Ph.D. thesis position at I.B.G.C Bordeaux (2022 – 2025)

Development of novel non-invasive and label-free imaging approaches for the characterization of mitochondrial defects and the diagnosis of mitochondrial diseases.

We are looking for Ph.D. student to join our Team (BioDynaMit) at I.B.G.C. Bordeaux for a Ph.D. thesis starting in October 2022. The student has to fulfill the academic criteria for a Ph.D. thesis at the doctoral school SVS (Sciences de la Vie et de la Santé) of the University of Bordeaux. Funds for the salary are secured for students with an excellent academic record. We seek to recruit a Ph.D. student with expertise in cell biology, mitochondrial biology and/or (energy) metabolism. Knowledge and/or interest in photonic microscopy and/or image analysis is a plus. The student can choose French or English as the working language.

Interested candidates are invited to send informal inquiries and/or formal applications to the thesis director (manuel.rojo@ibgc.cnrs.fr). Formal applications should include documents allowing to evaluate the academic record, a motivation letter, a C.V., and letter(s) of recommendation and/or name of referee(s).

Développement de nouvelles approches d'imagerie non invasives et sans marquage pour la caractérisation de défauts mitochondriaux et le diagnostic de maladies mitochondriales.

Nous recherchons un doctorant pour rejoindre notre équipe (BioDynaMit) à l'I.B.G.C. Bordeaux pour une thèse de doctorat débutant en octobre 2022. L'étudiant doit remplir les critères académiques pour une thèse de doctorat à l'école doctorale SVS (Sciences de la Vie et de la Santé) de l'Université de Bordeaux. Le salaire est assuré pour les étudiants ayant un excellent dossier académique. Nous cherchons à recruter un étudiant ayant une expertise en biologie cellulaire, biologie mitochondriale et/ou métabolisme (énergétique). Une connaissance et/ou un intérêt pour la microscopie photonique et/ou l'analyse d'images est un plus. L'étudiant peut choisir le français ou l'anglais comme langue de travail.

Les candidats intéressés sont invités à envoyer des demandes informelles et/ou des candidatures formelles au directeur de thèse (manuel.rojo@ibgc.cnrs.fr). Les demandes formelles doivent inclure des documents permettant d'évaluer le dossier académique, une lettre de motivation, un curriculum vitae et une (des) lettre(s) de recommandation et/ou le nom d'un (de) référent(s).

Development of novel non-invasive and label-free imaging approaches for the characterization of mitochondrial defects and the diagnosis of mitochondrial diseases.

Introduction. Mitochondria are double membrane-bound organelles that carry their own genome and host the machineries (OXPHOS and Krebs-cycle) enabling nutrient oxidation and concomitant synthesis of ATP, the universal energy currency. Mitochondria are dynamic organelles that move, fuse and divide. The fusion/fission equilibrium determines mitochondrial shape, that ranges from branched tubules to individual spheres. These dynamics, controlled by ubiquitously expressed dynamin-related proteins (DRPs) and modulated by OXPHOS, are essential for mitochondrial maintenance, function and degradation. Defects in mitochondrial OXPHOS are at the origin of mitochondrial diseases and mutations in two fusion factors (OPA1 or MFN2) are linked to neuropathies (DOA or CMT2A). The genetic complexity of mitochondrial dysfunctions, together with multisystemic and tissue-specific clinical spectra, pose major challenges in their diagnosis, in the characterization of pathogenic mechanisms, and in the exploration of therapeutic strategies.

Goal. This project aims (i) to implement novel non-invasive and label free approaches for imaging mitochondrial morphology and dynamics in cultured cells and (ii) to establish Deep Learning procedures allowing their data-driven, quantitative description. The thesis will be developed within a biology team with solid expertise in mitochondrial biology, fusion/fission dynamics and OXPHOS (BioDynaMit/IBGC, Bordeaux). Development and implementation of novel approaches for imaging and image analysis will be developed in collaboration with a photonics team (XLIM, Limoges). *In fine*, our work will allow the quantitative description of mitochondrial dynamics and/or morphology and the unambiguous identification and precise characterization of fusion/fission defects. This will enable reproducible and reliable diagnosis of mitochondrial diseases and will facilitate the search for (therapeutic) strategies leading to the restoration of "healthy" mitochondrial dynamics.

Project. To date, characterization of fusion/fission dynamics is mainly based on the pseudo-quantitative analysis of network morphology in fixed cells. Morphology is pseudo-quantified by establishing the percentage of cells with a 'fused-filamentous' or 'unfused-fragmented' mitochondria, but the criteria to define 'filamentous' or 'fragmented' differ between laboratories or even observers. Our goal is to observe mitochondrial dynamics in living cells (not to acquire a static image of fixed cells) and to obtain, through machine learning training, a score faithfully and unbiasedly quantifying mitochondrial morphology and/or dynamics.

The IBGC team has solid expertise in the analysis of mitochondrial OXPHOS, morphology and dynamics and the interrelationships between them. The team has generated animal and/or cellular models that are either wild-type or knock-out for fusion/fission factors (MFN1, MFN2, OPA1 or DRP1), as well as cells that express pathogenic mutations of MFN2 (an essential fusion factor) linked to Charcot-Marie-Tooth Disease of type 2A (CMT2A), a peripheral neuropathy. They also possess the means and know-how for the constitutive expression of fluorescent proteins targeted to mitochondria and to other organelles. The student will develop and improve the cellular models that (displaying highly characteristic and well-defined defects in mitochondrial bioenergetics, morphology and/or dynamics) will enable the development and validation of the novel imaging tools.

The LP2N team is currently developing label-free imaging microscopy methods to unlock stealthy and reproducible measurements in biological samples. Based on quantitative phase imaging using self-interferences, this modality is compatible with any microscope and living samples. The spatial resolution of the technique (<250 nm) grants the capability to study organelles including mitochondria with an unprecedented sensitivity and temporal resolution. We will use cells with characteristic fusion/fission profiles devoid of fission (DRP1 KO), outer membrane fusion (MFN1 and MFN2 KO) or inner membrane fusion (OPA1 KO) to train machine learning algorithms to identify and quantify the mitochondria network in a label-free manner. Simultaneous phase/fluorescence imaging in cells carrying fluorescent mitochondria will train the algorithm that will run on label-free samples. Long term and stress less imaging of mitochondrial dynamics (*i.e.* without fluorescence) will allow proper visualization and quantification of fusion and fission in healthy and in pathological cellular models.

For further information see:

BioDynaMit at ibgc: http://www.ibgc.cnrs.fr & http://www.ibgc.cnrs.fr/?page=equipe&eq=biodynamit
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Photonics team at LP2N (https://www.lp2n.institutoptique.fr), starting 01/05/2022 at XLIM (https://www.xlim.fr)
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