2019-11-20

EuReCa International PhD Program

PhD thesis project

2020 Call for application

From patients to ex vivo modeling of tumor ecosystems: role of Cancer-Associated Fibroblasts in breast cancer response to chemotherapy

General information

Call	2020
Reference	2020-05-PARRINI
Keyword(s)	Breast cancer, Tumor microenvironment, Cancer-associated fibroblasts, Tumor-on-chip, Chemotherapy

Director(s) and team

Thesis director(s)	Maria-Carla Parrini & Fatima Mechta-Grigoriou
Research team	Stress & Cancer
Research department	U830 Cancer, Heterogeneity, Instability and Plasticity (CHIP)

Description of the PhD thesis project

Breast cancer (BC) is the most common cancer among women. For the most aggressive or advanced cases, chemotherapy remains the main current treatment. The tumor microenvironment, which includes as major component the Cancer-Associated Fibroblasts (CAF), plays a key role in tumor progression and drug resistance. However, the underlying mechanisms remain poorly understood, mainly due to the lack of appropriate approaches to untangle the enormous complexity of the tumor ecosystems.

The host lab, directed by Fatima Mechta-Grigoriou, has recently characterized CAF heterogeneity in both breast and ovarian cancer patient samples, identifying at least 4 different CAF subsets, referred to as CAF-S1 to S4, which have distinct functions. In particular, CAF-S1 fibroblasts promote an immunosuppressive environment.

This PhD project will bridge several disciplines, Cell Biology, Clinical Oncology, Microfabrication & Microfluidics, and Artificial intelligence, to study the effects of chemotherapy on the tumor ecosystem. All the required collaborations are already established and highly active. The student will benefit from both retrospective and prospective breast cancer patient cohorts, thanks to long-lasting collaborations with clinicians of the Institut Curie hospital group.

Moreover, the complex cellular interplay of the tumor microenvironment (cancer, immune, endothelial cells and CAF) will be reconstituted and modeled using the emerging organs-on-chip technology. The student will integrate analysis of patients' samples (in vivo) and tumor-on-chip experimentation in microfluidics devices (ex-vivo), to achieve a comprehensive characterization of CAF involvement in chemotherapy response of breast cancers.

International, interdisciplinary & intersectoral aspects of the project

Interdisciplinary. This project is at the crossroad of 4 disciplines: Cell Biology, Clinical Oncology, Microfabrication & Microfluidics, Artificial intelligence. All the required collaborations are already established, most of them located at walking distance: Pathology Department and Surgery Department of Institut Curie hospital, Institut Pierre-Gilles de Gennes pour la Microfluidique, Ecole Normale Supérieure, and University Roma TorVergata.

Intersectoral. The host lab has strong connections with industrial partners (Roche, Fluigent, InnatePharma, Transgene, Inventiva), that currently support 3 PhD students.

International. A very active collaboration with Italy (University Roma TorVergata) contributes to the image analysis aspects of the project.

Recent publications

1. Fibroblast heterogeneity drives metastatic spread through distinct mechanisms in breast cancers. Pelon F, Bourachot B,Yann Y, Magagna I, Mermet-Meillon F, Bonnet I, Costa A, Givel A-M, Attieh Y,Barbazan J, Bonneau C, Fuhrmann L, Descroix S, Vignejevic D, Silberzan P, **Parrini MC**, Vincent-Salomon A, **Mechta-Grigoriou F**. In revision

2. PML-Regulated Mitochondrial Metabolism Enhances Chemosensitivity in Human Ovarian Cancers. Gentric G, Kieffer Y, Mieulet V, Goundiam O, Bonneau C, Nemati F, Hurbain I, Raposo G, Popova T, Stern MH, Lallemand-Breitenbach V, Müller S, Cañeque T, Rodriguez R, Vincent-Salomon A, de Thé H, Rossignol R, **Mechta-Grigoriou F**. Cell Metab. 2019 Jan 8;29(1):156-173.e10. doi: 10.1016/j.cmet.2018.09.002.

3. Fibroblast heterogeneity and immunosuppressive environment in Human breast cancer. Costa A, Kieffer Y, Scholer-Dahirel A, Pelon F, Bourachot B, Cardon M, Sirven P, Fuhrmann L, Bernard C, Kondratova M, Kuperstaine I, Zinovyev A, Magagna I, Givel A-M, **Parrini MC**, Soumelis V, Vincent-Salomon A, **Mechta-Grigoriou F** Cancer Cell. 2018 Mar 12;33(3):463-479.e10. doi: 10.1016/j.ccell.2018.01.011.

4. miR200-regulated CXCL12β promotes fibroblast heterogeneity and immunosuppression in ovarian cancers. Givel AM, Kieffer Y, Scholer-Dahirel A, Sirven P, Cardon M, Pelon F, Magagna I, Gentric G, Costa A, Bonneau C, Mieulet V, Vincent-Salomon A, **Mechta-Grigoriou F**. Nat Commun. 2018 Mar 13;9(1):1056. doi: 10.1038/s41467-018-03348-z.

5. Dissecting Effects of Anti-cancer Drugs and Cancer-Associated Fibroblasts by On-Chip Reconstitution of Immunocompetent Tumor Microenvironments. Nguyen M, De Ninno A, Mencattini A, Mermet-Meillon F, Fornabaio G, Evans SS, Cossutta M, Khira Y, Han W, Sirven P, Pelon F, Di Giuseppe D, Bertani FR, Gerardino A, Yamada A, Descroix S, Soumelis V, **Mechta-Grigoriou F**, Zalcman G, Camonis J, Martinelli E, Businaro L, **Parrini MC**. Cell Rep. 2018 Dec 26;25(13):3884-3893.e3. doi: 10.1016/j.celrep.2018.12.015.

Expected profile of the candidate

Candidates should have a strong motivation to explore Cancer Cell Biology by a challenging integration of different approaches. They are expected to be highly dynamic, quickly independent, capable to adapt to a competitive research environment, at ease in interpersonal relationships and in team work. Background in Cell Biology, Immunology and/or Oncology is strongly recommended. Technical skills in flow cytometry (FACS), immunohistochemistry (IHC), video-microscopy, image analysis, microfluidics, or computational biology are a plus but not compulsory.