5,6 and Ronny Drapkin 1,2,7, Trends in cancer, 2020, Vol. 6, No. 12

Numerous studies show that the mutual interactions between cancer cells and the various components of the microenvironment (immune cells, fibroblasts, extracellular matrix, etc.) determine the growth and invasion properties of the tumor, the production of metastases, and/or the sensitivity to treatments.

The publication 'Tumor innervation: Cancer has some nerve' presents a set of data concerning the innervation of certain tumors and the possibility that the nervous system regulates tumor progression.

You will propose a research project on this topic that could be completed in three years. It should be based on data from the bibliography and/or available -omics approaches (proteins, RNA). It may propose molecular, cellular, pharmacological approaches, and/or the use of animal models. You must be mindful of feasibility, particularly the availability, accessibility, and suitability of the necessary technologies.

B. Clinic cancer biology

Ref :

Research progress on morphology and mechanism of programmed cell death, Yao Chen^{1,6}, Xiaohua Li^{2,6}, Minfeng Yang^{3,4} and Song-Bai Liu, Cell Death and Disease (2024) 15:32

PCDs: Highways to death (S Dabernat, S Poglio, V Desplat).

Programmed cell death (PCD) refers to forms of cell death distinctive from accidental cell death (ACD). Accumulating evidence has revealed that PDC resistance is one of the key features of tumorigenesis. The apoptotic and autophagy-dependent cell death signaling pathways have been intensely studied, but other PDCs may be hidden assets to induce efficient cell death in cancer therapies.

Using the provided review as a background, you will propose a PhD research project to instrumentalize a specific programmed cell death in cancer (excluding apoptosis and autophagy). You will use the in vitro and/or in vivo animal models of your choice and implement innovative technologies to understand mechanisms of cell death resistance and/or restore tumor cell death. The choice of specific program cell death and model should be justified, the potential translational transfer being a priority, at least as a perspective. Your proposal should fit within the constraints of a three-year thesis.

4. Genetics

Réf :

Pioneer factors: roles and their regulation in development, Amandine Barral 1 and Kenneth S. Zaret, Trends in Genetics, February 2024

The article entitled "Pioneer factors: roles and their regulation in development", published in Trends in Genetics, February 2024, summarises the current state of knowledge about the roles of pioneer factors. In particular, the review discusses the activities of pioneer factors that contribute to the opening (modification) of chromatin and which subsequently lead to changes in gene expression. The influence of these molecular activities of pioneer factors is discussed in the context of reprogramming and differentiation of cells, and their influence on the development of diseases.

Based on this article and possibly other literature of your choice, you should propose a topic for an experimental PhD thesis that can be completed in three years. Your project should provide new knowledge about a regulatory mechanism, a role or a mode of action of pioneer factors, which will allow a better understanding of their influence on chromatin organisation and/or (patho)physiological cellular processes.

5. Immunology

Ref :

Mechanisms and consequences of sex differences in immune responses, Shannon E. Dunn, Whitney A. Perry 3 & Sabra L. Klein, Nature Reviews Nephrology | Volume 20 | January 2024 | 37–55

Biological sex significantly contribute to shape the immune responses, contributing to differences in the pathogenesis of infectious diseases in males and females, the response to viral vaccines or the prevalence of autoimmune diseases. Females typically develop higher innate, humoral and cellular immune responses to viral infections and in response to vaccine. At the same time, women are more prone to autoimmune diseases and experience more adverse reactions to vaccination. Immunotherapies (such as checkpoint inhibitor antibodies and cell therapy) are increasingly used in various fields of human diseases, including cancer, infectious diseases, and autoimmune diseases. Biological sex could be a parameter that influences patients' responses to these therapies. Based on the current state of the art, as well as the review by Shannon E. Dunn, propose a 3-year project that will investigate the mechanisms involved in biological sex disparities in immune responses (efficacy and adverse events) to immunotherapy in the disease model of your choice (autoimmune disorder, infectious disease, cancer, etc.), with potential in vitro and/or in vivo experiments, and/or human samples analysis.

6. Microbiology

Ref :

Batool M, Galloway-Peña J. Clinical metagenomics-challenges and future prospects. Front Microbiol. 2023 Jun 28;14:1186424. <https://doi.org/10.3389/fmicb.2023.1186424>

Wang H, Zhang W, Tang YW. Clinical microbiology in detection and identification of emerging microbial pathogens: past, present and future. *Emerging Microbes & Infections* 2022, VOL. 11 REVIEW <https://doi.org/10.1080/22221751.2022.2125345>

Emerging infectious pathogen/disease can be defined as infectious pathogen/disease that have newly appeared in a population or have existed but are rapidly increasing in incidence or geographic range.

The past years have shown that viral zoonosis between humans and animals is a major health threat; other microorganisms such as bacteria, parasites or micromycetes represent also emerging pathogens. Therefore, anticipating what allows a microorganism to cross the species barrier is key to understand the danger coming from such an event.

In this context please develop a research topic investigating the zoonotic potential of a bacterial, viral, fungal or parasitic microorganism by addressing a select cellular or molecular mechanism (e.g. entry, replication, relation to host immunity...) using several adapted methods (possibly to be combined, such as SILAC-LC-MS-MS, global kinase analysis, animal models, NGS, Metagenomics, metabolomics, qPCR, Bioinformatics and Machine Learning....)

Here is a non-exhaustive list of Emerging infectious pathogens:

<https://www.niaid.nih.gov/research/niaid-biodefense-and-emerging-infectious-disease-pathogens>

7. Neuroscience

A. Cellular approaches

Ref :

The neuronal cilium - a highly diverse and dynamic organelle involved in sensory detection and neuromodulation

[Nathalie Jurisch-Yaksi](#), [Dagmar Wachten](#) and [Jay Gopalakrishnan](#). *Trends in Neurosciences* 2024 May; 47(5):383-394 , DOI: [10.1016/j.tins.2024.03.004](https://doi.org/10.1016/j.tins.2024.03.004). PMID: [38580512](https://pubmed.ncbi.nlm.nih.gov/38580512/)

Regulation of the length of neuronal primary cilia and its potential effects on signaling

Macarelli V, Leventea E, Merkle FT. *Trends Cell Biol.* 2023 Nov;33(11):979-990. doi: [10.1016/j.tcb.2023.05.005](https://doi.org/10.1016/j.tcb.2023.05.005). Epub 2023 Jun 10. PMID: [37302961](https://pubmed.ncbi.nlm.nih.gov/37302961/)

The primary cilia is an organelle specialized for signal transduction and present on most vertebrate cells. It has uniquely evolved to sense the cellular environment and transmit extracellular signals.

Like most cells, neurons and glial cells also have a primary cilia. They play critical roles in brain development and their dysfunction are linked to diseases known as ciliopathies. Yet, how brain cells cilia organization and composition are regulated and what are their role in brain function remains poorly understood.

Based on the two complementary proposed reviews, the candidate will elaborate a three-year PhD project to dissect the molecular organization or the role of primary cilia on brain cells development, cell biology or physiopathology. The scientific question of your project can go from the regulation of cilia length, composition, intracellular transport, signaling, to the role of primary cilia in brain cells

development, polarization or synaptic functions, in any physiopathological context... Any experimental approaches or models to test your hypothesis is welcome.

B. Integrated approaches

Ref:

Social relationships and Health, J S House, K R Landis, D Umberson, Science, 1988
<https://pubmed.ncbi.nlm.nih.gov/3399889/>

The neural circuitry of social homeostasis: Consequences of acute versus chronic social isolation, Christopher R. Lee, Alon Chen, Kay M. Tye, Cell, 2021
<https://pubmed.ncbi.nlm.nih.gov/33691140/>

Changes in social habits and the recent experience with the SARS-COV-2 pandemic raised public attention to the effects of social isolation on mental health and well-being. Indeed, social isolation has been associated with various mental health issues, such as depression, anxiety disorders, cognitive impairment, all of which can severely impact an individual's quality of life.

These observations underscore the need to study the neurobiological mechanisms underlying the effects of social isolation on brain function in healthy and pathological conditions.

Using the listed publications as a guide, the candidate will develop a three-year project based on an integrative neuroscientific approach (e.g. recordings and/or manipulations of brain circuits' activity, theoretical modeling) to assess the behavioral consequences of social isolation (e.g. in social behaviors, sensory processing, memory, addiction or decision-making) and to understand the underlying brain circuits and mechanisms.

C. Neuroelectrophysiology

Ref :

Frontiers in Synaptic Neuroscience 01 frontiersin.org
Synaptic plasticity through a naturalistic lens, Charlotte Piette *, Nicolas Gervasi and Laurent Venance, 2023

Synaptic and cellular plasticity has long been recognized as crucial for learning, memory, and adaptive behaviors. These plastic changes should ideally modify the input-output transformations of neurons within a specific brain region to optimize the population's performance in computations that enable successful behaviors (e.g., perception, value-based decision-making, and movement).

The candidate is encouraged to develop a fictive PhD project that goes beyond the traditional view of synaptic and cellular plasticity (e.g., LTP or LTD) as mere indicators of memory formation. Instead, the project should propose more naturalistic and behaviorally relevant manipulations and protocols. Various forms of plasticity - pre- or post-synaptic, dendritic or

axonal, long- or short-term, potentiation or depression – may be explored. The chosen model may be rodents, drosophila, or humans, and any brain circuit, such as the cortex, thalamus, or cerebellum, can be studied. This includes principal cells, inhibitory neurons, glial cells, and neuromodulators.

The fictive project may be conducted in vitro and/or in vivo and may employ diverse methodologies, including electrophysiology (e.g., patch clamp or silicon probes), imaging (at single-cell or population levels), optogenetics, and chemogenetics. The behavioral aspect may investigate for example memory, avoidance, consummatory behavior, social interaction, sleep, respiration.

D. Clinical pathology

Ref :

Reus, G.Z., Manosso, L.M., Quevedo, J., Carvalho, A.F., 2023. Major depressive disorder as a neuro-immune disorder: Origin, mechanisms, and therapeutic opportunities. *Neurosci Biobehav Rev* 155, 105425.

Major depression (MD) is among the most common and disabling psychiatric disorders. In one third of cases, it fails to respond adequately to the standard treatment strategies classically based on the prescription of antidepressants primarily targeting brain monoaminergic systems. The review article below provides an overview of knowledge on the role of immune-inflammatory mechanisms in the pathophysiology of MD. It indicates the potential peripheral sources of inflammation known to contribute to activation of microglial cells and functional alterations of the neurotransmitter systems (glutamate/monoamines) and the hypothalamic-pituitary-adrenal axis, with deleterious effects on neurogenesis and neuroplasticity. This article also reports clinical trials referring to the utilization of several anti-inflammatory interventions in the management of treatment-resistant depression. In line with this, you will be invited to present a 3-year Ph.D. research project aiming at testing the antidepressant effectiveness of an anti-inflammatory drug and identifying its underlying biological mechanisms.

E. Neuronutrition

Ref :

Nutrition in adolescent growth and development

Shane A Norris, Edward A Frongillo, Maureen M Black, Yanhui Dong, Caroline Fall, Michelle Lampl, Angela D Liese, Mariam Naguib, Ann Prentice, Tamsen Rochat, Charles B Stephensen, Chiwoneso B Tinago, Kate A Ward, Stephanie V Wrottesley, George C Patton *Lancet*. 2022 Jan 8;399(10320):172-184. doi: 10.1016/S0140-6736(21)01590-7. Epub 2021 Nov 29.

During adolescence, growth and development are transformative and have profound immediate and late consequences on an individual's health not only on linear growth and body composition but also on the maturation of other physiological systems.

Inspired by the proposed review, you will develop a PhD project on the importance of healthy nutrition during adolescence. This virtual thesis will involve various experimental strategies, combining *in vitro*, *in vivo* and/or clinical approaches, and will have to be realised within three years.

8. Oenology

Ref :

Impact of climate change on grape berry ripening: An assessment of adaptation strategies for the Australian vineyard, Rogiers, S.Y., Greer, D.H., Liu, Y., Baby, T., Xiao, Z. (2022) Frontiers in Plant Science, 13, art. no. 1094633, DOI: 10.3389/fpls.2022.1094633

Viticultural Manipulation and New Technologies to Address Environmental Challenges Caused by Climate Change Qun Sun, Gabriel Granco, Leah Groves, Jully Voong, Sonet Van Zyl. (2023) Climate, 11, 83. DOI: 10.3390/cli11040083

In the context of climate change, the wine organoleptic quality is increasingly affected by more and more extreme abiotic factors. This quality is dependent on the quality of the berries, the fermentations and the wine aging.

Based on this research topic regarding the possible adaptations of viticultural practices on the grape berry and wine quality, you will proposed a PhD project to improve the knowledge regarding strategies to modulate the climate change impact on grape or wine metabolites which are responsible of the wine organoleptic quality. These wine metabolites with organoleptic properties or hygienic properties can be present in grape berries or produce during the pre-fermentation, fermentation or aging of the wine. You will develop the mechanistic aspects from a viticultural practices, chemical, biochemical, microbiological or wine making processes point of view.

9. Physiology

Ref :

Chow et al. (2022) Exerkines in health, resilience and disease. *Nat Rev Endocrinol.* 18(5):273-289. [doi: 10.1038/s41574-022-00641-2](https://doi.org/10.1038/s41574-022-00641-2).

Magliulo et al. (2022) The wonder exerkines-novel insights: a critical state-of-the-art review. *Mol Cell Biochem.* 477(1):105-113. [doi: 10.1007/s11010-021-04264-5](https://doi.org/10.1007/s11010-021-04264-5).

The benefits of exercise in enhancing health and treating disease are well-recognized but underlying molecular mechanisms are still not fully understood. One hypothesis is the action of a group of molecules named “exerkines”, which include a broad variety of signalling moieties released in response to acute and/or chronic exercise and which exert their effects through endocrine, paracrine and/or autocrine pathways. Those molecules can come in many forms, such as hormones,

metabolites, proteins, nucleic acids, and in some cases they can be transported via extracellular vesicles.

Based on the reviews provided and on the existing literature, you will propose a 3-year PhD project focusing on the functional interactions/communications between two (or more) organs of your choice (excluding the nervous system), involving one or more exerkines. The proposed project can include in vivo, ex vivo, and/or in vitro approaches and should be embedded in physiological and/or pathophysiological process or problematic. If any "omic" approaches are used, they should clearly be a minor part of the project at most.

10. Plant biology

A. Subject 1

Ref :

Bali S, Gleason C. Unveiling the Diversity: Plant Parasitic Nematode Effectors and Their Plant Interaction Partners. *Mol Plant Microbe Interact.* 2024 Mar;37(3):179-189. doi: 10.1094/MPMI-09-23-0124-FI.

Root-knot and cyst nematodes are two groups of plant-parasitic nematodes that cause the majority of crop losses in agriculture. The life cycle of plant-parasitic nematodes includes stages during which the parasite hijacks plant cell metabolism and disrupts plant defenses. Many efforts have been made to identify nematode factors involved in suppressing plant defense or plant cell physiology, and several nematode effector proteins have been characterized. However, to date, research aimed at identifying and characterizing nematode mobile effectors that could be involved in plant defense or metabolism systemic hijacking is very limited.

You are invited to propose a three-year PhD project using any plant/nematode system you consider important in terms of research or research and development in plant pathology or agriculture, which would allow for the identification and characterization of mobile effectors (RNAs or peptides, etc.) in plant-parasitic nematodes. You can employ approaches of your choice (such as cell biology, biotechnology, omics techniques, imaging techniques, etc.) to develop your project. The scientific approach(es) should be original and provide new knowledge, materials, or tools that could be used in plant science and/or applications.

B. Subject 2

Ref :

Shen K, Qu M, Zhao P. The Roads to Haploid Embryogenesis. *Plants (Basel).* 2023 Jan 5;12(2):243. doi: 10.3390/plants12020243.

The review article by Shen et al. highlights that despite research efforts to identify factors that can improve the production of double haploids in crops, many bottlenecks still affect the production of these plants used in breeding programs. They mainly point out that information regarding the

developmental switch(es) that affect microspore development and determine microspore fate has yet to be fully elucidated.

Using a strategy and crop model of your choice, propose an innovative three-year PhD project that can contribute to improve the understanding of the developmental switch(es) by identifying elements (hormones, chemical compounds, metabolites) that lead microspores to haploid embryogenesis, as well as the production of haploid plants from in vitro microspore culture.

11. Bioinformatics

Ref :

N. Gogoberidze and B. Cimini, Current Opinion in Biotechnology 2024, 85:103055

Combining style transfer with foundation models to improve automatic cell segmentation

In the last decade, deep-learning methods have reached a prominent position in computational tasks such as classification or segmentation. Improvements in network architecture, model efficiency and annotation quality have resulted in the development of foundation models: models that generalize well even in presence of unknown data. Nevertheless, these foundation models, such as Segment Anything Model (SAM), are mostly trained on natural images and usually perform in a suboptimal way with microscopy images. When applied on an image including numerous nuclei, they tend to either globally segment the whole distribution as a single object, or they only manage to segment a few subsets of the nuclei.

In this 3-year thesis project, we propose to use style transfer to fine-tune a SAM model to automatically segment all the instances of the nuclei. In a first step, the style transfer will be used to generate synthetic images from masks mimicking real microscopy acquisitions of nuclei. Then, they will be used in conjunction with the masks to fine tune the SAM model. Ultimately, this method will allow foundation models to perform well with any microscopy modality and biological object of interest.

12. Bioimaging

Ref :

Quantitative T2 mapping-based longitudinal assessment of brain injury and therapeutic rescue in the rat following acute organophosphate intoxication. Alita Jesal D Almeida, Brad A Hobson, Naomi Saito, Donald A Bruun, Valerie A Porter, Danielle J Harvey, Joel R Garbow, Abhijit J Chaudhari, Pamela J Lein. Neuropharmacology. 2024 May 15:249:109895. doi: 10.1016/j.neuropharm.2024.109895.

Tumor Targeting by $\alpha\beta3$ -Integrin-Specific Lipid Nanoparticles Occurs via Phagocyte Hitchhiker. Alexandros Marios Sofias,* Yohana C. Toner, Anu E. Meerwaldt, Mandy M. T. van Leent, Georgios Soultanidis, Mattijs Elschot, Haruki Gonai, Kristin Grendstad, Åsmund Flobak, Ulrike Neckmann, Camilla Wolowczyk, Elizabeth L. Fisher, Thomas Reiner, Catharina

de Lange Davies, Geir Bjørkøy, Abraham J. P. Teunissen, Jordi Ochando, Carlos Pérez-Medina, Willem J. M. Mulder, and Sjoerd Hak*. <https://dx.doi.org/10.1021/acsnano.9b08693>. ACS Nano 2020, 14, 7832–7846

Based on these articles, you are encouraged to design a research project aimed at examining the effects of a therapeutic strategy in a pathology of your choice, using non-invasive imaging techniques. This topic can be explored from a biological or technological perspective and should be achievable within a 3-year timeframe as part of a thesis. You are also encouraged to consider a multimodal approach.