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FINAL REPORT

Project / Program Title		Immunosuppression and Non-Melanoma Skin Cancer in Renal Transplant Recipients
Name		Dr Michael Thomas Burke
Award Received		2015 Jacquot Research Entry Scholarships in Nephrology
Report Date		26 August 2018
Chief Investigator / Supervisor		Associate Professor Nicole Isbel
Administering Institution		PA Research Foundation
Funding Period	Start Date:	1 February 2015
	Finish Date:	1 February 2016

PROJECT SUMMARY

Australian kidney transplant recipients have a twenty times greater risk of developing skin cancer compared with the general population. When skin cancer does develop in transplant patients the surgical results can be disfiguring and, if not detected early, these cancers can be fatal. Skin cancers develop secondary to both past sun exposure and the unwanted side effects of transplant medications on the skin. This project examined how genetics influences the risk of transplant drugs causing skin cancer, whether statistical evidence supports claims of an anti-cancer effect for specific transplant medications and evaluation of the molecular and immune pathways by which certain immunosuppressive medications may influence the risk of skin cancer.

PROJECT AIMS / OBJECTIVES

Study 1) To identify predictors for the development of Non Melanoma Skin Cancer by assessing the association between post transplantation NMSC and:

- Immunosuppressive drugs (type, exposure and clearance)
- Pharmacogenetic factors that influence immunosuppressant drug exposure, immunosuppressant effects and the immune response
- Traditional risk factors- sun exposure, smoking and time since transplantation

Study 2) To determine whether sirolimus acts to reduce NMSC by inhibiting the genetic expression of specific BCL-2 proteins important in apoptosis resistance (Published).

Study 3) To determine the proportion and predictors of fatal NMSC in KTRs

Study 4). To determine how different immunosuppressive drugs affect numbers of T-cell subset populations in renal transplant recipients. (Published)

SIGNIFICANCE AND OUTCOMES

Study 1 when completed will inform predictors for the development of keratinocyte cancer (KC) in renal transplant recipients by assessing the association between post transplant (KC), traditional skin cancer risk factors and immunosuppressive drugs and pharmacogenetic factors.

Study 2 showed differences in the expression of BCL-2 molecules in skin cancers depending on the type of immunosuppressant treatment used in a renal transplant recipient . The BCL-2 family of molecules are important in regulating apoptosis and may be a target for future therapies aimed at treating skin cancers in transplant recipients.

Study 3 reported on Non Melanoma Skin Cancer in Kidney Transplant Recipients and showed that skin cancer is an important contributor to mortality in renal transplant recipients, particularly Caucasian males. In descending order of frequency, squamous cell, basal cell and Merkel cell carcinomas represent the most common types of NMSC causing death. Results from this study help risk stratify patients and direct the screening for skin cancer in kidney transplant recipients.

Study 4 Demonstrated that immunosuppressive drug class and sun exposure modify the abundance of multiple T-cell subsets in the skin of KTRs. Correlation analysis revealed that the prevalence of T reg cells in KTR blood does not accurately reflect the prevalence of Tregs in KTR skin. This is the first study to examine the validity of performing flow cytometry in peripheral blood to predict tissue specific immune phenotype. Immune cell populations in skin weere shown to be influenced by both sun exposure and patients' immunosuppressive treatment.

PUBLICATIONS / PRESENTATIONS

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3. Jiyad Z, Olsen CM, **Burke MT**, Isbel NM Green AC. Azathioprine and Risk of Skin Cancer in Organ Transplant Recipients: Systematic Review and Meta-Analysis. American Journal of Transplantation. 2016 Dec; 16(12): 3490-3503.
4. **Burke M,** Morais C, Oliver K, Lambie D, Gobe G, Carroll R, Staatz C, Sinnya S, Soyer P, Winterford C, Haass N, Campbell S, Isbel N. Expression of Bcl-xL and Mcl-1 in the Non-Melanoma Skin Cancers of Renal Transplant Recipients. American journal of clinical pathology. 2015 April; 143; 500-504.
5. **Burke MT**, Isbel N, Barraclough JA, Jung JW, Wells JW, Staatz CE. Genetics and nonmelanoma skin cancer in kidney transplant recipients. Pharmacogenomics. 2015 Jan; 16(2): 161-72.
6. Jung JW, Overgaard NH, **Burke MT**, Isbel N, Frazer IH, Simpson F, Wells JW. Does the nature of residual immune function explain the differential risk of non-melanoma skin cancer development in immunosuppressed organ transplant recipients? Int J Cancer. 2016 Jan 15; 138 (2): 281-92.