PERIOCULAR MALIGNANCY AND EYELID RECONSTRUCTION

A thesis submitted for the degree of Doctor of Philosophy

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DEDICATION

To my parents, Kim and Eileen, and my husband Chris.

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ABSTRACT

Non-melanoma skin cancer is the most common cancer in Australia. Basal cell carcinoma and squamous cell carcinoma are the two most frequently encountered types of non-melanoma skin cancer, and together they make up over 90% of all skin cancers. The periocular region is involved in 10% of cases and is associated with significantly more disease-related morbidity due to the local effect of both the disease and the surgical treatment on ocular adnexa. Therefore, it is imperative that high-risk tumours are correctly identified to ensure appropriate management and surveillance. Surgical excision remains the gold standard treatment but functional reconstruction of the eyelid represents an ongoing challenge. Despite the wide range of autologous and artificial eyelid substitutes, there is yet to be an ideal replacement for the specialised eyelid tissue called the tarsus. The tarsus is responsible for both structural support and physical form, making its adequate substitution fundamental to functional outcomes. Numerable uncertainties remain regarding the staging and management of periocular non-melanoma skin cancer which, combined with our lack of ideal eyelid tarsus substitutes, represents the basis for work undertaken as part of this thesis.

Previous studies contributing to our knowledge of periocular basal cell carcinoma histological subtypes and treatment of invasive disease are first reviewed in Chapter 2. Chapter 3 subsequently summarises our understanding of periocular squamous cell carcinoma with a particular focus on the utilisation and prognostic role of the most up-to-date American Joint Committee on Cancer (AJCC) staging system for the eyelid carcinoma.

In order to determine the required properties for the ideal tarsus tissue substitute, Chapter 4 analyses the normal biomechanical properties of the eyelid tarsus tissue. This study, the first of its kind for human tarsus tissue, provides a benchmark for bioengineering studies described in the following chapter. In Chapter 5, we describe the development of a novel bioengineered three-dimensional scaffold which is tailor-made to behave biomechanically like natural tarsus. In order to improve *in vivo* compatibility, we also successfully cultured fibroblasts from eyelid skin samples which were then seeded onto our bioengineered scaffolds, the results of which are described in Chapter 6.

Finally, insights into the presentation, staging and management of periocular basal cell carcinoma and squamous cell carcinoma, along with our novel bioengineered eyelid tarsus substitute are placed in the context of the previous literature in Chapter 7, before possible directions for future studies are discussed in Chapter 8.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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PUBLICATIONS AND PRESENTATIONS

Chapter One

1. Review: Sun MT, O'Connor AJ, Wood J, Casson R, Selva D. Tissue Engineering in Ophthalmology: Implications for Eyelid Reconstruction. Ophthalmic Plastic and Reconstructive Surgery 2016 [epub ahead of print]
2. Review: Sun MT, Wu A, Figueira E, Huilgol SC, Selva D. Management of periorbital basal cell carcinoma with orbital invasion. Future Oncology 2015;11:3003-10.
3. Manuscript: Wu A, Sun MT, Huilgol SC, Madge S, Selva D. Histological subtypes of periocular basal cell carcinoma. Clinical and Experimental Ophthalmology 2014;42:603-7.
4. Manuscript: Herbert HM, Sun MT, Selva D, Fernando B, Saleh G, Beaconsfield M, Collin R, Uddin J, Meligonis G, Leatherbarrow B, Atuallah S, Irion L, McLean C, Huilgol S, Davis G, Sullivan T. Merkel Cell Carcinoma of the Eyelid: Management and Prognosis. JAMA Ophthalmology 2014 Feb;132(2):197-204.
5. Manuscript: Watanabe A, Sun MT, Pirbhai A, Ueda K, Katori N, Selva D. Sebaceous Carcinoma in Japanese Patients: Clinical Presentation, Staging and Outcomes. British Journal of Ophthalmology 2013 Nov;97(11):1459-63
6. Presentation: Sun MT, Herbert HM, Selva D, Fernando B, Saleh G, Beaconsfield M, Collin R, Uddin J, Meligonis G, Leatherbarrow B, Atuallah S, Irion L, McLean C, Huilgol S, Davis G, Sullivan T. Merkel Cell Carcinoma of the Eyelid: Management and Prognosis. Annual

Royal Australian and New Zealand College of Ophthalmologists Annual Scientific Congress 2013

7. Presentation: Watanabe A, Sun MT, Pirbhai A, Ueda K, Katori N, Selva D. Sebaceous Carcinoma In Japanese Patients: Clinical Presentation, Staging and Outcomes. Annual Royal Australian and New Zealand College of Ophthalmologists Annual Scientific Congress, 2013

Chapter Two

8. Manuscript: Sun MT, Wu A, Huilgol SC, Selva D. Accuracy of Biopsy in Subtyping Periocular Basal Cell Carcinoma. Ophthalmic Plastic and Reconstructive Surgery 2015;31:449-51.
9. Research Letter: Sun MT, Figueira E, Huilgol SC, Selva D. Minimum Histological Safety Margins in Periocular Basal Cell Carcinoma. British Journal of Ophthalmology 2014;98:706.
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Chapter Three

11. Manuscript: Sun MT, Andrew NH, O'Donnell B, McNab A, Huilgol S, Selva D. Periocular Squamous Cell Carcinoma: TNM Staging and Recurrence. Ophthalmology 2015;122:1512-6.
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Management and Prognosis. European Society of Ophthalmology Annual Congress, 2015

Chapter Four

13. Manuscript: Sun MT, Pham DT, O'Connor AJ, Wood J, Casson R, Selva D, Costi J. The Biomechanics of eyelid tarsus tissue. Journal of Biomechanics 2015;48:3455-9.
14. Presentation: Sun MT, Pham D, O'Connor A, Wood J, Casson R, Selva D, Costi J. The Biomechanics of Eyelid Tarsus Tissue. British Oculoplastic Surgical Society Annual Congress, 2015

Chapter Five and Six

15. Presentation: Sun MT, O'Connor A, Wood J, Casson R, Milne I, Biswa D, Selva D. Bioengineering Eyelids. Annual Royal Australian and New Zealand College of Ophthalmologists Annual Scientific Congress 2016