PhD PROJECT PROPOSAL

CENTURI
TURING CENTRE
FOR LIVING SYSTEMS

PROJECT TITLE: Dynamic systems modelling of novel anticancer treatment response integrating mathematics, -omics, imaging, and tumoroid biology

Supervisor 1 (with name, email, affiliated laboratory and doctoral school affiliation)
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Supervisor 2 (with name, email and affiliated laboratory and doctoral school affiliation)
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Abstract (10 lines)*

Predictions of biological functions and cell communication behaviours in tissues with disorganised structural patterning and heterogeneous cellular populations that constitute "cancer communities" remain a major challenge, particularly regarding treatment responses. This is especially true for complex cancer types characterised by extraordinary molecular heterogeneity, so-called "non-oncogene addiction" in which tumorigenicity is linked to the action of non-mutated genes, and for cancer cells capable of evading immunotherapies. Building on our discovery of novel drug combinations with remarkable effectiveness and the ability to distinctly remodel the tumour immune landscape, this project is designed to assess their efficacy on patient-derived tumoroids. Imaging and -omics datasets will be used to establish dynamic systems models that recapitulate the loss of equilibrium states within cancer communities and/or the acquisition of new equilibrium states in resistant communities. The outcomes will converge in a new clinical trial aimed at documenting treatment strengths and predicting responses in cancer patients.

Keywords*

-omics, bioinformatics, tumoroids, anticancer response prediction, liver cancer, transcriptomics, Ordinary Differential Equations (ODE), asymptotic analysis, in silico experiments

Scientific question and Objectives (10 lines)*

Focusing on liver cancer, the scientific topics related to this project involve the use of dynamic modelling to predict and optimise treatment responses to combinatorial onco-immunotherapies in order to: a) exploit vulnerabilities induced by an initial treatment to achieve eradication with a subsequent treatment; b) design temporally pulsed effective treatments, incorporating drug holiday phases, to titrate the extent of effectiveness on responsive cancer communities while preserving their intrinsic ability to inhibit the expansion of less responsive communities; c) select the most suitable immunotherapeutic agents according to the immune landscape remodelling triggered by different onco-therapies. The objectives are: **1)** to generate tumoroids from HCC patients within a clinical trial; **2)** to assess their response to three novel drug combinations we have discovered, comparing strength, response, and immune remodelling specificity, using viability assays, imaging, and -omics; **3)** to use these outcomes for biological modelling of responsiveness by applying established dynamic systems.

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Proposed approach (experimental / theoretical / computational) and research plan (20 lines)*

1) Building on experimental approaches we recently developed to generate tumoroids with a high efficiency rate while maintaining the intrinsic properties of primary tumours, we will use advanced methodologies to establish patient-derived tumoroids within a clinical trial commencing in 2026.

2) Established protocols will be used to assess the effectiveness of three novel drug combinations we recently identified, employing an automated system for combinatorial assessment of drug combinations at multiple doses and conditions, simultaneously on a panel of patient-derived disease models.

3) Effectiveness will be documented both qualitatively and quantitatively using viability assays and imaging, while underlying mechanisms will be identified through -omics and spectral cytometry.

4) A dynamical system will be designed to investigate the effectiveness of various treatment protocols, taking tumour heterogeneity into account, while integrating the complexity of the immune microenvironment and potential resistance to treatment. Asymptotic analysis of the model will help elucidate the impact of different therapeutic strategies on tumour-immune dynamics and treatment outcomes.

Interdisciplinarity and Implication of the two labs (15 lines)*
(In this section the collaboration of the two laboratories will be explained in details to explain why the project cannot be conducted by one team alone)

Maina Lab is an expert in signalling and functions with associated mechanisms in tissue homeostasis, tumour initiation, progression, response to treatment, and treatment-driven remodelling of the tumour immune landscape. The lab has generated mouse-cell-tumoroid models and applies -omics, genetic, bioinformatic, and functional/molecular approaches for interdisciplinary research fully devoted to cancer biology and treatment. The lab will train the recruited PhD student in a range of approaches, including -omics and bioinformatic analysis, molecular and biological assays, tumoroid models, and imaging.

The Hubert Lab has a strong expertise in the mathematical modelling and numerical analysis of complex biological processes. Its research focuses on the development and study of partial differential equation models to describe cell migration, tumour dynamics, and the effects of anticancer treatments. The group combines multiscale modelling, theoretical analysis, and advanced computational methods to gain insight into mechanisms relevant to biology and health.

Oncologists at the Institut Paoli-Calmettes and St Joseph Hospital in Marseille, who are involved in the clinical trial designed to generate patient-derived tumoroids, will discuss strategies and outcomes in the perspective of a new trial focused on combinatorial treatments explored through this project.

Specify with whom the person recruited will collaborate and on what aspects *

The student will work in the Maina Lab on biological, molecular, -omics, and bioinformatics studies, and will be involved in the Hubert Lab in constructing the mathematical model and conducting in silico experiments to predict the impact of new therapeutic protocols. Moreover, the student will

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participate in regular meetings with oncologists to integrate a clinical perspective into this interdisciplinary project.

PhD student's expected profile*

We are seeking a PhD candidate, preferably with a background in biology and a strong interest in cancer biology, signalling, treatment response, and cancer–immune cell crosstalk, who is highly motivated to acquire mathematical skills for applying dynamic systems modelling in cancer research. The candidate should have strong expertise in advanced cell culture methodologies, preferably with experience in tumoroids, and in approaches to uncover mechanistic insights, including the use of -omics, bioinformatics, and spectral cytometry. Interdisciplinary experience gained during previous training will be particularly valued. However, we also welcome candidates with exceptional skills in mathematical modelling who are fully committed to advanced training in biological and signalling methodologies.

Is this project the continuation of an existing project or an entirely new one?
In the case of an existing project, please explain the links between the two projects (5 lines)*

This new project, arising from recent discussions between Dr Hubert and Dr Maina, aims to apply mathematical modelling of "cancer communities" to broaden understanding of the effectiveness of novel combinatorial therapies. It forms part of a broader joint research programme, in which further mathematical modelling will be developed to reconstitute the heterogeneity of the tumour and its microenvironment, and to explore how local variations in cellular composition and immune activity influence treatment response. It is part of a new research line on cancer biology and treatment that the two labs are establishing, merging their complementary expertise in mathematics and biology, and ensuring translatability and clinical relevance through established collaborations with oncologists at the Institut Paoli Calmettes and St Joseph Hospital.

Two to five references related to the project*

Cannet F., Sequera C., Michea Veloso P., El Kaoutari S., Methia M., Richelme S., Cherni A., Dupont M., Borg J.P., Morel C., Boursier Y., Maina F. *Tracing specificity of immune landscape remodelling associated with distinct anticancer treatments.* **iScience,** Feb 20;28(3):112071 (2025). PMID: 40124507.

Cécile Carrère. *Optimization of an in vitro chemotherapy to avoid resistant tumours.* **Journal of Theoretical Biology**, 2016, 413, pp.24-33.

Shen, J.; Tu, X.; Li, Y. Mathematical Modeling Reveals *Mechanisms of Cancer-Immune Interactions Underlying Hepatocellular Carcinoma Development.* **Mathematics** 2023, *11*, 4261.

Foo, J. & Michor, F. *Evolution of resistance to targeted anti-cancer therapies during continuous and pulsed administration strategies.* **PLoS Comput Biol 5**, e1000557 (2009).

Hastings, J. F. et al. *Analysis of pulsed cisplatin signalling dynamics identifies effectors of resistance in lung adenocarcinoma.* **Elife 9** (2020).

Greene, J. M., Gevertz, J. L. & Sontag, E. D. *Mathematical Approach to Differentiate Spontaneous and Induced Evolution to Drug Resistance During Cancer Treatment*. **JCO Clin Cancer Inform 3**, 1-20 (2019).

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Two main publications from each PI over the last 5 years*

Maina:

Sequera C.*, Grattarola M.*, Cannet F., Dobric A., Michea Veloso P., Methia M., Richelme S., Elkaoutari S., Kousteridou P., Debayle D., Kübler L., Nuciforo S., Boursier Y, Dupont M., Pizzimenti S., Barrera G., Dupuy J.W., Saltel F., Heim H.M., Vasseur S., Adhoute X., Guillaumond-Marchai F., Borg J.P., Morel C., Maina F. *The HDAC inhibitor romidepsin renders liver cancer vulnerable to RTK targeting and immunologically active.* **Nature Communications**, Aug 25;16(1):7919 (2025). PMID: 40855049.

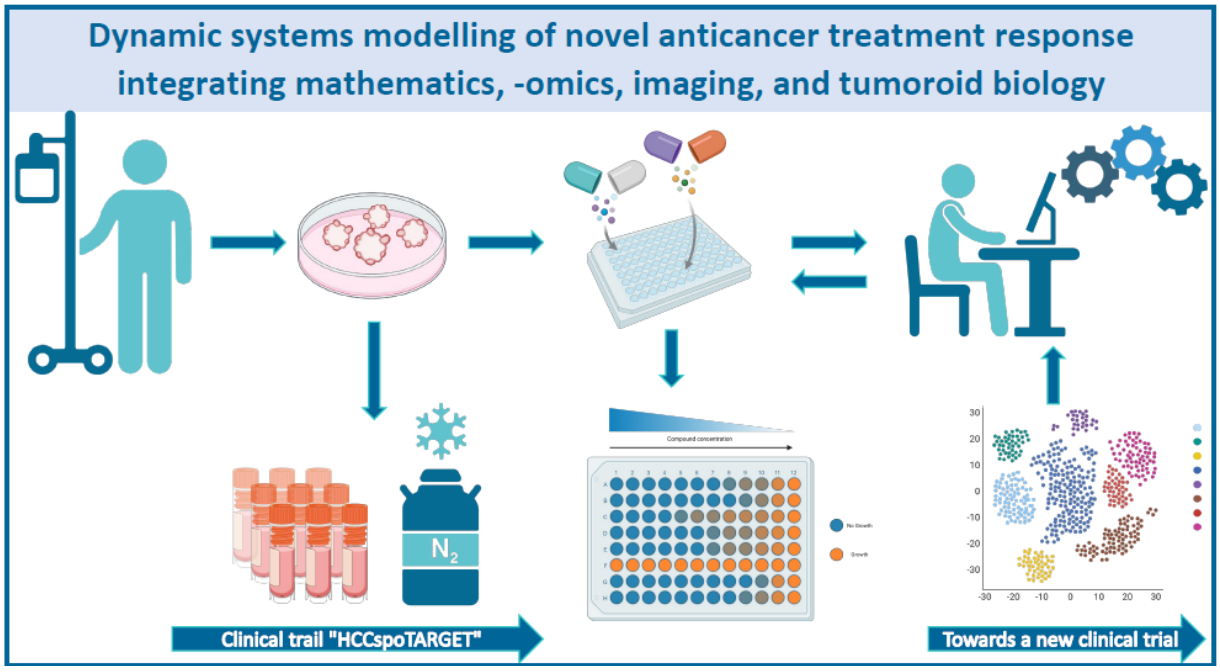
Grattarola M.*, Pons N.*, Cannet F., Kaya M., El Kaoutari A., Morel C., Dobric A., Borg J.P., Sequera C., Maina, F. *Establishment of a mouse hepatocellular carcinoma tumoroid panel recapitulating inter- and intra- heterogeneity for disease modelling and combinatorial drug discovery.* **Cell Communication and Signaling**, Oct 2;23(1):410 (2025). PMID: 41039593.

Hubert:

S. Chauvet, F. Hubert, F. Mann, M. Mezache *Tumorigenesis and axons regulation for the pancreatic cancer: A mathematical approach.* **Journal of Theoretical Biology**, Volume 556, 2023.

C. Tayou Fosto, S. Girel, F. Anjuère, V. Braud, F. Hubert, T. Goudon *A mixture-like model for tumor-immune system interactions.* **Journal of Theoretical Biology**, Volume 581, 2024.

Project's illustrating image



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