PROJECT TITLE: Therapeutic targeting of novel key candidate molecules to prevent chronic liver disease progression to liver cancer

FIELD OF RESEARCH CODE: 1103

PROJECT SYNOPSIS:

My group’s research on chronic liver disease, fibrosis and cancer has been NHMRC-funded since 2012. This PhD project will benefit from data generated in the current NHMRC project (APP1160323, CIA Tirnitz-Parker, 2019 - 2022) and the recently awarded Cancer Research Trust Project Grant (CIA Carlessi, 2020-2021).

Background: Hepatocellular carcinoma (HCC) is the most common primary liver cancer, representing the 4th leading cause of cancer-related death worldwide. The Word Health Organization estimates that more than 1 million people will die from liver cancer in 2030. Despite recent advances, the 5-year survival remains dismal at less than 20%. The main HCC risk factors are viral hepatitis, alcohol abuse and increasingly non-alcoholic fatty liver disease,
which parallels the growing global obesity epidemic. Current therapy options for HCC are extremely limited, and available systemic treatments only prolong the life expectancy of patients by two to three months. Thus, breakthroughs in prevention and therapy are urgently needed. Extensive studies from my group have identified the cytokine receptor fibroblast growth factor-inducible protein 14 (Fn14), as a promising therapeutic candidate that regulates the responses of two key cellular players in chronic liver disease: (1) liver progenitor/stem cells, which can replace lost epithelial tissue but also represent potential tumour precursor cells and (2) fibrosis-driving hepatic stellate cells. Targeting the Fn14 receptor in chronic liver disease may represent a novel therapeutic strategy to inhibit or prevent disease progression to cancer.

Project Rationale: (A) Currently only one Fn14 receptor isoform has been identified and studied extensively. In addition to its canonical isoform 1, Fn14 has now been computationally annotated to have at least two other isoforms that are unknown in the literature and yet to be functionally characterised. We hypothesise that isoform 2 (appears to lack the ligand binding domain) performs ligand-independent signalling, while isoform 3 (appears to lack the transmembrane domain) acts as a circulating inhibitor that binds the ligand tumour necrosis factor-like weak inhibitor of apoptosis (TWEAK). (B) Recent experiments using single nucleus RNA sequencing (snRNA-seq) analyses, funded through two seed grants provided by the Gastroenterological Society of Australia and the Cancer Research Trust (CRT), have identified novel markers of liver progenitor/stem cells, which may represent therapeutic targets.

Project: The PhD student will have the significant benefit of being able to start the PhD project with already identified key therapeutic candidates that we aim to target to prevent chronic liver disease progression to cancer. They will learn cutting-edge techniques, including confocal microscopy, analysis of snRNA-seq data, co-culture using modified Boyden chambers, live cell imaging etc. **Aim 1:** Characterisation of the biological signalling response of Fn14 isoforms 2 and 3 in comparison to the canonical isoform 1 in vitro in liver progenitor/stem cell and hepatic stellate cell (co-)culture systems via overexpression and CRISPR/Cas9-mediated deletion. **Aim 2:** Characterisation of the biological signalling response of Fn14 isoforms 2 and 3 in comparison to the canonical isoform 1 in vivo using delivery of overexpressing vectors or CRISPR/Cas9-mediated deletion in our novel (unpublished) model of HCC: hydrodynamic tail vein injection of myristoylated AKT, coupled with a high-fat diet. **Aim 3:** Investigate selected novel candidates, identified through recent snRNA-seq analyses, as described in Aims 1 and 2, for potential single or combination therapy approaches to prevent chronic liver disease progression to cancer.

Significance: The PhD student will be trained in an internationally competitive research environment and will have the opportunity to contribute to the field through the generation of clinically relevant and potentially impactful data that we aim to publish in leading, high impact factor journals in the field.
PROJECT LEAD CONTACT:

Name: Nina Tirnitz-Parker
School: School of Pharmacy and Biomedical Sciences
Faculty: Health Sciences
Email: N.Tirnitz-Parker@curtin.edu.au
Contact Number: 08 9266 9695