Targeted Project / AY 2026 -2027

Lab-in-the-Loop AI Framework for Perturbation Studies in Skin Organoids

Project Reference: TRG-SAN-ML26

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Main BBSRC strategic theme: Transformative technologies

Secondary BBSRC strategic theme: Understanding the rules of life

Project outline:

Lab-in-the-loop (LITL) is a dynamic research framework in which computational models and experiments continuously inform and refine each other in real-time. They move beyond the standard, sequential "hypothesize → experiment → analyze" model and tackles two major limitations in scaling biological research: i) strategising low throughput sample availability that is common in biological research, and ii) high dimensional complexity of biological systems.

In recent years, organoids have emerged as a transformative complex model system, offering key advantages over traditional model organisms and 2D cell cultures, due to their capability to self-organize and closely mimic the spatial cellular architecture and functions of human tissues. This makes them an ideal tool for studying tissue development, disease mechanisms, therapeutic strategies and perturbation responses. Although organoids are scalable, they are labour-intensive and costly to produce and maintain, which makes large-scale, exhaustive perturbation experiments impractical to perform. This limitation makes them an ideal candidate for a LITL approach, where experiments can be strategically guided by computational models to maximize insight while minimizing resource use (Clevers, 2016).

We have established a robust protocol for generating hair-bearing iPSC-derived skin organoids in our laboratory. They are the first fully complex model of human skin that includes important skin appendages such as hair follicles and sweat glands (Lee and Koehler, 2021; Gopee et al., 2024). Building upon this foundational work, and we are generating a perturbation atlas of these skin organoids using drug compounds, genetic (CRISPR), and also by introducing immune cell precursors in order to understand the gene programs driving cellular organization, cell identity and lineage specification via single cell and spatial multi-omic approaches.

In this project, we propose to develop an integrated AI-driven, lab-in-the-loop system to design, simulate, and validate drug and genetic perturbation experiments using skin organoids. The system leverages a multi-agent framework where a design agent hypothesises perturbations and combinations inspired by BioDiscoveryAgent (Zhou et al., 2024), an agent to simulate these interactions, incorporating prior knowledge from databases such as KEGG, and GO, and an agent that can critically evaluate the outcomes of the simulations (Lee et al., 2025). The multiagent AI

scores the gene targets, which can then be used for designing experiments, the outcomes of which can be used as a feedback loop to train the model.

This model will increase the efficiency and precision of in vitro organoid perturbation studies and enhance the reproducibility and scalability of experiments towards higher-order perturbations. Applying this approach to skin organoids will significantly aid our understanding of gene programs involved in skin development, including immune cell-driven organogenesis, scarless wound-healing, and dysregulation driving skin pathologies. This project will provide an actionable concept whereby large-scale organoid perturbations and LITL work synergistically to drive scalable research.

References

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