arrow bone marrow transplant foundation
targeting a cure

Research

ISSUE 02 INSERT 2011

Supporting our future scientists with Arrow / HCC PhD scholarships

Arrow offers financial assistance to PhD students across Australia through a scholarship program that funds promising research into leukaemia or stem cell therapy. This year Arrow awarded PhD research scholarships to: Bradley Hoad; Adele Baker and Alireza Ardjmand, and continued to support the work of: Sewa Rijal and Amanda Smith.

Bradley Hoad (Left); Adele Baker (Centre); Alireza Ardjmand (Right)

Bradley Hoad

Queensland University of Technology, Institute of Health and Biomedical Innovation

Project summary

Leukemias arise when the genes that normally regulate cell growth and maturation are lost through genetic mutation. For decades scientists have focused on DNA damaging chemicals and radiation as the culprits of these mutations. It now appears that the processes governing the repair of DNA damage may be more critical in promoting leukaemia than the damaging event itself. Our study aims to characterise the role of nucleophosmin in DNA repair. Nucleophosmin is a nuclear protein found mutated and over expressed in several cancers however none as frequently as acute myeloid leukaemia. In fact, nucleophosmin is commonly used as a biomarker for the disease. This project will now investigate the apparently critical role nucleophosmin plays in maintaining genome stability. Uncovering nucleophosmins role in this pathway may reveal new targets for anti-leukaemia drugs.

Adele Baker

PhD student, The University of Melbourne. Peter MacCallum Cancer Centre, Melbourne. Gene Regulation Laboratory. Supervisor: A/Prof Ricky Johnstone.

Project summary

The aim of my project is to identify key molecular targets for the treatment of acute leukaemia (AL) driven by mixed lineage leukaemia (MLL) fusion protein mutations.

The MLL mutation accounts for 60-80% of all infant acute leukaemias. It is an aggressive tumour that usually results in a poor prognosis outcome even when treated with high amounts of poly-chemotherapy. Genetically, paediatric and adult AL patients can be characterised by their distinct genetic rearrangements of the MLL gene. I aim to study disease onset and progression by producing mice that develop acute myeloid leukaemia (AML) with the MLL mutation fused to two out of the six most common oncogenic fusion partner proteins. I can then determine the oncogenic potential of these two different MLL fusion protein mutations; and investigate what drives or activates the onset and process of these MLL fusion proteins. This will provide a platform for developing new drug targets and therapies for patients.

Alireza Ardjmand

PhD Student, School of Biomedical Sciences & Pharmacy, Cancer Research Unit University of Newcastle

Project Summary

The survival of patients with acute leukaemia has gradually improved through the development of new diagnostic and treatment protocols. These advances have been driven by research to identify specific markers expressed by leukaemia cells. Nevertheless, there are still major challenges to overcome, particularly to identify those patients who will fail therapy. Emerging evidence suggests the persistence of a small unique population of drug resistant cells called Leukemic Stem Cells (LSC's) that are ultimately responsible for disease relapse.

Since LSC's share many markers with their normal haemopoeitic counterparts they are difficult to identify. My PhD project tests the hypothesis that Fat1 is a biologically important target protein expressed specifically by LSC's. If substantiated, specific monoclonal antibodies against Fat1 could be used to both identify and kill LSCs. Importantly, since Fat1 is not expressed on normal cells; this approach promises to provide a new treatment that will minimise collateral damage to normal blood cells.

Sewa Rijal

Monash University

Project summary

Defining the role of phosphoinositides phospahtases (PIPs) in the regulation of Pi3-kinase function in acute myeloid leukaemia (AML): a translational approach.

Abnormal expression of a family of genes encoding "Hox" proteins is an established cause of maturation failure in AML. 70-80% of AML patient samples also display abnormal activation of the phosphoinositide 3-kinase (PI 3-K)/Akt pathway, a master regulator of cell survival and proliferation. Accumulating evidence also suggests that the PI 3-K/Akt axis may be implicated in the resistance of AML cells to conventional chemotherapy. PI 3-K is normally made inactive in the cell by special proteins called phosphoinositide phosphatases (PIPs).

My PhD aims to accurately identify abnormal patterns of PIP expression in a large set of AML patient samples using a highly sensitive "massspec" based detection of gene amplification called the Sequenom® QGE. Further, we also aim to study whether mice with PIP deficiency can propagate AML by over-expressing HOX genes via mouse transplantation experiments.

We have successfully designed oligos that can be multiplexed to amplify key PIPs in our first set of 38 AML samples and 10 controls for the Sequenom® QGE pilot study – to identify whether the mRNA of these PIPs are under expressed in disease state. To study whether the protein expression is also lost, we are staining the bone marrow trephines of these AML patients and controls with antibodies specific to each PIP. This will give us a first ever global expression profile of PIPs in AML both at mRNA and protein level. This will be an ongoing study until we examine 150-200 AML samples. In regards to the mouse transplantation experiments, we have successfully optimised the preparation of Hox encoded virus particles to be used for infecting PIP deficient mouse fetal livers. Infection is currently being undertaken and mice will be injected with these genetically manipulated fetal liver cells to see whether AML can propagate on a PIP deficient background when combined with over expression of Hox proteins. We aim to thoroughly examine three to four key PIPs, as determined by the Sequenom QGE experiments, in these mouse model studies.

Amanda Smith

University of Newcastle, Medical Biochemistry

Project summary:
The first half of my PhD project focused on a specific protein altered in cancer, c-KIT, that was found to block an enzyme, protein phosphatase 2A (PP2A) which is now widely considered to be a cancer suppressor. It was established that when expressed in cells, the abnormal forms of c-KIT found in human cancers had increased ability to block the function of PP2A and drive increased growth rate, survival and colony forming ability – all of which are hallmarks of cancer growth.

To investigate whether we could utilise this knowledge and reverse the blockade of PP2A activity in the c-KIT+ cells I utilised a pharmalogical compound, FTY720, which has been shown to increase PP2A activity. By treating cells in culture with FTY720 I was able to increase PP2A activity, reduce the expression of c-KIT protein and in turn reverse the cancer like characteristics of the cells exhibited prior to treatment.

Taken together with data produced by another PhD student in our laboratory, these findings were published in the Cancer Research Journal in July last year. I have also presented this work at a number of conferences both in oral and poster format.

The second half of my PhD combines two main points of investigation.

- How does FTY720 elicit these effects on PP2A.
- Is this a mechanism relevant to patients in the clinic.

The way in which FTY720 elicits its effects on PP2A has not been fully elucidated. I am currently utilising several techniques to examine the binding of FTY720 to the PP2A enzyme itself, levels of PP2A protein in cells prior to and following treatment, and levels of other proteins that may change following treatment with FTY720.

While cells in culture provide an excellent way to gain knowledge regarding the basic molecular biology of cancer, it is also important to transfer our findings to a more clinical setting. We have recently joined a study in collaboration with IMVS in South Australia, and another with the Calvary Mater Hospital Cancer Research group, to investigate the cancer mechanisms outlined above and the potential use of FTY720 as a patient therapy by using bone marrow and peripheral blood samples from acute myeloid leukaemia patients.

Arrow researchers recognised for their results

We are pleased to report that Arrow funded scientists and PhD students have had the results of their research published in renowned scientific publications as follows:

American Journal of Hematology
January 2011
Article: 'Expression Profiling of Cytogenetically Normal Acute Myeloid Leukemia Identifies MicroRNAs that Target Genes Involved in Monocytic Differentiation.'
Authors: **Mark Lutherborrow, Former Arrow/HCC Senior Research Scientist; Adam Bryant, Former Arrow/HCC PhD Scholar; Vivek Jayaswal; David Agapiou; Catalina Palma, Current Arrow/HCC Research scientist; Yee Hwa Yang and David Ma.**

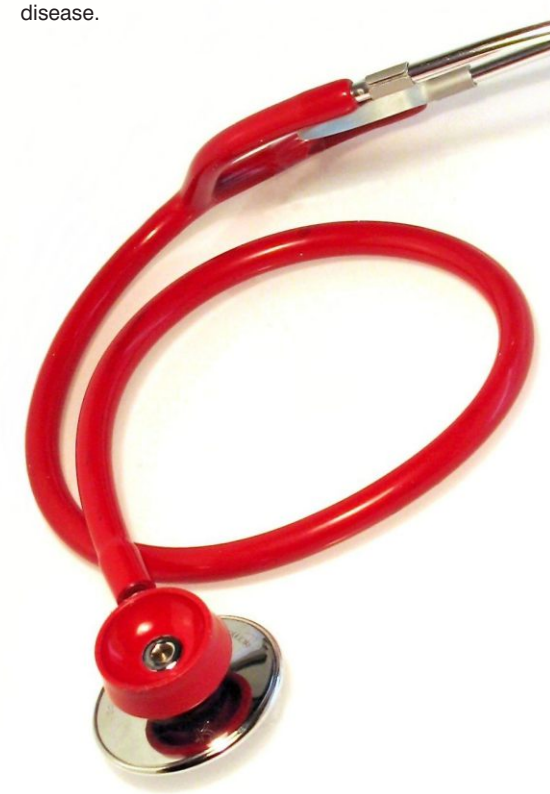
BMC Medical Genomics
March 2011
Article: 'Discriminating lymphomas and reactive lymphadenopathy in lymph node biopsies by gene expression profiling'
Authors: **T.Loi, Former Arrow/HCC PhD Scholar; A.Campain; A.Bryant, Former Arrow/HCC PhD Scholar; T.Molloy, Former Arrow/HCC Senior Research Scientist; M.Lutherborrow, Former Arrow/HCC Senior Research Scientist; J.Turner; Y.Yang; D.Ma**

BMC Genomics
2011
Article: 'Identification of microRNA-mRNA Cliques using Microarray Data'
Authors: **V.Jayaswal; M.Lutherborrow, Former Arrow/HCC Senior Research Scientist; D.Ma; Y. Yang.**

Research update from Catalina Palma

We are pleased to report that Arrow-HCC Research Scientist, Catalina Palma, and Professor David Ma's team at the Blood Stem Cell and Cancer Research Unit, St Vincent's Hospital, Sydney, continue to make good progress on a gene profiling study that uses cell line models of leukaemia to identify unique differences in gene (microRNA) levels in different types of Acute Myeloid Leukaemia.

The genetic manipulation of these cell lines is achieved by inserting genes or blocking their expression to determine how these genes contribute to the uncontrolled growth and immature features which are hallmarks of leukaemia. Together the team hope that an improved understanding of the role that these genes play in leukaemia development will lead to advances in diagnosis and treatment of the disease.



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