

Doctorate (Ph.D.) or Master (M.Sc.) position

Exploiting single cell capture to study molecular mechanisms of DNA DSB repair

During radiotherapy, ionizing radiation (IR) efficiently kills cancer cells by directly inducing highly-genotoxic DNA double strand breaks (DSB). The efficiencies of DSB are critical determinants in the response to cancer radiotherapy; indeed substantial evidence indicates that enhanced DSB capacity in individual patients is a major determinant in tumour radioresistance. Moreover, (i) the considerable number of patients displaying severe radiosensitivity, who suffer from extreme IR-induced destruction of healthy tissue, and (ii) the occurrence of radiotherapy-induced secondary cancers, are both presumably associated with reduced DSB capacity. In view of the above, there is a pressing need to better understand the fundamental mechanisms of DSB, towards improving the clinical management of patients undergoing radiotherapy.

Following exposure of cells to IR, multiple DNA repair proteins are rapidly recruited to DSB sites, forming nuclear foci which can only be monitored visually by fluorescence microscopy. Importantly, abnormal persistence (slow resolution) of foci is a well-established indicator of defective DSB in general.

Isolation and subsequent characterization of single cells based on their ability to resolve IR-induced nuclear foci has never been accomplished. To address this, we recently developed a method termed Single-Cell Magneto-Optical Capture (scMOCa) that allows, for the first time, arbitrary tagging of individual cells among a heterogeneous population within a microscopy field and their subsequent isolation and clonal expansion. By targeting individual live cells from within a heterogeneous population exhibiting differential capacity to resolve IR-induced DNA repair foci, we will set the stage for genome-wide profiling and functional analyses on the resulting clonally-derived cell populations.

Keyword: Cancer genomic, single-cell sequencing, DSB repair, biophotonics, biomedical engineering.

We are looking for a motivated PhD student with background in molecular biology, biomedical sciences or biomedical engineering. Knowledge of DSB biology or sequencing technologies would be an asset. Interested candidates can communicate with the PI, Santiago Costantino santiago.costantino@umontreal.ca

Background literature:

Binan L, Bélanger F, Lemay J-F, Pelletier-De Koninck JC, Roy J, Drobetsky E, Wurtele H, and Costantino S. (2019). Opto-magnetic capture of individual cells based on visual phenotype. eLife <https://elifesciences.org/articles/45239/figures>

Binan L, Mazzaferri J, Choquet K, Lorenzo LE, Wang YC, Affar EB, De Koninck Y, Ragoussis J, Kleinman CL, Costantino S. Live single-cell laser tag. Nat Commun. 2016 May 20;7:11636. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4876456/>