Improving treatment options and preclinical modelling for high- risk neuroblastoma

Project 1: Targeting BCL2 family proteins in high- risk neuroblastoma

Supervisors: Dr Alvin Kamili, Dr Caroline Atkinson, Dr Jamie Fletcher
Suitable for Honours or PhD studies

Background: Patients with high-risk neuroblastoma (HR-NB) have a survival rate of only 50%. BCL2 family proteins regulate cellular life-death decisions (A), including in response to chemotherapy, and are promising targets for this disease. Our preliminary studies with the specific BCL2 inhibitor venetoclax, conducted as part of the PRISM personalised medicine clinical trial, suggest that high BCL2 expression is common, and that some tumours respond to venetoclax monotherapy (B). However, combination therapy will be more effective for a larger proportion of children. This project explores the optimal approach to venetoclax combination therapy through drug screening and preclinical testing.

Research Plan:

Aim 1: Identify drugs that synergise with venetoclax in patient-derived xenograft (PDX) models in culture.

Aim 2: Confirm synergistic interactions in selected models of HR-NB PDX *in vivo*

Aim 3: Identify biomarkers of venetoclax activity and mechanisms of resistance using single cell analysis of relapsed PDX tumours

Methodologies: Cell proliferation assay, western blotting, co-immunoprecipitation, high-throughput drug screening, single cell analysis, animal studies of drug efficacy, and others.

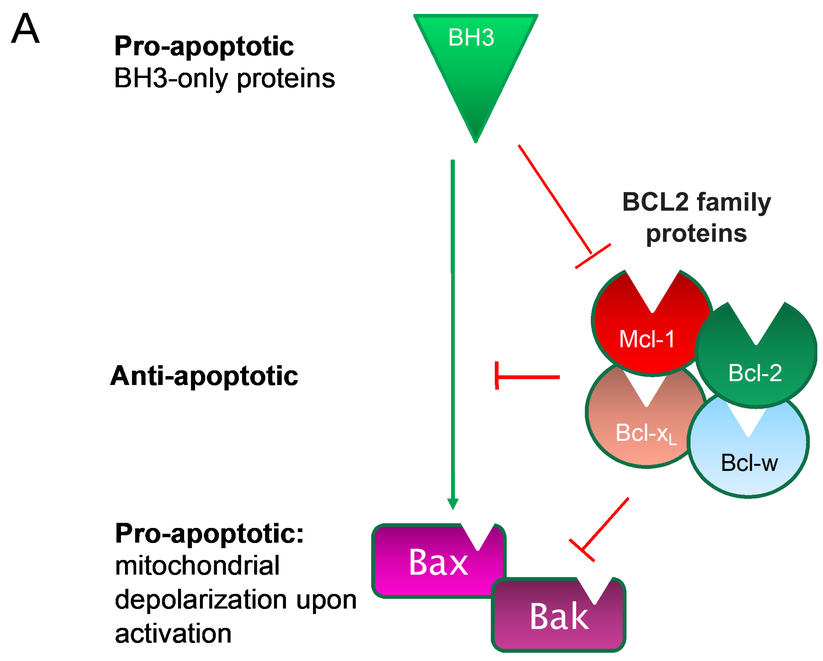

Figure A. Schematic overview of BCL2 family proteins in apoptotic pathway

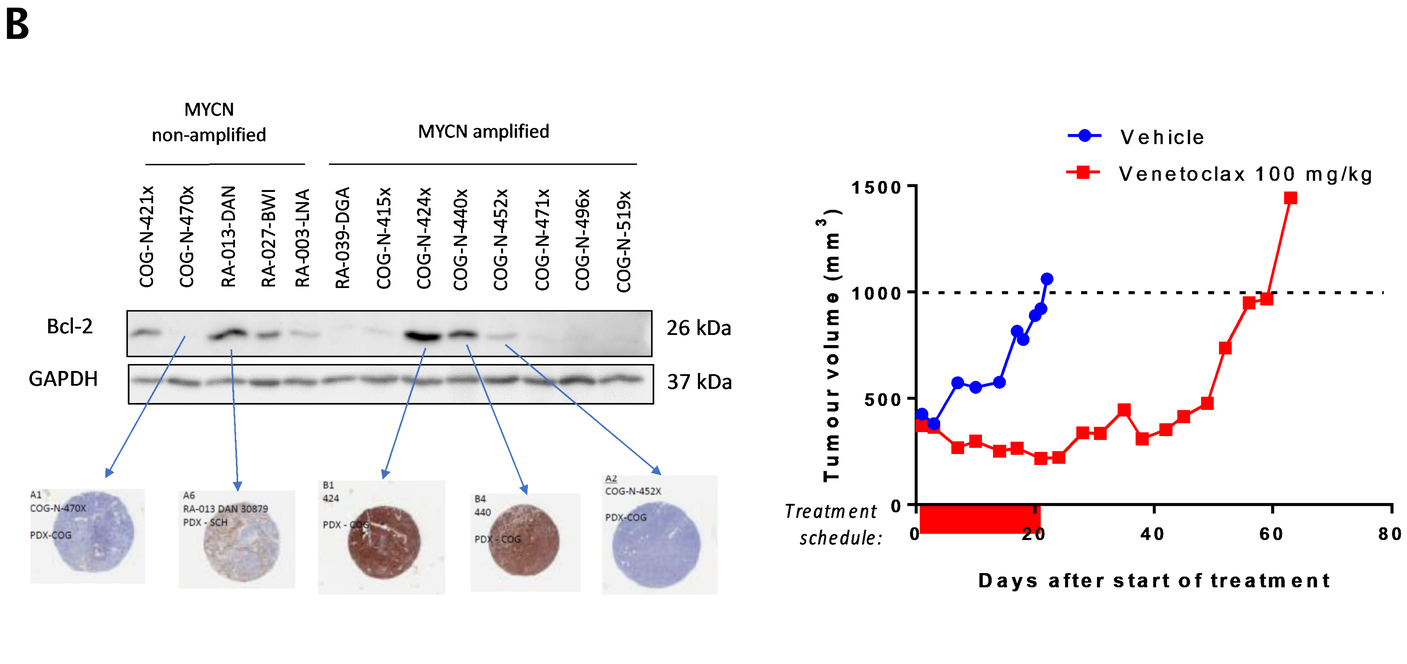

Figure B. BCL2 protein expression in HR-NB models (left). Preclinical activity of the BCL2 inhibitor venetoclax in a HR-NB PDX model (right).

Project 2: New patient- derived mouse models of metastatic high- risk neuroblastoma

Supervisors: Dr MoonSun Jung, Dr Caroline Atkinson, Dr Jamie Fletcher

Suitable for Honours or PhD Studies

Background: Most high-risk neuroblastoma patients have metastatic disease at diagnosis. Currently, most preclinical mouse models do not represent metastasis. Those that do were developed using established cancer cell lines (pictured), and typically differ from the original patient tumours as a result of adaptations to growth in tissue culture. In contrast, patient-derived xenografts (PDXs) are generated directly from the patient tumour, and thus retain most of their key characteristics. No PDX models of metastatic neuroblastoma exist to date. The models developed in this project will support studies into the biology and treatment of metastatic disease. Further, this project will validate the use of liquid biopsy for disease monitoring in metastatic PDX models. This will help overcome barriers to the more widespread uptake of these models, including the requirement for small animal imaging.

Research Plan*:

Aim 1: Develop bioluminescent PDX cells

Aim 2: Develop and characterise imageable neuroblastoma metastasis models in mice

Aim 3: Test liquid biopsy methods for monitoring metastatic disease and compare to current imaging approaches

*Aims expanded to studies of metastasis genes for PhD studies

Methodologies: Animal studies, cellular and molecular biology techniques, viral transduction, flow cytometry, rt qPCR.

Metastatic neuroblastoma visualised by combined CT and bioluminescence imaging in a NOD-SCID mouse engrafted with a neuroblastoma cell line. Tumours are visible in the long bones, spine, ribs and skull.