THE GIS **SPEAKER SERIES**

Genome Institute of Singapore
GIS

Thursday 25 April 2024
4.00pm – 5.30pm

Via Zoom

Host: Shyam Prabhakar

Mechanisms of cell plasticity in breast cancer

Dr Céline Vallot

Group Leader, Institut Curie

Time: **4:00pm – 4.45pm**

About The Speaker

Céline Vallot is a group leader at Institut Curie since 2017. Her lab works on the dynamics of epigenomes in breast cancer during treatment and the early phases of tumorigenesis, combining experimental and computational approaches. Céline is the recipient of an ERC Starting Grant and has co-founded the Single-Cell Initiative of Institut Curie, a facility enabling the analysis of single cells in space and times at various scales (DNA, RNA, epigenomes, proteins). Céline is also the scientific founder of the company One Biosciences, powering single cell profiling for the discovery of novel biomarkers and therapeutic targets.

About The Seminar

The dynamic nature of chromatin and transcriptional features are expected to participate to tumor evolution. Our group focuses on the study of the dynamics of histone modifications in cancer cells upon cancer treatment as well as during the initial steps of tumorigenesis. We develop experimental and computational approaches to map histone marks at single-cell resolution, enabling the investigation of the dynamics of chromatin marks in tumor samples (Grosselin et al. Nat Genet 2019; Prompsy et al. Nat Comm 2020).

We have recently combined single-cell epigenomic and transcriptomic approaches to lineage tracing strategies to reveal the initial epigenomic events driving tolerance to chemotherapy in triple-negative breast cancer (Marsolier & Prompsy et al., Nat Genet 2022). We show that the repressive histone mark H3K27me3 is a lock to the activation of a drug-persistent expression program in breast cancers. Under chemotherapy, very few cells can survive the treatment, and these cells have a remodeled repressive epigenome, with targeted loss at key promoters. Using demethylase inhibitor in combination to chemotherapy, we improve the response rate and delay recurrence both in vitro and in vivo.

We also study mechanisms of cell plasticity in early breast tumorigenesis in vivo. We have recently mapped state transitions during Brca1-tumorigenesis in the mouse. We discovered that luminal progenitor cells undergo a partial epithelial to mesenchymal transition at the onset of tumorigenesis (Landragin &Saichi, unpublished 2022).

Dissecting melanoma evolution one cell at the time

Professor Chris Marine

Science Director, VIB

Time: **4.45pm – 5.30pm**

About The Speaker

Jean-Christophe (Chris) Marine is Professor at KU Leuven (Belgium), senior VIB group leader and Director of the VIB center for Cancer Biology. He received numerous national and international awards for his work on cytokine signaling and cancer biology. He, for instance, received the outstanding research award from SMR in 2019 and was elected EMBO member in 2020. His interests focus on the mechanisms by which cancer-specific non-mutational (i.e. epigenetic and (post-) transcriptional) events shape tumour evolution. Using innovative genetic tools and leveraging cutting-edge technologies such as single-cell multiomics, spatial transcriptomics and proteomics, the Marine lab has made several key contributions to our understating of melanoma biology and, in particular, the mechanisms underlying melanoma initiation, growth, metastatic dissemination, emergence of inter-and intra-tumor heterogeneity, plasticity and resistance to both targeted and immune checkpoint therapy.

About The Seminar

Although melanoma is notorious for its high degree of heterogeneity and plasticity, the origin and magnitude of cell state diversity remains poorly understood. Equally, it is not known whether melanoma growth and metastatic dissemination are supported by overlapping or distinct melanoma subpopulations. By combining mouse genetics, unbiased lineage tracing and quantitative modelling, single-cell and spatial transcriptomics, we provide evidence of a hierarchical model of tumour growth that mirrors the cellular and molecular logic underlying embryonic neural crest cell fate specification and differentiation. Our findings indicate that tumorigenic competence is associated with a spatially localized perivascular niche environment, a phenotype acquired through a NOTCH3-dependent intercellular communication pathway established by endothelial cells. Consistent with a model in which only a fraction of melanoma cells is fated to fuel growth, temporal single-cell tracing of a population of melanoma cells harbouring a mesenchymal-like state revealed that these cells do not contribute to primary tumour growth but, instead, constitutes a pool of metastatic-initiating cells that can switch cell identity while disseminating to secondary organs. Our data provide a spatially and temporally resolved map of the diversity and trajectories of cancer cell states within the evolving melanoma ecosystem and suggest that the ability to support growth and metastasis are limited to distinct pools of melanoma cells. The observation that these phenotypic competencies can be dynamically acquired upon exposure to specific niche signals warrant the development of therapeutic strategies that interfere with the cancer cell reprogramming activity of such microenvironmental cues.