Project 2: Predicting Cell-Type-Specific Endocrine Disruption by

Environmental Chemicals

Supervisors: Roser Vento-Tormo (*Wellcome Sanger Institute*), Jess Ewald (*EMBL-EBI*)

Project summary: Hormones coordinate communication between tissues by binding specific receptors that regulate cell identity, metabolism, proliferation, and differentiation. Environmental chemicals can interfere with these signalling pathways by acting as receptor agonists or antagonists, contributing to endocrine disruption and altered tissue function. Regulatory testing has historically focused on the classical EATS pathways (estrogen, androgen, thyroid, and steroidogenesis), yet the recently published Hormone Cell Atlas demonstrates that endocrine signalling involves more than 100 hormone receptors acting across diverse human tissues (Fei et al. 2026). For most of these receptors, little is known about their susceptibility to environmental chemicals or the cell types in which disruption is most likely to occur.

This project will integrate these emerging resources to develop a framework for predicting cell-type-specific endocrine disruption beyond the classical EATS pathways. We will compare complementary computational approaches for predicting interactions between chemicals in the human chemical exposome and human hormone receptors. As an interpretable baseline, we will quantify molecular similarity between environmental chemicals and endogenous hormone ligands using established cheminformatics methods (e.g. molecular fingerprints and Tanimoto similarity). These predictions will be complemented by molecular docking and recently developed protein–ligand foundation models, such as Boltz-2, Chai-2. The resulting receptor interaction predictions will be integrated with the Human Cell Atlas (https://data.humancellatlas.org/), including the embryonic and
extra-embryonic developmental atlases (Webb et al. 2026; Arutyunyan et al. 2023) and the newly generated Reproductive Cell Atlas (Cohen et al. 2026), to identify the tissues and cell types across the lifespan most likely to respond to individual chemicals. In addition, we will also integrate data with spatial data for a subset of tissues including reproductive tissues, lymphoid tissues, skin, lung, gut. Rather than asking whether a chemical is simply an endocrine disruptor, the project aims to predict which receptor is perturbed, which cells express that receptor, and which cellular niches are impacted, and from this where disruptions are most likely to occur and what phenotype may be linked to.

A subset of high-confidence predictions will then be evaluated experimentally using endometrial and placental organoids established in the Vento-Tormo laboratory. Single-cell

RNA sequencing will be used to characterise changes in cell state, signalling pathways, and cell-cell communication following chemical exposure, providing an orthogonal test of the computational predictions. By integrating predicted receptor binding with cell-type-specific transcriptional responses, the project will generate a mechanistic framework for linking environmental chemicals to endocrine signalling across human tissues.

The Vento-Tormo laboratory contributes expertise in human reproductive biology, cell-cell communication, organoid models, and single-cell genomics, together with expertise in navigating the Human Cell Atlas and newly generated Reproductive Cell Atlas. The Ewald laboratory contributes expertise in computational toxicology, machine learning, chemical biology, and the analysis of large-scale perturbation datasets. This new collaboration will provide the Fellow with experience spanning AI-based molecular modelling, human tissue models, and single-cell analysis, enabling the development of interdisciplinary approaches for studying chemical effects on human biology.

Scientific & professional training: At the Wellcome Sanger Institute, the Fellow will receive training in human organoid culture, experimental models of reproductive biology, and single-cell RNA sequencing, including experimental design and downstream analysis of cell-state and cell-cell communication. At EMBL-EBI, they will develop expertise in protein–ligand interaction prediction, cheminformatics, machine learning, and computational toxicology, alongside methods for integrating chemical, structural, and single-cell datasets. The Fellow will participate in joint supervision, lab meetings, seminars, and conferences across both institutes, contributing to collaborative publications and open-source computational tools.

Potential for new research directions: The framework developed during this fellowship could readily be extended beyond endocrine signalling to other receptor-mediated pathways, including immune and developmental signalling. More broadly, it will establish methods for combining AI-based predictions of chemical–protein interactions with single-cell reference atlases and human organoid models, providing a general strategy for prioritising environmental chemicals for mechanistic investigation and improving human-relevant chemical safety assessment.