Title of the project
Identify functional vulnerabilities at early and advanced cancer stages and model cell population dynamics during treatment

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If applicable, name of co-supervisor 2:

Abstract (10 lines)

Promising frameworks emerge from computational biology and deep learning, designed to analyse patient -omics data and screen outcomes for precision medicine. Among them, "synthetic lethality and rescue-mediated precision oncology via the transcriptome" (SELECT) is a novel framework that identifies and uses genetic interactions of drug targets to predict the response to cancer therapies [1]. Few examples have documented the superiority of SELECT compared with other transcriptomic-based predictors. Using liver cancer as a biological system [2,3], we propose to adapt SELECT for predicting vulnerabilities across heterogeneous populations of patients, and functionally test them in complementary biological models. Merging SELECT with UPMaBoSS, a framework for modelling populations of interacting cells [4], we will simulate cell population dynamics to predict and follow the behaviour of heterogeneous cell subgroups and the emergence of new subtypes.

Keywords: synthetic lethal interactions, prediction of vulnerabilities, modelling heterogeneous populations, in vitro/ex vivo/in vivo biological models, liver organoids

Objectives (5 lines)

1. Using SELECT, identify "predicted vulnerabilities" in patients, focussing on synthetic lethal/rescue interactions, by analysing multiple transcriptomics databases from patients and mouse models (at early and advance stages). **2.** Functionally test predicted vulnerabilities, longitudinally, in complementary in vitro/ex vivo/in vivo models. **3.** Integrate genetic interactions identified by SELECT in an explanative dynamical model and perform stochastic simulations of cell population dynamics (using UPMaBoSS) to document the emergence of population subtypes.

Expected profile (5 lines)

The candidate should have knowledge in computational biology and mathematical modelling for the analysis of transcriptomics and prediction of genetic interactions. He/she should be able to exploit frameworks like those mentioned in the objectives, adapting them to specific biological systems and questions. Previously acquired interdisciplinary experience combining mathematics and biology will be particularly considered.

Candidate biologists interested in applying mathematical modelling will also be considered.

Is this project the continuation of an existing project or an entirely new one?
This project has been designed to exploit two powerful frameworks recently published, SELECT and UPMaBoSS, merging the expertise of **Maina lab**, on signalling and vulnerabilities identifications from screen studies, and of the **Remy lab**, on mathematical modelling and prediction. Through this project, **a)** identification of predicted vulnerabilities (with Remy lab expertise) will be tested in a variety of biological models (Maina lab interests), while **b)** powerful frameworks will be integrated to follow dynamics of heterogeneous populations (Remy lab interests), whose robustness will be experimentally documented (Maina lab expertise).

In the case of an existing project, please explain the links between the two projects (5 lines)
This new project emerges from a fruitful collaboration between the two labs during the past year and half on a project that aims to contextualise signalling fluctuations in resilient versus vulnerable biological systems exploiting proteomic data.

2 to 5 references related to the project

1) Lee SL. Et al. Synthetic lethality-mediated precision oncology via the tumor transcritprome. **Cell** 2021.

2) Cassol F. et al. *Tracking dynamics of spontaneous tumours in mice using Photon Counting Computed Tomography*. **iScience** 2019.

3) Fan Y. et al. *A Phosphokinome-based screen uncovers new drug synergies for cancer driven by liver-specific gain of non-oncogenic RTKs*. **Hepatology** 2017.

4) Stoll et al. *UPMaBoSS: a novel framework for dynamic cell population modelling.* **Frontiers** 2022.

3 main publications from each PI over the last 5 years

E. Remy:

- L. Cantini, P. Zakeri, C. Hernandez, A. Naldi, D. Thieffry, E. Remy, A. Baudot. Benchmarking joint multi-omics dimensionality reduction approaches for cancer study. **Nature Communications** 12, 124 (2021). PMID: 33402734.

- L. Hérault, M. Poplineau, A. Mazuel, N. Platet, É. Remy, and E Duprez. Single-cell RNA-seq reveals a concomitant delay in differentiation and cell cycle of aged hematopoietic stem cells. **BMC biology**, 19(1) :1–20, (2021). PMID: 33526011.

- L. Pio-Lopez, A. Valdeolivas, L. Tichit, É. Remy, and A. Baudot. Multiverse: a multiplex and multiplex-heterogeneous network embedding approach. **Scientific Reports**, 11, (2021). PMID: 33888761.

F. Maina:

- Arechederra M., Bazai S., Abdouni A., Sequera C., Mead T.J., Richelme S., Daian F., Audebert S., Dono R., Lozano A., Gregoire D., Hibner U., Allende D., Apte S.S., Maina F. ADAMTSL5 is an epigenetically activated gene that confers tumorigenic properties and drug resistance in hepatocellular carcinoma. **Journal of Hepatology** 2021, 74(4):893-906. PMID: 33197513.

- Fan Y., Bazai S.K., Daian F., Arechederra M., Richelme S., Temiz N.A., Yim A., Habermann B.H., Dono R., Largaespada D.A., Maina F. Evaluating the landscape of gene cooperativity with RTKs in liver tumorigenesis. **Journal of Hepatology** 2019, 70(3): 470-482. PMID: 30529386.

- Arechederra M., Daian F., Yim A., Sehrish S.K., Richelme S., Dono R., Saurin A.J., Habermann B.H., Maina F. Hypermethylation of gene body CpG islands predicts high dosage of functional oncogenes in liver cancer. **Nature Communications** 2018, 9(1):3164. PMID: 30089774.