Florey Medical Research Foundation's Veronika Sacco Clinical Cancer Research Fellowship
Update Report: July 2014

Title of Project
Investigating the role of the bone microenvironment in the development and progression of Myeloma

Background:
Multiple myeloma (MM) is the second most common haematological malignancy after non-Hodgkin's lymphoma. Approximately 1500 new cases are diagnosed in Australia each year, accounting for 1.3% of all newly diagnosed cancer cases. Despite recent advances in therapy, the 10-year survival rate remains at only 17%. It is therefore evident that a curative therapy is still lacking. MM is caused by the uncontrolled growth of malignant plasma cells within the bone marrow. Clinical features of MM include the development of painful bone lesions, renal failure, suppressed hematopoietic function, reduced immunoglobulin production and increased bone marrow angiogenesis. MM is preceded in all cases by the asymptomatic, pre-malignant condition monoclonal gammopathy of undetermined significance (MGUS). There is an annual progression rate of MGUS to MM of 1% per year; however the time to progression varies greatly between patients.

Recent studies suggest that the local bone microenvironment wherein the malignant plasma cells reside plays an important role in modulating the development and progression of MM disease. This specialised microenvironment stimulates the proliferation and survival of malignant plasma cells. Components of the microenvironment therefore present key, novel, therapeutic targets to indirectly modulate MM disease. In addition, the genetics of MM plasma cells are extremely complex, with malignant plasma cells displaying a vast array of chromosomal, single nucleotide, transcriptional and epigenetic changes. Unique combinations of these genetic alterations are likely to be critical for driving tumour development, however identifying and characterising these changes remains a significant challenge.

Summary of key findings:
The C57BL/KaLwRij pre-clinical mouse model of myeloma is unique in its ability to spontaneously develop myeloma (with clinical features similar to human disease) at a low frequency and allows for the *in vivo* growth of mouse myeloma plasma cells (5TGM1) following intravenous injection. My studies utilise this model, alongside analysis of MM patient samples, to investigate changes in the bone marrow microenvironment in MM disease, as well as identifying and characterising changes in expression of genes that may modulate MM disease development. Notably, my studies (as outlined below) highlight the validity of employing the C57BL/KaLwRij mouse model to identify factors that are consistently involved in MM disease development in patients.

The bone microenvironment is a key player in the development of MM disease. Studies in our laboratory demonstrate that the cellular composition of the bone marrow is altered in the presence of MM plasma cells, both in the animal model and in MM patients. We show an increased number of mesenchymal stromal cells (MSC) present in the marrow of MM patients, which is likely to promote the progression of MM disease. Studies such as these, identifying key changes in the bone microenvironment, are critical for the potential future development of novel treatment strategies to limit MM disease progression.

Using the C57BL/KaLwRij mouse model, we have identified a number of genes that are significantly up - or down-regulated in the C57BL/KaLwRij mice compared to closely-related control mice that do not develop myeloma.

Specifically, we have shown that expression of the *Samsn1* gene is lost in the C57BL/KaLwRij mice. We identify a chromosomal deletion encompassing the entire *Samsn1* coding region as a mechanism for this loss of expression in the mice. Our studies show that re-expression of Samsn1 in the 5TGM1 myeloma plasma cell line completely inhibits tumour development. In addition, we show that SAMSN1 expression is also reduced in the plasma cells of MM patients compared with healthy controls. These studies suggest that the loss of SAMSN1 expression plays an important role in the development of MM in a subset of patients.

Studies are ongoing to determine which of the other identified genes are important for myeloma development and/or disease progression in both the mouse model and in MM patients. These studies will aid in better understanding the genetic basis of MM and potentially identify novel pathways that may be therapeutically targeted to limit MM disease.

Meeting Presentations:

Nov 2013 - Frontiers in Skeletal Biology, Garvan Institute, Sydney (Oral presentation)

June 2013 - 18th Congress of the European Haematology Association (EHA), Stockholm, Sweden (Poster presentation)

Publications:

Noll JE*, Hewett DR*, Williams SA*, Vandyke K, Kok C, To LB, Zannettino ACW (2014) Samsn1 is a tumor suppressor gene in multiple myeloma. *Neoplasia* Accepted [*impact factor 5.47]*

Noll JE, Williams SA, Tong CM, Wang H, Quach JM, Purton LE, Pilkington K, To LB, Evdokiou A, Gronthos S, Zannettino ACW (2014) Myeloma plasma cells alter the bone marrow microenvironment by stimulating the proliferation of mesenchymal stromal cells. *Haematologica* 99:163-171 [*impact factor 5.935; citations 1*]

Noll JE, Williams SA, Purton LE, Zannettino ACW (2012) Tug of war in the haematopoietic stem cell (HSC) niche: do myeloma plasma cells compete for the HSC niche? *Blood Cancer J.* 2:e91 [*impact factor 1.4; citations 13*]

Book Chapters:

Noll JE, Vandyke K, Zannettino ACW (2014) The role of the “cancer stem cell niche” in cancer initiation and progression. *Adult stem cell niches* ISBN 980-953-307-1144-6