Single-cell multiomics to characterise how high grade serous ovarian cancer (HGSOC) originates and evolve

Roser Vento-Tormo (Sanger) & Isidro Cortes-Ciriano (EBI)

Every year 220,000 women worldwide are diagnosed with high grade serous ovarian cancer (HGSOC) worldwide, making it the fourth leading cause of cancer-related death among women. There is a significant need to understand how HGSOC develops and evolves, which is crucial for early diagnosis and improved clinical outcomes.

The Vento-Tormo has created the first single-cell spatiotemporal datasets of reproductive tissues across the entire human lifespan, including development, pre- and post-puberty and pre-post menopause(Garcia-Alonso et al. 2021, 2022; Arutyunyan et al. 2023; Marečková et al. 2023). This provides an unprecedented opportunity to study how regulatory programmes influence the identities of ovarian and fallopian cell identity. By generating datasets from early and late stages of HGSOC and integrating them with extensive reproductive datasets across the lifespan we can identify the likely progenitors responsible for the early events of malignant transformation. This is crucial for understanding the molecular and cellular events involved in HGSOC origin and evolution.

To achieve these goals, it is essential to map the phenotypes of cancer cells to their genotypes (i.e., somatic mutations driving malignant transformation) at single-cell resolution. While this has been technically challenging, the Cortes-Ciriano group at the EMBL-EBI has developed SComatic(Muyas et al. 2024), a computational method to map genotypes to phenotypes at scale across single-cell data modalities, such as single-cell RNAseq and single-cell ATAC-seq. The key innovation is that somatic mutations (point mutations, indels and copy number aberrations, all of which are common in HGSOC), can be detected de novo, that is, without the need for matched genome sequencing data. Preliminary work on single-cell RNASeq data from HGSOC has already shown that we can map the clonal architecture of these tumorus, providing a lens into both the evolutionary trajectory of tumours but also the possibility to study which cell programmes mediate cancer growth.

By combining the data and expertise in reproductive tissue biology at the Vento-Tormo with the computational expertise in single-cell multi-omics and cancer evolution in the Cortes-Ciriano group, we aim to decode, for the first time, the cell states and regulatory networks underpinning the onset and evolution of HGSOC.

The candidate aims to achieve the following objectives:

1.Generate a spatiotemporal map of fallopian tubes from early and late diagnosis cases of HGSOC.

2. Apply computational tools to identify the early events driving malignant transformation in HGSOC and describe the role of the microenvironment in HGSOC.

3. Study the interplay between genomic aberrations in the tumour and the tissue microenvironment.

WIth these goals, the candidate seeks to create the most comprehensive atlas of ovarian cancer cell states and the tumour microenvironment. Additionally, computational tools will provide an unprecedented resolution for the spatial mapping of cellular components, progenitor descendant populations, transcription factors, and ligands of the fallopian tube microenvironment that initiate the malignant transformation in HGSOC and are involved in its evolution. Finally,

Training

The postdoctoral fellow will benefit from an exceptional training and mentorship program, designed to develop interdisciplinary skills and foster the potential to generate novel lines of research in the future. The Fellow will be embedded in two groups with distinct expertise: the Vento-Tormo team (Wellcome Sanger Institute) and the Cortes-Ciriano group (EBI). This arrangement will provide a unique opportunity for multidisciplinary development.

The candidate will train in both wet and dry lab environments, using and developing single-cell genomics technologies from the Vento-Tormo team. In addition, the candidate will learn to develop computational tools for cancer data analysis, enhancing their statistical skills and exposure to cancer data. Altogether, the candidate will coordinate projects from start to finish, gaining expertise in all aspects of single-cell analysis and exposure to the biological knowledge of women's health and reproductive tissues.

Both the Vento-Tormo and Cortes-Ciriano teams offer one-on-one mentorship with regular meetings. This personalised guidance will support the candidate's professional development and research progress. In addition, the candidate will be encouraged to participate in lab meetings from both groups which will enable the candidate to bring new ideas and engage in collaborative discussions. The candidate will also have the opportunity to join international conferences, broadening their network and exposure to cutting-edge research.

The training program positions the candidate to explore the intersection of genomics data and single-cell transcriptomics, a field with significant research potential. Additionally, the focus on ovarian cancer and women's health—areas that are currently under-studied—offers ample opportunities for pioneering research. This comprehensive training and mentorship will equip the candidate with the skills and knowledge necessary to lead innovative and impactful research in the future.

References

Arutyunyan, Anna, Kenny Roberts, Kevin Troulé, Frederick C. K. Wong, Megan A. Sheridan, Ilia Kats, Luz Garcia-Alonso, et al. 2023. "Spatial Multiomics Map of Trophoblast Development in Early Pregnancy." *Nature*, March, 1–9.

Garcia-Alonso, Luz, Louis-François Handfield, Kenny Roberts, Konstantina Nikolakopoulou, Ridma C. Fernando, Lucy Gardner, Benjamin Woodhams, et al. 2021. "Mapping the Temporal and Spatial Dynamics of the Human Endometrium in Vivo and in Vitro." *Nature Genetics* 53 (12): 1698–1711.

Garcia-Alonso, Luz, Valentina Lorenzi, Cecilia Icoresi Mazzeo, João Pedro Alves-Lopes, Kenny Roberts, Carmen Sancho-Serra, Justin Engelbert, et al. 2022. "Single-Cell Roadmap of Human Gonadal Development." *Nature*, July. https://doi.org/10.1038/s41586-022-04918-4.

Marečková, Magda, Luz Garcia-Alonso, Marie Moullet, Valentina Lorenzi, Robert Petryszak, Carmen Sancho-Serra, Agnes Oszlanczi, et al. 2023. "An Integrated Single-Cell Reference Atlas of the Human Endometrium." *bioRxiv*. https://doi.org/10.1101/2023.11.03.564728.

Muyas, Francesc, Carolin M. Sauer, Jose Espejo Valle-Inclán, Ruoyan Li, Raheleh Rahbari, Thomas J. Mitchell, Sahand Hormoz, and Isidro Cortés-Ciriano. 2024. "De Novo Detection of Somatic Mutations in High-Throughput Single-Cell Profiling Data Sets." *Nature Biotechnology* 42 (5): 758–67.