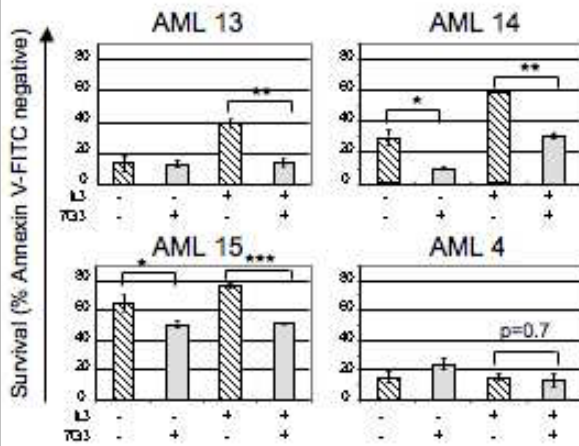


PETER NELSON LEUKAEMIA RESEARCH FELLOWSHIP ANNUAL RESEARCH REPORT 2008

Project Title	Targetting the Leukaemic Stem Cell
PNLRF Research Fellow	Dr Hayley Ramshaw
Institution	Centre for Cancer Biology, SA Pathology
Lay Summary	a. Please provide a lay summary of 1 – 2 paragraphs explaining what your research explored
	<p>Leukaemia is a devastating form of blood cancer affecting both young and old. Current therapy is poorly tolerated and the majority of patients ultimately die of relapse. Our laboratory has developed a novel non-chemotherapy treatment for leukaemia which specifically aims to target the cells that are more than likely responsible for relapse. These cells are called leukaemia stem cells and have some overlapping features with normal bone marrow stem cells. These cells have been shown to divide slowly and are resistant to the current forms of chemotherapy commonly used today. It is imperative that new treatments are developed to specifically eliminate these AML stem cells in an effort to provide long-term management of the disease, if not cure.</p> <p>The antibody that we have developed targets CD123 which is the receptor for a growth factor important in the development of blood cells. I am investigating the role of this growth factor receptor which is expressed at high levels on leukaemia stem cells but not normal stem cells</p>
	b. Please advise the benefits this research provides to the community / cancer patients
	<p>Current therapies for patients with AML do not kill the stem cell and thus the patients often relapse with the disease following treatment. Older or weaker patients can also struggle to cope with the side effects from chemotherapy. The antibody that I am investigating may provide a non-toxic therapy for leukaemia stem cells.</p>
Scientific Report	<p>Progress to Date:</p> <p>Using Fluorescent Activated Cell Sorting (FACS) I have purified stem cells (according to a CD34⁺CD38⁻ phenotype) from a number of leukaemia and normal samples. I have been sourcing a sample that contains sufficient numbers of normal stem cells for this work as these cells are very rare under steady state conditions. Samples used for this work include normal bone marrow, umbilical cord blood and mobilised cells from solid tumour patients.</p>

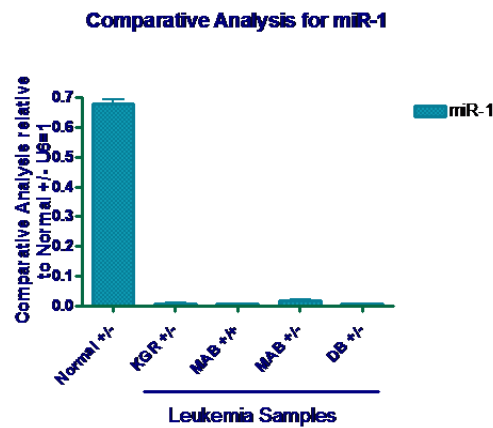
Purified leukaemic stem cells from AML patients have been shown to be killed by treatment with the antibody 7G3. This is a specific reagent that targets the

interleukin-3 (IL-3) receptor (CD123), a protein known to be up-regulated on leukaemia stem cells when compared to normal stem cells. As shown in Figure 1 these cells from a number of patients with AML have reduced viability in the presence of 7G3.



cells was measured after this time.

Figure 1: CD34⁺CD38⁻ cells were isolated from AML patients and then treated with IL-3, 7G3 or both for 72 hours. The viability of the



Some very preliminary data has been generated investigating the potential role for microRNA regulation of AML CD34⁺CD38⁻ cells. RNA was isolated from both AML and normal CD34⁺CD38⁻ cells and subjected to microRNA RT-PCR. When comparisons were made between the normal and the leukaemic stem cells differences were noted in the expression of some microRNAs, including hsa-miR-1 (see figure 2).

Figure 2: CD34⁺CD38⁻ cells were purified from AML and normal patients and RNA extracted. This was subjected to analysis for a variety of microRNA species. The amount of miR-1 microRNA in the cells was significantly different between normal and AML patients.

Publications

Jin, L., Lee, E.M., **Ramshaw, H.S.**, Busfield, S., Peoppl, A.G., Wilkinson, L., Guthridge, M.A., Thomas, D., Boyd, A., Gearing, D., Vairo, G., Lopez, A.F., Dick, J.E., Boyd, R.B. CD123 (IL-3 Receptor α Chain) Neutralization By A Monoclonal Antibody Selectively Eliminates Human Acute Myeloid Leukemic Stem Cells. Manuscript currently under review.