Characterization of the interactions between HIF1, STAT3 and Glucocorticoid receptor.
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Glucocorticoid-mediated stress and hypoxia are deeply connected at molecular, cellular and endocrinological levels. The aim of this project is to dissect how glucocorticoid (GC) signaling pathway plays a role in the stabilization and the activation of the hypoxia-specific transcription factor HIF-1α, both under physiological and pathological conditions. Our published and currently submitted results, together with a careful analysis of the literature, identifies three check point of HIF-1α stabilization that may be under control of Glucocorticoid signaling pathway: the transcription of HIF-1α gene, the stabilization of Hif1a protein and the STAT3-dependent transcriptional activity of Hif1a. Indeed, HIF genes seem to be direct targets of Glucocorticoid Receptor (GR) transcription factor. Moreover, while in normoxia HIF-1α is hydroxylized by Prolyl-hydroxilase (PHD) and recognized by pVHL that catalyzes its degradation by proteasome, glucocorticoids are able to modulate HIF activities by targeting VHL to the proteasome, thus stabilizing HIF1a. Finally, the STAT3 gene, a well known stemness marker in ES cells, normal tissues and cancer, absolutely required for the activity of HIF-1α, is synthetic lethal with the glucocorticoid receptor. Therefore, it is tempting to speculate a convoluted cross regulation of HIF based on activation of STAT3 and glucocorticoid receptor. The characterisation of this molecular model may be a powerful tool to understand the molecular basis of several diseases, including cancer and inflammation.

CircRNA roles in leukemias.
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CircRNA are attractive molecules for cancer research since, by sequestering miRNAs and RNA-binding proteins, or by encoding specific peptides, they play pleiotropic regulatory roles and impact key oncogenic axes. CircRNAs can provide new markers and targets for therapy.
The deregulation and functional roles of circRNA in different leukemias will be studied prevalently with a bioinformatic approach.

Tracking the link between variants and ecological niches.
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Metabolic and functional capabilities of a genome are determined by the encoded genes, therefore these basic functional units are the drivers of the microorganisms adaptation to different conditions including pathological states. By using genome-centric approaches, including single-molecule sequencing and variant discovery, the aim is to track the links between gene content, genomic variants and the ability to adapt to ecological niches, providing a conceptual framework for predictive ecology based on genomic data.

Is cryptochrome circadian activity regulated by a Ca2+/CaM signaling mechanism?
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Cryptochromes are flavin-containing proteins recruited by the circadian clock machinery, either as clock-components that control the daily behavioural and physiological rhythms and as photoreceptors that mediate entrainment of the circadian clock to light. Although increasing evidences suggest the involvement of CRYs in numerous additional signaling pathways, the nature of the transduction signaling involving CRYs remains largely unknown. We have previously suggested in Drosophila a novel mechanism regulated by Ca^{2+}/CaM, probably acting in consolidating the light-response stimulation [Mazzotta GM, (2018) Front Mol Neurosci11:280]. This project aims at characterizing the role of a Ca^{2+}/CaM signaling in the regulation of cryptochrome activity, answering to open questions: 1) Do mammalian CRYs act through a PDZ scaffolding/CaM mediated signaling pathway? 2) Is a CaM dependent signaling involved in the light-independent activation of Drosophila CRY? Experiments with human proteins will provide insights about the involvement of a Ca^{2+}/CaM mediated signaling pathway in the modulation of CRYs activity. By using Drosophila as model, we will be able to perform *in vivo* experiments that will help to deeply dissect this signaling pathway.

New circulating biomarkers for predicting acromegaly responsiveness to Somatostatin Analogues (SSA) therapy.
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SSA represent the first-line medical treatment in acromegalic patients for which surgery is not successful or indicated. In more than 50% of cases, however, SSA are ineffective and therefore a large proportion of patients are treated with an expensive drug without any benefit for a long time. Currently, no robust biomarkers predicting such response is available.
Circulating miRNAs, detectable in various body fluids, are considered a reliable prognostic and therapeutic biomarker for many diseases, including tumors. The identification of specific miRNA signatures in the pituitary tumors, led us to the hypothesis that some deregulated miRNAs could have a role in SSA resistance in acromegaly. Aim of this study is hence to find and validate a serum miRNA signature as circulating biomarker predictive of SSA sensitivity in acromegaly patients.

Innovative therapeutic strategies for Arrhythmogenic Right Ventricular Cardiomyopathy.
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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart muscle disease that predisposes to the occurrence of ventricular arrhythmias and sudden death, particularly in the young and athletes. Most therapies are palliative and aimed at relieving symptoms and preventing disease progression. The aim of this project is to identify potential therapeutic compounds active on ARVC cardiomyocytes derived from patients' pluripotent stem cells and to test the ability of a specific compound to prevent fibrofatty infiltration in ARVC murine models.

Modelling POLG-related mitochondrial disorders: a platform using yeast, worm and zebrafish for disease analysis and drug discovery.
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This project aims to identify candidate drugs with therapeutic effects on mitochondrial (mt) pathologies linked to POLG or POLG2 genes, encoding the mtDNA polymerase and its accessory subunit. The project will adopt a multi-species approach, based on drug pre-screen in Polg-mutated yeast (mip1) and *C. elegans* (polg-1) strains, followed by drug validation in zebrafish Polg and Polg2 mutants.
Through a collaboration with the University of Parma, the screen of drugs in yeast will be performed by evaluating the rescue of respiratory growth defects due to mtDNA instability ("petite" phenotype) in mip1 mutants. More in-depth analysis will include quantitative evaluation of Mip1 expression, respiratory activity and mtDNA levels.
Positive hits will be analyzed in worm models (in collaboration with the "Institut de Biologie Intégrative de la Cellule", Paris), as well as in zebrafish Polg and Polg2 mutants, produced and characterized at the University of Padova. The efficacy of drug candidates will be evaluated in relation to the rescue of pathological phenotypes, including mtDNA depletion, impaired respiratory activity and altered mt-nucleus retrograde signaling.

ADAR-editing in mollusk species: in between physiology and antiviral responses.
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RNA-specific Adenosine Deaminase (ADAR) enzymes, highly conserved in metazoans, introduce single nucleotide changes in both self and non-self dsRNAs. Tissue- and site-specific editing can lead to new isoforms and functional diversification of host proteins. We demonstrated significant ADAR-1 editing in the oyster response to Ostreid herpesvirus 1. However, the physiological consequences for the host and the outcome in terms of viral fitness requires investigation. Based on available knowledge and advanced research procedures, the project aims to study the role of ADARs in normal and infected mollusks.