PROJECT 2

DoS: Giovanni Tonon

Title: Unraveling how bacteria strategies are exploited by cancer cells to survive therapy

Curriculum: BAIO

Link to OSR/UniSR personal page: http://research.hsr.it/en/divisions/experimental-oncology/functional-genomics-of-cancer/index.html

Project description:

Background and rationale: model systems, including bacteria, have informed key advances in understanding mammalian biology. Recent indications point to a large set of strategies implemented by bacteria to withstand antibiotic treatments, which go well beyond the simple acquisition of genetic mutations (1,2). Bacteria exposed to drugs, even at exceedingly high concentrations, enter into a transient tolerant state, which is conductive to the acquisition of more permanent genetic and epigenetic modifications conferring resistance. If, and how, these programs are also implemented in cancer cells remain largely unknown.

Objectives: Building upon preliminary data, and a set of tools and expertise in the lab, including a newly devised single cell method able to capture both the genetic and epigenetic landscapes (GET-seq), a large collection of organoid-based cell culture systems derived from liver metastasis of colon cancer samples (3) and CRISPR/Cas9 screens, we aim to identify in human cancer cells the key mechanisms driving tolerance, with the final goal to target these pathways and prevent the emergence of drug resistance.

Collaborations and environment: This project will benefit from several ongoing national and international collaborations, including several labs at the ICR in London and the Hebrew University in Jerusalem. We strive to provide a scientific environment that fosters passion and creativity, scientific rigorousness and dexterity, and reciprocal training, in a pleasant and respectful yet competitive lab environment.

Expected Outcome: drug resistance remains the main cause of cancer death. Our goal is to define and prevent the mechanisms underlying it, targeting strategies developed by bacteria to withstand antibiotic treatment.

Skills to be acquired by the student:

This project is rooted in an international grant that engages various groups in Italy, UK and Israel, and entails exchanging programs and tightly-knotted collaborations between scientists from different venues, from cell biologists and molecular biologists, to mathematicians, engineers and clinicians. A broad range of molecular biology, cell biology, biochemistry and genomics approaches. We will exploit *in vitro* models, namely labeled and barcoded tumor cells, as well as *in vivo* models. We will finally validate the results in patient specimens,

with the final goal to overcome resistance. Specifically, besides established techniques of cell culture and genetic manipulation of cells, including CRISPR/cas9 technologies, to ablate and knock-in genes and bar codes, significant emphases will also be devoted to genomic approaches including ATAC-seq, ChIP-seq and RNA-seq, to broadly define the features of single tumor cells, and determine the heterogeneity of cancer cell populations.

References

1. Lambert G, Estévez-Salmeron L, Oh S, Liao D, Emerson BM, Tlsty TD, et al. An analogy between the evolution of drug resistance in bacterial communities and malignant tissues. Nature reviews Cancer. 2011 May;11(5):375-82.

2. Brauner A, Fridman O, Gefen O, Balaban NQ. Distinguishing between resistance, tolerance and persistence to antibiotic treatment. Nature Reviews Microbiology. 2016;14(5):320-30.

3. Vlachogiannis G, Hedayat S, Vatsiou A, Jamin Y, Khan K, Lampis A, et al. Patient-derived organoids model treatment response of metastatic gastrointestinal cancers. Science. 2018;359(6378):920-6.