EuReCa International PhD Program

PhD thesis project

2021 Call for application

Extracellular Vesicles in invasion, metastasis and ferroptosis resistance: a specific role for CD133/Prominin in aggressive gastrointestinal carcinoma

General information

Call	2021
Reference	2021-03-DANGELO_WATSON
Keyword(s)	Extracellular vesicles; Prominin/CD133; metastasis; ferroptosis resistance; cancer

Director(s) and team

Thesis director(s)	Gisela D'Angelo & Sarah Watson
Research team	Structure and Membrane Compartments
Research department	UMR 144 - Cell Biology and Cancer

Description of the PhD thesis project

The major goal of our research is to gain a better understanding of the biogenesis and functions of extracellular vesicles (RVs). They originate from the endosomal network (exosomes) or from the plasma membrane (microvesicles). Carrying a defined but mixed cargo of biomolecules, EVs possess versatile biological activities with the ability to modulate the molecular configuration and behavior of target cells, while they can also be involved in disease states.

We use several model systems, like Drosophila, primary and transformed cells in culture, and human tissues. These different in vivo and in vitro model systems are combined cell biological molecular and biochemical to powerful multiscale imaging methods and electron microscopy modalities.

The spread of cancer cells from the primary tumor into surrounding tissues and metastasis to distant organs is the primary cause of cancer morbidity and mortality. Recent data suggest that EVs released by cancer cells may stimulate tissue invasion and dissemination of tumor cells to target tissues. The CD133/Prominin protein, prominently associated to EVs, is a prognostic marker in different cancer types: high levels of CD133 having been correlated with adverse outcome in colorectal, pancreas and brain tumors and favor chemotherapy resistance. We have recently shown that CD133/Prominin promotes the generation EVs and their secretion from epithelial cells.

The main aim of the project is to unravel the nature and role of EVs bearing CD133/Prominin, and other components modulating cell signaling and iron metabolism at inducing invasion, metastasis, and ferroptosis resistance in cancer. The project combines cell biology with state-of-the-art imaging at different resolution levels, biochemistry, molecular biology, chemistry, and in vivo translational research. This work should provide evidence for the development of new therapeutic tools that could interfere with EV production and prevent invasion and metastasis in most cancer types.

International, interdisciplinary & intersectoral aspects of the project

The project is at the interface between cell biology, cancer, and anti-cancer therapy.

The student will visit and/or interact with the lab of H. Peinado (Spanish National Cancer Research Center), who has, together with D. Leyden, evidenced the metastatic capacities of EVs and is currently developing new and more effective approaches to understand how the tumor microenvironment influences metastasis, and to prevent their spread. Their expertise and knowledge will be crucial to accompany and to advise the PhD student.

The PhD student will also collaborate with V. Agache, Physicist (CEA/LETI Grenoble, France) for isolation of EVs by microfluidics. V. Agache is deeply versed in-flow microfluidic sorting device coupled to high precision sensors to isolate cells and EVs.

Recent publications

1. Hurbain I, Macé AS, Romao M, Sengmanivong L, Ruel L, Basto R, Therond P, Raposo G, **D'Angelo G**. Microvilli-derived extracellular vesicles govern morphogenesis in Drosophila wing epithelium bioRxiv. 2020. DOI: 10.1101/2020.11.01.363697

2. Adams SD, Csere J, **D'Angelo G**, Carter E, Arnandis T, Kocher H, Grose R, Raposo G, Mardakheh F, Godinho SA. Centrosome amplification mediates small extracellular vesicles secretion via lysosome disruption bioRxiv. 2020. DOI: 10.1101/2020.08.19.257162

3. van Niel G, **D'Angelo G**, Raposo G. Shedding light on the cell biology of extracellular vesicles. Nat Rev Mol Cell Biol. 2018 Apr; 19(4): 213-228: DOI: 10.1038/nrm.2017.125

4. **Watson S**, de la Fouchardière C, Kim S, Cohen R, Bachet JB, Tournigand C, Ferraz JM, Lefevre M, Colin D, Svrcek M, Meurisse A and Louvet C. Oxaliplatin, 5-FU and Nab-Paclitaxel as perioperative regimen in patients with resectable gastric adenocarcinoma: a GERCOR phase II study (FOXAGAST) European Journal of Cancer, 2019 Jan; 107: 46-52.

5. **Watson S**, Perrin V, Guillemot D, Reynaud S, Coindre JM, Karanian M, Guinebretière JM, Freneaux P, Le Loarer F, Bouvet M, Galmiche-Rolland L, Larousserie F, Longchampt E, Ranchere-Vince D, Pierron G, Delattre O, Tirode F. Transcriptomic definition of molecular subgroups of small round cell sarcoma Journal of pathology 2018 May; 245(1): 29-40.

Expected profile of the candidate

Applicants should be highly motivated to explore in vivo and in vitro diverse aspects of fundamental cell biology, cancer and anti-cancer therapy.

A solid capacity for independent and creative thinking would be considered.

Background in cell biology and molecular biology is strongly recommended. Background in biochemistry is a plus but not compulsory.

The project highly relies on light and electron microscopy approaches and live imaging techniques, for which the applicant should have either experience or a strong motivation to learn.