arrow bone marrow transplant foundation
targeting a cure

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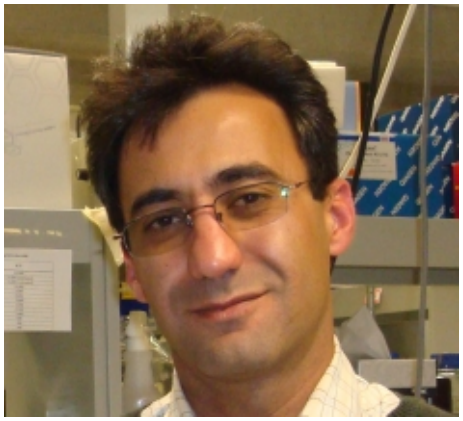
Arrow / HCC PhD scholarship project updates

With support from the Hawkesbury Canoe Classic (HCC), Arrow offers financial assistance to PhD students through a scholarship program which supports research into better treatments, and ultimately a cure, for leukaemia and other diseases treatable by stem cell therapies. Following from the PhD project overviews provided in the last edition of Transplant Voice, below is an outline of how our current PhD students are progressing:



Alireza Ardjmand

Alireza Ardjmand's paper published in Nature

Publication date: 25th November, 2011.

Arrow / HCC scholarship recipient, Alireza Ardjmand, from the Cancer Research Unit, University of Newcastle, has had his paper published in the world renowned journal, Nature. The following excerpt from the published paper looks at improving the survival of patients with acute lymphoblastic leukaemia (ALL).

The Fat1 cadherin is overexpressed and an independent prognostic factor for survival in paired diagnosis—relapse samples of precursor B-cell acute lymphoblastic leukemia

Improved survival of patients with acute lymphoblastic leukemia (ALL) has emerged from identifying new prognostic markers; however, 20% of children still suffer recurrence. Previously, the altered expression of Fat1 cadherin has been implicated in a number of solid tumors. In this report, in vitro analysis shows that Fat1 protein is expressed by a range of leukemia cell lines, but not by normal peripheral blood (PB) and bone marrow (BM) cells from healthy donors. In silico analysis of expression of array data from clinical leukemias found significant levels of Fat1 transcript in 11% of acute myeloid leukemia, 29% and 63% of ALL of B and T lineages, respectively, and little or no transcript present in normal PB or BM. Furthermore, in two independent studies of matched diagnosis -- relapse of precursor B-cell (preB) ALL pediatric samples (n¼32 and n¼27), the level of Fat1 mRNA expression was prognostic at the time of diagnosis. High Fat1 mRNA expression was predictive of shorter relapse-free and overall survival, independent of other traditional prognostic markers, including white blood cell count, sex and age. The data presented demonstrate that Fat1 expression in preB-ALL has a role in the emergence of relapse and could provide a suitable therapeutic target in high-risk preB-ALL.

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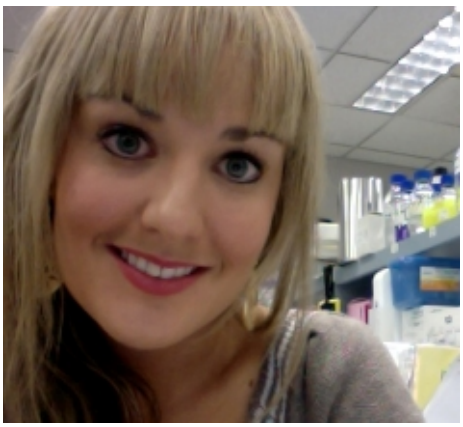
Adele Baker advances Acute Myeloid Leukaemia research

Adele Baker, Arrow / HCC PhD scholarship recipient from The University of Melbourne, is a step closer to developing new drug targets and therapies for Acute Myeloid Leukaemia (AML) following the successful outcome of a project being undertaken at the Peter MacCallum Cancer Centre, Melbourne, under the supervision of Prof. Ricky Johnstone and Dr Jake Shortt. Adele's project aims to identify key molecular targets for the treatment of AML driven by the mixed lineage leukemia-AF9 (MLL-AF9) translocation.

Project Overview

MLL has been found to be involved in 73 different translocations and 54 partner genes have been cloned. Infant acute leukaemias are classified as aggressive tumours that need high amounts of poly-chemotherapy for treatment, although the outcome is still poor. Genetically, the group of paediatric leukaemia patients is characterised by distinct genetic rearrangements of the MLL gene, located at 11q23. Only six frequent partner (fusion) proteins constitute 85% of all clinical cases of MLL, one of which is AF9. Fusion proteins are generally transcriptional activators that induce ectopic expression of target genes in hematopoietic precursor cells.



Adele Baker

I have successfully developed mouse models harbouring the MLL-AF9 translocation and have treated the cells ex vivo using multiple small molecule inhibitors. With some success in this area I have also begun further in vivo studies using these small molecule inhibitors in mice with MLL-AF9 to mimic the response found in vitro.

Furthermore, future studies in vitro using these small molecule inhibitors on primary human patient cells with the MLL-AF9 translocation (readily available from tissue banking at the Peter MacCallum Centre) will provide a platform for developing new drug targets and new therapies for MLL-AF9 patients.

Bradley Hoad

Bradley Hoad finds new link between leukaemia and breast cancer

Queensland University of Technology, Institute of Health and Biomedical Innovation.

Leukemias arise when the genes that normally regulate cell growth and maturation are lost through genetic mutation. One mutation we frequently see in leukaemia involves the nucleophosmin gene. Nucleophosmin has several roles exploited by cancer including increasing cellular proliferation and size. My PhD project aims to elucidate a novel role for nucleophosmin in maintaining healthy DNA.

Through the first year of my PhD project we have been able to show that nucleophosmin is required for the efficient repair of DNA damage. Loss of healthy nucleophosmin function prevents homologous recombination, which is a mechanism employed by the cell to rapidly repair DNA damage and to prevent genetic mutation. This is an exciting find as one of the most well known breast cancer susceptibility genes, BRCA1, functions in this same pathway. Nucleophosmin now appears to be a guardian of the genome and we believe its loss may result in the mass genetic alterations we see in leukaemia.

Sewa Rijal

Project Overview

Acute Myeloid Leukaemia (AML) is an aggressive blood cancer resulting from acquired molecular changes in precursor cells, which reside in the bone marrow. These molecular lesions usually promote increased growth and survival of immature white blood cells. The accelerated growth of leukaemic cells and their resistance to standard chemotherapy frequently occurs in association with over-activity of the phosphoinositide 3-kinase (PI 3-K) and Akt proteins. Unlike solid tumours, no activating mutations have been found in either of the genes encoding these proteins. Phosphoinositide phosphatases (PIPs) regulate the PI3K/Akt axis by acting as an "off-switch" and their deficiency has been associated with abnormal activation of PI3K/Akt in a variety of solid tumours. There are at least a dozen such PIPs but the expression and function of these PIPs have not been examined in detail in haematological malignancies, including AML.

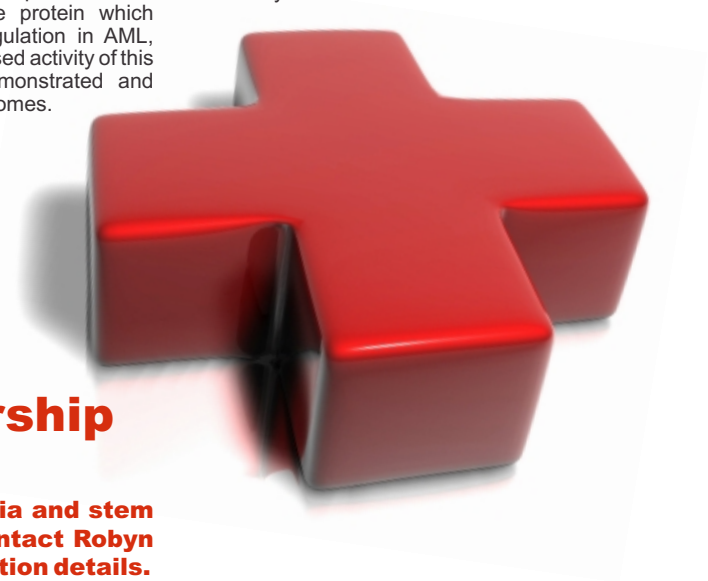
We have conducted a detailed survey of PIPs in AML patient samples. There were no significant changes in the gene expression levels between AML and normal bone marrow (BM) samples for the majority of PIPs examined except for the case of one particular phosphatase protein which showed an unexpected up-regulation in AML, compared to normal BM. Increased activity of this protein in AML was also demonstrated and correlated with poor patient outcomes.

We are now investigating
1. How this phosphatase is activated in AML?
2. What role it plays in driving the disease?
3. What does this phosphatase act on that is responsible for its activity?

Findings from the Cancer after Stem Cell Transplantation (CAST) Study

In 2011, Arrow contributed $33,469 towards the data collection costs of the CAST study which aims to evaluate rates of mortality and second cancers in recipients of HSCT in Australia. Data from the Australasian Bone Marrow Transplant Recipient Registry and the National Death Index were used to examine long-term mortality outcomes in 4547 survivors of autologous HSCT aged 15 years or older, a subset of the 14 000 person CAST cohort.

Results from these analyses showed that overall mortality in 2-year survivors was significantly increased compared to the age- and sex-matched Australian general population, extending beyond 10 years from HSCT. While relapse was the most common cause of death, mortality from second malignancy, circulatory disease and respiratory disease was also increased above rates observed in the general population, highlighting the importance for long-term follow-up of patients following HSCT. Further analyses of mortality outcomes and analyses of second cancers in HSCT recipients is currently underway.



2012 Arrow / HCC PhD Scholarship applications closing soon!

Funding submissions for PhD students researching leukaemia and stem cell therapies will close at the end of April 2012. Please contact Robyn Flood on (02) 8382 2698 or email info@arrow.org.au for application details.

Arrow currently supports several research projects and patient support services at St Vincent's Hospital, Sydney. To show your support please consider making a donation today.

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