

EuReCa International PhD Program
PhD thesis project
2023 Call for application

Deciphering the dynamics of gene co-expression at the single cell level to understand patterning and epithelium-to-mesenchyme transition in development and cancer

General information

Call	2023
Reference	2023-07-MONSORO-BURQ
Keyword(s)	Multimomics analysis, Development, Cancer, Single cell, Advanced imaging.

Director(s) and team

Thesis director(s)	Anne-Hélène Monsoro-Burq
Research team	Signaling and neural crest development
Research department	UMR3347 / U1021 - Signaling, radiobiology and cancer

Description of the PhD thesis project

While tumors include very heterogeneous neighbour cells, early embryonic tissues are often patterned in a graded manner with fields of similar cells. However, recent single cell (SC) transcriptomics uncover micro-heterogeneities in otherwise similar cells, which could prefigure patterning transitions or cell behaviors such as epithelial-mesenchymal transition (EMT) and cell migration. It remains unknown if cells differing only by few specific gene expressions are neighbors forming a mosaic tissue or organized in homogeneous groups spatially.

This question especially applies to transitional tissues such as the neural crest or metastases and is critical to understand development or the aberrant reactivation of embryonic programs in cancer. Spatial transcriptomics is a key emerging approach revealing combined gene expressions in single cells in their in vivo environment. We focus on the control of neural crest patterning, EMT and cell migration in embryos and on metastasis in cancer. Our SC analyses point at specific gene co-expressions at the individual cell level to control these processes.

This Ph.D. project will establish a temporal single cell map of gene co-expression in these processes, using SC transcriptomes, spatial SC imaging, and crispr-cas9-guided genetic perturbations both in xenopus embryos and a zebrafish model of metastasis. It will be conducted at Institut Curie with secondments and co-supervision of academic (USA) and industrial (France) supervisors.



Objectives

This Ph.D. project is fully integrated in the team's larger project and benefits from preliminary data and well-established approaches mastered by the team or the collaborators. This project will focus specifically on a key patterning event defined from our recent single cell (SC) analyses, identifying an important cell state transition in cranial neural crest cells, and potentially driving their highly invasive character (they massively populate long-distance tissues forming our vertebrate head). This program involves several neural crest derivatives (pigment, neurons, bone...), and the interplay between fate choices and migratory behaviors will be explored.

The first objective will establish the spatial molecular map of gene co-expressions at SC level, by integrating a highly structured team steered by our group (funded ANR project), which establishes spatial transcriptomics to detect multiple gene co-expressions during early development. This map will reveal the spatial organization of the cells undergoing fate and behavior decisions, driving hypotheses for experimental perturbations *in vivo*.

Second objective will use experimental embryology tools to understand the logic of these regulations in the controlled context of embryonic EMT.

Third objective will use human melanoma cell lines well characterized in the team to evaluate if the identified gene co-expressions are reactivated in those cells and if they are involved in the cell's invasiveness *in vivo*.

International, interdisciplinary & intersectoral aspects of the project

International

International co-supervision by Prof. Leon Peshkin, Harvard Medical School, Systems Biology Department, with whom we have a long-standing collaboration (article on single cell transcriptomics in developing neural crest currently in revision, second article being written). The PhD student will visit for one-month secondment and do analysis of SC data.

Intersectoral

Collaboration and secondment at industrial (SME) partner (Azelead, Montpellier, France) who has a patented model of *in vivo* metastasis for melanoma cells in zebrafish. We have an on-going collaboration with them (ITN network that I coordinate) and two current collaborations with current PhD students in the lab. PhD candidate will do 2 one-month secondments in the industrial partner

Interdisciplinary

Ph. D. Student will receive training in bioinformatics and statistics to be able to understand, use and modify the team's custom-made pipelines for single cell transcriptome analysis; will also receive training in advanced imaging, *in vivo* (spatial transcriptomics and cell migration). PhD student in parallel will be trained in biology (*in vivo* and *in vitro* cell and developmental biology).

Recent publications

1. Alkobtawi M, Pla P, Monsoro-Burq AH*. BMP signaling is enhanced intracellularly by FHL3 controlling WNT-dependent spatiotemporal emergence of the neural crest. *Cell Rep*. 2021 Jun 22;35(12):109289. doi: 10.1016/j.celrep.2021.109289. PMID: 34161771.
2. Kristin B Artinger*, Anne H Monsoro-Burq*. Neural crest multipotency and specification: power and limits of single cell transcriptomic approaches. *Faculty Reviews* 2021 10:(38) (14 Apr 2021). <https://doi.org/10.12703/r/10-38>



3. Scerbo P and Monsoro-Burq A.H.* (2020) The vertebrate-specific VENTX/NANOG gene empowers neural crest with ectomesenchyme potential, *Science Advances* 29 Apr 2020: Vol. 6, no. 18, eaaz1469 DOI: 10.1126/sciadv.aaz1469, PMID: **32494672**
4. Plouhinec JL, Medina-Ruiz S, Borday C, Bernard E, Vert JP, Eisen MB, Harland RM, Monsoro-Burq AH*. A molecular atlas of the developing ectoderm defines neural, neural crest, placode, and nonneural progenitor identity in vertebrates. *PLoS Biol.* 2017 Oct 19;15(10):e2004045. doi: 10.1371/journal.pbio.2004045. eCollection 2017 Oct. PubMed PMID: 29049289; PubMed Central PMCID: PMC5663519.
5. Figueiredo AL, Maczkowiak F, Borday C, Pla P, Sittewelle M, Pegoraro C, Monsoro-Burq AH*. PFKFB4 control of AKT signaling is essential for premigratory and migratory neural crest formation. **Development.** 2017 Nov 15; 144(22):4183-4194. doi: 10.1242/dev.157644. Epub 2017 Oct 16. PubMed PMID: 29038306.

Expected profile of the candidate

Candidates should demonstrate an excellent academic background, including cell biology, molecular biology, genetics and epigenetics, with theoretical and practical training. A background in developmental biology, in advanced microscopy, or bioinformatics will be a plus. Laboratory experience is essential : At least one long laboratory internship, and practical experience in cell biology, molecular biology or biochemistry.

The project highly relies on sample preparation from xenopus or zebrafish embryos as well as cell culture., analysed by molecular and cellular analysis, advanced imaging and (single cell) transcriptomics or epigenomics. The candidate will demonstrate a strong motivation, supported by previous training experience. Letters of recommendation from previous supervisors or professors will be requested.

