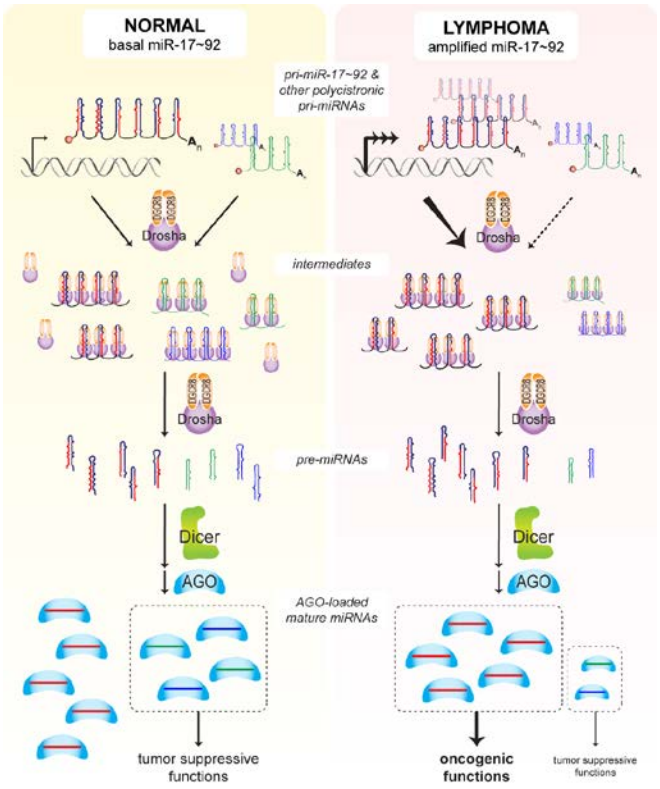
GUEST SPEAKER SEMINAR

Molecular Genetics
UNIVERSITY OF TORONTO

Re-defining the oncogenic miR-17~92 / PTEN pathway



The micro(mi)RNAs encoded by the miR-17~92 polycistron are commonly over-expressed in cancers and orchestrate a wide range of oncogenic functions. A functional target for the miR-17~92 miRNAs is the mRNA encoding the phosphatase PTEN, the dosage of which is of critical importance for tumour-suppressive functions. Our results unveil previously unrecognized paradigms of interplay between polycistronic miRNAs and the PTEN mRNA in cancers. Firstly, I will present a novel mechanism for miR-17~92 oncogenic function through the disruption of endogenous miRNA processing. Upon oncogenic over-expression of the miR-17~92 primary transcript (pri-miR-17~92), the Microprocessor complex (Drosha/DGCR8) remains associated with partially processed intermediates that aberrantly accumulate. The sequence of these intermediates reveals a series of hierarchical and conserved steps in the early processing of the pri-miR-17~92 transcript. Saturation of the Microprocessor by miR-17~92 intermediates leads to the broad, but selective, down-regulation of co-expressed polycistronic miRNAs, including key tumor-suppressive miRNAs. Thus the newly identified early steps of polycistronic miR-17~92 biogenesis contribute to the oncogenic re-wiring of gene regulation networks. Secondly, I will present evidence of a dynamic and profound re-organization of PTEN transcripts through 3'UTR alternative polyadenylation sites acrss cell types and culture conditions. Surprisingly, our detailed functional analysis revealed that prevalent, longer PTEN 3'UTR isoforms confer resistance to miR-17~92 miRNAs, in spite of encoding a plethora of predicted binding sites. The significance for the tumour-suppressive role of PTEN mRNA, and the current state of validation of miRNA-binding sites will be discussed.

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Host: Dr. Julie Claycomb

Date: Friday April 13th, 2018
Time: 10:30AM
Place: 661 University Avenue
MaRS Centre
West Tower, Room 1522