An integrative approach to tissue-specific effects of microRNA regulatory networks

Supervisor: Margarida Gama-Carvalho (BioISI) | **Co-supervisor:** Nham Tran, UTS

Objectives: Generate a comprehensive map of tissue-specific miRNA-dependent regulatory networks in normal and cancer cells, improving current target-prediction methods

Background: The Gama-Carvalho lab has recently uncovered an unexpected role in T lymphocyte activation for a member of the miR-34/449 family, well known for its role in neuronal differentiation, stem cell maintenance and cancer. Interestingly, most of the known targets for this miR do not exhibit tissue specific expression. In parallel, the Tran lab has shown that the expression of a highly specific 'myomiR', miR-499, is dysregulated in oropharyngeal cancers, eventually contributing to tumorigenesis. These observations raise the question of how miRs influence distinct phenotypic outcomes across different tissue types. Our ongoing bioinformatics work has revealed the prevalence of miR sequence variants that can potentially impact tissue-specific regulation, compounded by 3'UTR sequence variation. Furthermore, results from the Tran lab show that cooperative interactions between highly expressed and low abundance miRs influence regulatory outcomes. In spite of the increasing data availability, these aspects are not currently incorporated into target prediction algorithms.

Methodology: Using an approach strongly based in bioinformatics, the student will resort both to public data and new data acquired during the project for miRNome, transcriptome and miRNA-mRNA interactions to generate a detailed map of miR-mRNA regulation for these two miRs in their tissue-specific contexts. The student will develop interactive maps to visualise overall miR impact in cell-specific regulation, which will be projected onto the data arena (Biomedical engineering @UTS). Interactive maps will provide a dynamic representation of the cell-type specific transcriptome, miRNome and target sites including sequence variations, and the corresponding correlations in expression levels. This novel form of visualization will allow in depth analysis of tissue-specific differences in the regulatory networks, supporting the identification of emerging patterns and critical miRNA-mRNA interactions. Predicted miRNA-mRNA interactions will be experimentally validated using mimic transfection and reporter assays and the results used to improve the model and visualization pipeline. Finally, the overall findings will be consolidated into a novel target-prediction algorithm that can take into account the tissue-specific environment under study.

Type of fellowship: National