



RACP Foundation Research Awards

FINAL REPORT

Project / Program Title		Gene expression profiling of high grade B-cell lymphomas with NanoString nCounter technology. Validation of a novel diagnostic platform and implementation into clinical use for prognostication and therapeutic decision-making.
Name		Dr Grace Gifford
Award Received		2016 Arnott Research Entry Scholarship
Report Date		29 March 2017
Chief Investigator / Supervisor		A/Prof William Stevenson
Administering Institution		The University of Sydney
Funding Period	Start Date:	8 March 2016
	Finish Date:	4 March 2017

PROJECT SUMMARY

My project improves current diagnosis of a common, aggressive form of non-Hodgkin's lymphoma, diffuse large B-cell lymphoma (DLBCL). While cases of this disease may appear the same under the microscope, they are in fact tremendously diverse at the genetic level. These variations result in the divergent outcomes of cure or relapse/death, the latter accounting for up to 30-40% of all DLBCL patients. Despite of being clinical importance and well known for almost two decades, advancing genetic diagnosis for DLBCL in the clinic has been slow due to predominantly technical and financial challenges.

To date, I have shown that that state of the art molecular diagnosis can be deployed in the Australian setting. The project was the first to report using very small biopsies and bone biopsies for digital gene expression profiling. Genetically based subclassification of an aggressive form of lymphoma was performed. There is a subtype that is associated with a much poorer overall survival with standard multi-agent chemo-immunotherapy. The results should be encouraging to clinicians who face resource limitations as novel genetic based diagnosis is now available to the clinic. These paves the way for precision therapy to improve cure in aggressive lymphomas.

PROJECT AIMS / OBJECTIVES

- 1) cell of origin (COO) assignment for DLBCL on the nanoString nCounter system
 - COO classification was possible for 96% of study samples using a locally adapted protocol
 - there is a statistically significant survival difference between the 3 COO subgroups

2) use gene expression signatures that relates to poor survival in patients on in vitro lymphoma cell lines

- certain pathways have clinically significant effects and are in the process of being validated in cell lines

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 $\chi^2=7.01$, $P=0.029$), 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

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, Nevell 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