

	PROPOSAL AS DIRECTOR OF STUDIES & RESEARCH PROJECT	MO-PHDMM-1 Rev. 06 del 04/03/2022
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PROJECT I

DoS: Giovanni Tonon

Title: UNRAVELING THE COOPERATIVE STRATEGIES OF CANCER CELLS

Curriculum: Basic and Applied Immunology and Oncology

Link to OSR/UniSR personal page:

<https://research.hsr.it/en/divisions/experimental-oncology/functional-genomics-of-cancer/giovanni-tonon.html>;

<https://www.unisr.it/en/docenti/t/giovanni-tonon>

Project description

Cancer remains too often an incurable disease, suggesting that the framework which we use to define and treat cancer is inadequate. The common dogma posits that cancer is a Darwinian disease, where the tumour cells and clones compete one against the other, so that only the fittest survive, either in the absence of treatments or after therapy. This perception colors also the framework that is used to design therapies and which defines treatment protocols for cancer patients.

We and few others¹⁻⁴ are proposing an alternative framework, which we argue is more effective in describing the biology of cancer and may greatly help in designing much more effective therapies. The analysis of patient samples, and carefully designed experiments, posits that cancer is a disease of cooperation, whereby tumour cells, endowed with variable genetic, epigenetic and phenotypic features need to work together, for their own survival and growth. The rules governing this society of cancer cells, and how this community reacts and withstands therapies is almost entirely unknown. We know even less how to interfere with the generation and to trigger the collapse of this robust ecological system.

We propose to exploit engineered cancer cell lines and patient-derived organoids, available in the lab, to define the rules governing cooperation among cells. We will use single-cell approaches which define both the transcriptomic and the genetic/epigenetic landscape, developed in the lab⁵, as well as spatial transcriptomics, to unravel the mechanisms underlying cancer cell cooperation. Experiments in mouse models will define how impacting on the cooperation strategies among tumour cells could harm cancer cell growth, before and after treatment and will inform cancer evolution models which we will develop with mathematicians, and computational scientists, long-standing collaborators in the UK and in the USA. Finally, genetic and epigenetic CRISPR-Cas9 screening will define the key genes and networks which are required to harmonize this cancer society. Genetic ablation or modulation of these pathways would then be tested, to find novel therapeutic strategies to tackle cancer growth and survival.

Skills to be acquired by the student

This project is rooted in an international grant that engages leading groups in the most prestigious cancer centers in the UK and the USA, and entails exchanging programs and tightly knotted collaborations between scientists from different venues, from cell biologists and molecular biologists, to mathematicians, engineers and clinicians. The student will be exposed to a broad range of molecular biology, cell biology, engineered in vitro and in vivo models, biochemistry and genomics approaches, including various flavors of CRISPR/cas9 technologies developed in the institution by collaborators⁶.

References

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