PROJECT 1

DoS: Giovanni Tonon

Title: Single-cell genomic approaches to unravel cancer resistance.

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: Cancer patients die because their tumor cells become resistant to drugs. Sadly, despite efforts that started decades ago, we have only a very limited knowledge of why cancer cells withstand treatments. It is clear that traditional approaches are inadequate to finally unravel this plague. Single-cell genomic analysis is heralding a revolution in biology (1,2), profoundly changing our appraisal of the most basic and crucial oncogenic mechanisms. Data from the literature, and preliminary data accrued in the lab, suggest that single cell genomics, and most importantly epigenetics, may finally provide a much-needed entry point to understand drug resistance in cancer patients.

Objectives: Leveraging upon single-cell genomics approaches, including an approach that we recently invented which record both the genetic and epigenetic profile of cancer cells at the single cell level, which we named GET-seq, tied together with organoid-based cell culture systems developed by a collaborator (3), we aim to define in carefully controlled experimental settings the genomic and phenotypic features of metastatic colon cancer cell subpopulations, with the final goal of unraveling the epigenetic, genetic and transcriptomic mechanisms responsible for drug resistance.

Collaborations and environment: This project will benefit from several ongoing national and international collaborations, including several labs at the ICR in London, University of Cambridge and the MD Anderson cancer center in Houston, USA. 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: Our goal is the unraveling of the genetic and epigenetic rules that underlie drug resistance, and devise strategies to preemptively overcome it, exploiting single cell genomic approaches.

Skills to be acquired by the student:

This project is rooted in an international grant that engages various groups in Italy, and 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. 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. Macosko EZ, Basu A, Satija R, Nemesh J, Shekhar K, Goldman M, et al. Highly Parallel Genome-wide Expression Profiling of Individual Cells Using Nanoliter Droplets. Cell; 2015;161:1202-14.

2. Klein AM, Mazutis L, Akartuna I, Tallapragada N, Veres A, Li V, et al. Droplet Barcoding for Single-Cell Transcriptomics Applied to Embryonic Stem Cells. Cell. Elsevier Inc.; 2015;161:1187-201.

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;359:920-6.