arrow bone marrow transplant foundation
targeting a cure

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Arrow/HCC Research Scientist and PhD Scholarship Recipient Updates

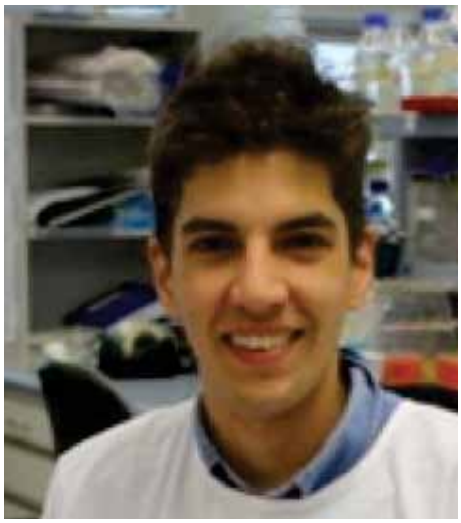
Thanh Vu

Introducing Thanh Vu

We are pleased to welcome Dr. Thanh Vu to the position of Arrow/HCC funded research scientist at the Blood Stem Cell and Cancer Research Unit at St Vincent's Hospital, Sydney. Thanh replaces Catalina Palma (who has taken on the position of Senior Research Scientist) and is continuing Catalina's research into the role of microRNAs and their therapeutic potential in acute leukaemia.

About Thanh

Thanh completed her bachelor degree in biomedical science at the University of Newcastle in July 2007 with honours and a university medal. After working with Prof. Roger Smith at Mothers and Babies Research Centre, John Hunter hospital for six months, Thanh moved to Sydney to pursue her PhD degree in Prof. Merlin Crossley's laboratory at the University of Sydney. Thanh's PhD project investigated the biological roles of a gene, Krüppel-like factor 3, in immune cells using a mouse model, and revealed the importance of this gene in the development and migration of immune cells. Upon the completion of her thesis in 2011, Thanh worked with Prof. Derek Hart at the ANZAC Research Institute, Concord Hospital, on a project to develop immunotherapy for cancers. Thanh was awarded her PhD in May, 2012, and joined the Blood Stem Cells and Cancer Research unit, St Vincent's Centre for Applied Medical Research as a postdoctoral scientist in August 2012.



Marcus Lefebure

Marcus Lefebure

Arrow/HCC PhD scholarship project summary:
Lymphomas are comprised of a broad spectrum of diseases that are linked to normal cellular counterparts in the haematopoetic and lymphoid compartments. As a group, lymphomas account for the fifth most common disease cohort in Australia and they affect all age groups without prejudice. Marcus' PhD, which began in late 2011, is aimed at defining critical mutations in cells that allow normal lymphoid cells to become cancerous lymphoid cells.

By understanding and defining the critical mutations and pathways that are activated during the development of lymphoma, researchers arm themselves with a new arsenal of information to aid in diagnosing and treating lymphomas based on which mutation(s) they are driven by. Such improvements would hopefully lead to improved therapies that can minimise side effects and, resultantly, improve patient quality of life.

Sewa Rijal

PhD 2013 progress update.
Project title: Defining the role of Phosphoinositide Phosphatases (PIPs) in the regulation of PI3-kinase function in acute myeloid leukaemia (AML): a translational approach

Acute myeloid leukaemia (AML) is an aggressive blood cancer resulting from an increased production of immature white blood cells in the bone marrow. The accelerated growth of these 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. Phosphoinositide phosphatases (PIPs) are key proteins that tightly regulate the PI3K/Akt pathway and as such have been established to be important genes 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.

Following a detailed survey of the gene expression of all human PIPs in AML patient samples, no significant changes were found in the expression levels for the majority of PIPs examined – except for the case of one particular phosphatase protein which showed an unusual up-regulation in AML compared to normal bone marrow. Increased expression of this protein was also demonstrated and correlated with poor patient outcomes. Transgenic over-expression of this protein into human AML cells decreased overall survival from leukaemia in mice transplantation experiments where these cells were also highly resistant to death from chemo drugs. Sewa has also successfully established mouse model studies to over-express this protein specifically in the hematopoietic system in order to study its function in detail and the molecular mechanisms underlying its pathogenesis in AML.

Adele Baker PhD progress update

Adele's project is being undertaken through The University of Melbourne at the Peter MacCallum Cancer Institute in Melbourne, Victoria under the supervision of Prof. Ricky Johnstone.

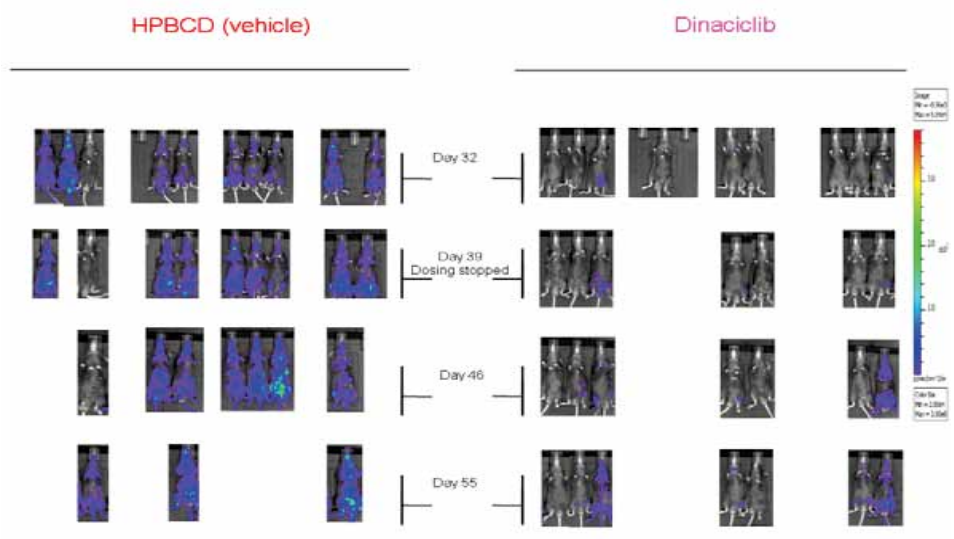
PhD results for the first 2 years of candidature to date:

The aim of this project is to identify key molecular targets for the treatment of acute myeloid leukemia (AML) driven by mixed lineage leukaemia-AF9 (MLL-AF9) mutation. AML accounts for approximately 25% of all leukaemias in adults of the western world and MLL has been found 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, paediatric and adult acute leukaemic patients are characterised by distinct genetic rearrangements of the MLL gene. MLL has been found in 73 different translocations and 54 partner genes. Only 6 frequent partner genes constitute 85% of all clinical cases of MLL, one of which is mixed lineage leukemia-AF9 (MLL-AF9).

MLL-AF9 is capable of leukemic transformation and disrupting cell cycle regulation thus driving the survival of leukemia. We have produced mice that develop acute leukemia driven by MLL-AF9 +/- the oncogenic driver NRAS representing two tumour models identified in humans. These mice were utilised to study the oncogenic potential and key molecular targets for novel therapies. In collaboration with Merck, Dinaciclib (SCH 727965) has proven to be a superior pan cyclin-dependent inhibitor with low nanomolar potency against CDK9. We have found that this compound is highly cytotoxic to the leukemic cells in comparison to conventional chemotherapies and recently published therapies for this disease. The compound shows effective anti-proliferative activity in the tumours and inducing cell death at very low concentrations.

In the luminescence image below the MLL-AF9 tumor can be tracked over time for progression and development of disease. Colours from blue to light blue represent a heavy tumour burden. Comparing the mice that were given the vehicle drug (HPBCD) to those dosed with Dinaciclib, a marked decrease in tumor burden is evident in those mice (mice in the right panel). Dinaciclib is proving to be a possible novel therapy for MLL-AF9. Over the next 12 months further studies will include human primary cell studies and biochemical analysis to understand the exact cause of cell death and mechanism of action and core essential genes required for successful therapy. Upon this we hope to publish in a high impact paper.



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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