**Research Project Proposal**
Academic year 2019-20

**Project Nº 57**

**Title:**
Understanding tumor plasticity and non-genetic drug resistance mechanisms of BRAF mutant melanoma

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**Summary**
The vast majority of melanoma patients who initially respond to treatment, later develop resistance. This is because cancer therapeutics almost inevitably leave residual cancer cells behind, called Minimal Residual Disease (MRD), which provide a reservoir from which relapse inexorably emerge.
Acquired de novo mutations to overcome the drug pressure is a very well accepted mechanism of drug resistance. However, it has been proposed an alternative mechanism of resistance, the dynamic non-genetic reprogramming of tumor cell states in response to therapy. A drug-tolerant phenotype (i.e. ability to survive on therapy, but not proliferate) can be transiently acquired through nonmutational mechanisms in melanoma.
Studying resistance of BRAF-mutant melanoma to MAPK-targeted therapy using patient-derived tumor xenografts (PDXs), the host laboratory has recently reported the emergence of a novel cell state, the Neural Crest Stem-like (NCSC)cells. Strikingly, they observed that the presence of the NCSCs invariably positively correlates with non-genetic resistance.
The aim of this project is to decipher the melanoma cell state driving non-genetic resistance, the dynamics and nature of this non-genetic mechanisms underlying acquisition of resistance to targeted therapy in melanoma. Firstly, exploring the presence of NCSCs in different melanoma PDX models before and on treatment. Secondly, characterizing the role of different drug tolerant states during early resistance using single cell omics approaches such as scRNAseq, scATAC-seq.

**References**

Toward Minimal Residual Disease-Directed Therapy in Melanoma, Rambow et al, Cell. 2018 Aug 9;174(4):843-855.e19. doi: 10.1016/j.cell.2018.06.025. Epub 2018 Jul 12.

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| **yes** | | **Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?** |
| **no** | **x** | |