



## RACP Foundation Research Awards

### FINAL REPORT

<b>Project / Program Title</b>	Molecular classification of aggressive non-Hodgkin lymphoma: Translating gene expression profiling technology into clinical practice	
<b>Name</b>	Dr Grace Gifford	
<b>Award Received</b>	2017 Arnott Research Entry Scholarship	
<b>Report Date</b>	19 March 2018	
<b>Chief Investigator / Supervisor</b>	William Stevenson	
<b>Administering Institution</b>	Sydney University; School of Medicine	
<b>Funding Period</b>	Start Date:	5 March 2017
	Finish Date:	2 March 2018

#### PROJECT SUMMARY

My project demonstrated that state of the art molecular diagnosis is usable to improve the diagnosis of this common and aggressive lymphoma in adults. I reported the use of very small biopsies and bone biopsies for digital gene expression profiling. The technique was accurate and reproducible, and able to identify poorer prognosis subtypes with inferior clinical outcomes.

Gene expression signatures that correlates with poorer survival in the cohort were selected for further study in lymphoma cell lines. Certain metabolic pathways relating to abnormal energy consumption and utilization have been assessed. This relates to a cancer's need to provide energy to sustain its malignant growth. Variation to a lymphoma's available energy source may improve the effectiveness of anti-cancer drugs.

#### PROJECT AIMS / OBJECTIVES

Identification of pathways aberrant in poorer prognosis lymphoma: statistical analysis on primary lymphoma samples

Variation in the lymphoma environment: cell lines were cultured in reduced oxygen, reduced serum and/or reduced glucose environment. Effect on cell growth, inhibitors (cytotoxicity and cell cycle) assessed.

#### SIGNIFICANCE AND OUTCOMES

This project adds new knowledge to clinical and laboratory haematology. Results are summarized as follows:

- 1) Genotyping small core biopsies with locally developed protocol are reproducible, accurate and have good internal consistency. Most patients in Australia do not have excisional biopsies for diagnosis, and archival tissues surmount referral biases from rural/regional centres.
- 2) The ABC subtype had an inferior OS (log-rank =7 .01, P=0.029), a 6.1 times increased risk of death (95% confidence interval 1.2 to 31.5, P=0.03), with death occurring early (25% by 2.9 years). Cure for this subtype represents an unmet clinical need - future prospective trial is underway pending HREC approval and funding
- 3) Gene expression correlates with clinical outcomes: Relapse in the primary lymphoma cohort was associated with higher expression of genes including LDHa and HIF1a. Results such as these are now further explored using cell line manipulation focusing on drug-able targets.
- 4) Gene expression profiling using trephine biopsies is feasible. My project is the first to publish this (British Journal of Haematology, February 2017); it is anticipated that this will become an invaluable source for diagnostics in the future
- 5) Variation in the lymphoma environment and available bio-energetic resource can tremendously modulate the effect of inhibitors - both novel and 'traditional' cytotoxic chemotherapeutic agent. How this is translated into clinical practice will require elucidation of specific metabolic pathways that are particularly subverted in lymphomas to minimize the effect on healthy/non-malignant tissues.

#### **PUBLICATIONS / PRESENTATIONS**

Abstract: Haematology Society of Australia and New Zealand, annual meeting, Melbourne October 2016

Publications:

Gifford G, Gill A, Stevenson W. Molecular subtyping of diffuse large B-cell lymphoma: update on biology, diagnosis and emerging platforms for practising pathologists. Pathology. January 2016

Gifford G, Gabrielli S, Gill A, Greenwood M, Wong K, Best G, Novell D, McIlroy K, Kliman D, Ilmay-Gillespie L, Tiley C, Miranda S, Armytage T, Stevenson W. Lymphoma cell-of-origin assignment by gene expression profiling is clinically meaningful across broad laboratory contexts. British Journal of Haematology. February 2017

Kea no C, Tobin J, Francis S, Gifford G et al. Digital multiplex gene expression shows that the adverse prognosis of EBV-positive Diffuse Large B-cell Lymphoma is independent of Cell-of-Origin, and is influenced by the tumor microenvironment. Manuscript submitted 2018.