LS24-012 - Engineering synthetic enhancers and gene circuits to understand and overcome cancer therapy resistance

Zusammenfassung

Recent advances in oncogene targeted therapies and immunotherapies have transformed cancer treatment. Unfortunately, many patients relapse due to acquired drug resistance, or fail to respond to treatment because of an immune-evasive tumor microenvironment (ieTME) that incapacitates T cell responses. We have recently shown that iTMEs arise during the acquisition of drug resistance through unique gene-regulatory changes and cell states in both cancer and tumor-infiltrating immune cells, leading to cross-resistance between targeted therapies and immunotherapies.

To understand and ultimately overcome targeted and immunotherapy therapy resistance, we propose a transformative synthetic biology approach leveraging our comprehensive expertise in cancer biology, gene regulation, single-cell multiomics, and artificial intelligence (AI). We will engineer synthetic regulatory DNA elements, gene-expression cassettes and circuits that direct transgene expression to the unique cell states present in therapy resistant tumors, thereby enabling 1) monitoring of resistance acquisition, 2) precise delivery of immune-activating cytokines to tumors and 3) reinvigoration of T cells. For this proof of concept, we will exploit established Braf-mutant melanoma and colorectal cancer mouse models accompanied by clinical correlates. The proposed project promises to deliver groundbreaking advancements in cancer research and pave the way for the next generation of cell- and gene-therapy-based treatments.

Wissenschaftliche Disziplinen:
Oncology (40%) | Genomics (30%) | Immunotherapy (30%)

Keywords:
Cancer biology Tumor immunology Therapy resistanceImmunotherapyGene regulationEnhancersGene-regulatory codeSynthetic enhancersAI / Deep learningConvolutional Neural NetworkTransfer learning

---

Principal Investigator:	Anna Obenauf
Institution:	IMP - Research Institute of Molecular Pathology
Co-Principal Investigator(s):	Alexander Stark (IMP - Research Institute of Molecular Pathology)

Status: Vertrag in Vorbereitung

Weiterführende Links zu den beteiligten Personen und zum Projekt finden Sie unter
https://wwtf.at/funding/programmes/ls/LS24-012/