Principal Investigator: **Dr Charbel Darido**

Project title: **Profiling the Oral Microbiome in Novel Barrier Impaired Mouse Models of OSCC**

Final report:

Oral Squamous Cell Carcinoma (OSCC) is the most common cancer of the head and neck region. Most OSCC patients present with advanced stage disease, and treatment is met with high levels of recurrence and metastasis. The use of clinical features to classify the malignancy of oral lesions is difficult because they vary in appearance and size and are open to subjective interpretation by clinicians. While a histopathologic diagnosis is generally more indicative of the malignant changes, it does not inform which premalignant lesion is at risk of progression to OSCC. The oral epithelial tissue serves as a semi-permeable protective "barrier" that is under constant immune surveillance and homeostatic repair to ensure both physical and selective permeability functions that are pivotal for preventing OSCC. When barrier integrity is compromised, it exposes the oral tissue to microbial imbalance and pathogen outgrowth that may promote cancer development. The metagenomics revolution in both sequencing and its analytic pipelines is fostering an explosion of interest in how the oral microbiome impacts physiology and propensity to disease.

In this project funded by the ANZHNCS, we have sequenced the 16S rRNA microbial DNA of novel genetic, carcinogenic and viral mouse models of OSCC that recapitulate the full sequence of the human disease from premalignant lesions to OSCC. The sequencing analysis investigated the role of the microbiome and its association with disease status and was validated by 16S rRNA fluorescence *in-situ* hybridization (FISH). While the study is still at its infancy in establishing microbial hallmarks of OSCC initiation, it was able to determine a dysbiosis phenotype associated with microbial imbalance and loss of alpha-reductase at the primary barrier-impaired stage. Our data confirmed that a microbial signature could be associated with OSCC initiation in mice, providing opportunities to introduce preventative studies and risk classification of premalignant lesions. Further investigations will validate the results in patient samples with the expected outcomes to ultimately revolutionize how we manage oral premalignancy in the clinic, prevent oral cancer, and reduce mortality and morbidity associated with OSCC.