BCHM 421/422 – 2019/2020

Project Outline: Chronic myeloid leukaemia (CML) is a clonal disorder arising from the reciprocal translocation of chromosomes 9 and 22, resulting in a chimeric oncogene BCR-ABL1 that encodes a constitutively active tyrosine kinase. First-line treatment with tyrosine kinase inhibitors (TKIs), such as Imatinib, have revolutionized CML care. The unfortunate caveat is that most patients must take the inhibitors indefinitely; thus TKIs represents life-long treatment, resulting in ever-increasing costs to sustain remissions.
In our previous work, we used a comparative screen of normal vs CML stem cells and identified signalling hubs critical to ***intracellular*** signalling in primitive progenitor (CD34+) primary CML cells (1). Now our group would like to explore ***extracellular*** signalling events that happen in the tumour microenvironment that contribute to leukaemogenesis, namely extracellular vesicles(EVs), that mediate cell-to-cell communication events.

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Project Title: How extracellular vesicles effect stem cell function in Chronic Myeloid Leukaemia

Keywords: Chronic Myeloid Leukaemia, K562, extracellular vesicles, colony-forming assays

Project Goals: Analyze functional effects of CML EVs on normal stem cells

Experimental Approaches: Extracellular vesicles will be purified from K562 cell lines. Normal CD34+ cells (sourced additional from both bone marrow samples from healthy donors (Kingston General Hospital Clinical Flow Laboratory) will also be purified. The CD34+ cells will be cultured with the K562 leukaemia EVs. Extracellular vesicle-cultured cells will be functionally analyzed using specialised stem cell assays, and flow cytometry.

References:

1. Abraham, S. A. et al. Dual targeting of p53 and c-MYC selectively eliminates leukaemic stem cells. Nature 534, 341-346, doi:10.1038/nature18288 (2016).

2. Holyoake, T. L. & Vetrie, D. The chronic myeloid leukemia stem cell: stemming the tide of persistence. *Blood* **129**, 1595-1606, doi:10.1182/blood-2016-09-696013 (2017)

3. van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. Nat Rev Mol Cell Biol. Apr;19(4):213-228doi: 10.1038/nrm.2017.125. (2018)