

## 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). In the same screen we identified Rab 27a, Rab11BP and Yip1 as candidate proteins important to CML maintenance, that we have not investigated up to this point. Several reports have documented the regulatory function of Rab27a and Rab11 in extracellular vesicle (EV) biogenesis in multiple studies and cell lines. These three proteins have yet to be characterised in CML. We will therefore, determine their function of Rab27a, Rab11BP and Yip1 in EV biogenesis in CML.

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**Project Title:** Extracellular Vesicle Biogenesis in Chronic Myeloid Leukaemia

**Keywords:** CRISPR, cloning, extracellular vesicles, leukaemia

**Project Goals:** Determine if Rab27a, Rab11BP and Yip1 play a mechanistic role in Chronic Myeloid Leukaemia extracellular vesicles biogenesis

**Experimental Approaches:** CRISPR constructs will be designed and used to knock out Rab27a, Rab11BP and Yip1 in CML blast crisis cell line K562 and CD34+ primary cells. Using cells devoid of Rab27a, Rab11bp and Yip1, we will measure EVs concentration, using the ZetaView nanoparticle tracking analyzer. We will be able to directly assess if these significantly deregulated candidate proteins identified in our CML screen truly affect CSC EV biogenesis, a process that we hypothesis will be important in the pathogenesis of CML.

### References:

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