ASSC Australian Skin and Skin Cancer Research Centre

SCIENTIFIC MEETING 13 OCTOBER 2016
Session 2: Showcase Presentations

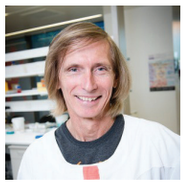
Dr David Wood

Postdoctoral Research Officer, Australian Centre for Ecogenomics, The University of Queensland

Title: A Natural History of the Actinic Keratosis Microbiome in Immunocompetent Men
Authors: David Wood, Richard Linedale, Nancy Lachner, Jean-Marie Tan, Stephanie Lim, Nicola Angel, Ian Frazer, Peter Soyer, Mark Morrison, Philip Hugenholtz

Significance: Cutaneous squamous cell carcinoma is one of the most common cancers in Australia and the identification of microbial taxa associated with AK, cSCC and non-lesional skin in some subjects aids in understanding disease pathology and may lead to the development of treatments.

Content: Human skin hosts complex resident bacterial and fungal microbial communities that differ between body site and individual. We applied culture-independent community profiling to longitudinally investigate the actinic keratosis (AK) and cutaneous squamous cell carcinoma (cSCC) microbiome in a cohort of ten immunocompetent men with a history of cSCC, and identified and isolated taxa associated with lesion and non-lesional skin.



Professor Nicholas Hayward

Head, Oncogenomics Laboratory and Deputy Coordinator of the Cancer Program
QIMR Berghofer Medical Research Institute

Title: The Australian Melanoma Genome Project

Significance: This is the first large study to survey the complete genomes of melanomas, giving 50 times more information than previous work which has focussed on the coding regions of genes. Many genes were found to have damaged control mechanisms and may be previously unsuspected drivers of melanoma.

Content: Cutaneous, acral and mucosal subtypes of melanoma were evaluated by whole-genome sequencing. The heavily mutated landscape of coding and non-coding mutations in cutaneous melanoma displayed signatures of known and novel ultraviolet radiation mutagenesis. In marked contrast, acral and mucosal melanomas were dominated by structural changes and mutation signatures of unknown aetiology, not previously identified in melanoma. The number of genes affected by recurrent, disruptive mutations to non-coding sequences was similar to that affected by likely driver mutations to coding sequences. Mutations affecting the TERT promoter were the most frequent of all, however neither they nor ATRX mutations, associated with the alternative telomere lengthening mechanism, were correlated with greater telomere length. Most melanomas had potentially actionable mutations, and most of these were in components of the mitogen-activated protein kinase and phosphoinositol kinase pathways.

Dr Orla Gannon

Post Doctoral Researcher, The University of Queensland Diamantina Institute

Title: What is the role of the epigenome in the control of squamous differentiation and squamous neoplasia.
Authors: Orla Gannon, Nicholas Saunders

Significance: Epigenetic regulation of gene expression is an important means by which transcription is controlled during development, malignancy and tissue homeostasis. We investigated several epigenetic marks in normal skin and SCC to discover novel differentiation genes and identify therapeutic targets.

Content: Using ChIP seq, we profiled the genome wide distribution of epigenetic marks H3K27me3 and H3K9me3. H3K9me3 demethylation marked a novel gene, DUX4, which had not previously been shown to be expressed in the skin. DUX4 causes cell death and we present evidence that it regulates processes in the final stage of squamous differentiation. In contrast, ChIP seq profiling of H3K27me3 in normal epithelial keratinocytes revealed that whilst EZH2 is important for expression of squamous differentiation genes, the specific genome wide localization of H3K27me3 does not influence gene expression. Paradoxically, inhibiting EZH2 overcame the differentiation block in SCC cells in vivo suggesting that targeting H3K27Me3 modifiers may have therapeutic potential.

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Professor David Whiteman PhD FAFPHM FAAHMS

Deputy Director and Group Leader, Cancer Control
QIMR Berghofer Medical Research Institute

Title: incidence, multiplicity and risk of keratinocyte cancer – an update from the QSKIN study.

Significance: The costs of diagnosing and treating basal cell carcinomas (BCC) and squamous cell carcinomas (SCC) are the highest of all cancers in Australia. However, information regarding incidence, multiplicity and risk are scarce as keratinocyte cancers (KCs) are not captured by most registries. To address these gaps, we initiated the QSKIN Study in 2010 recruiting 43,794 Queensland residents from a population register (participation 24%).

Contents: During the first three years of follow-up, 6936 (17%) participants had at least one KC excised; 1626 (4%) had 3 or more excisions. Of lesions with known histology, there were 9713 BCCs (in 4080 people) and 3505 SCCs (in 1782 people). We developed a tool to predict the risk of developing KC using backwards stepwise logistic regression models. The primary model retained terms for 10 items, including history of >20 prior skin cancers excised (OR 8.6), >50 skin lesions destroyed (OR 3.4), age >70 years (OR 3.5) and fair skin color (OR 1.8). Discrimination was high (Area under ROC 0.80, 95%CI 0.79-0.81) and the model appeared well calibrated. Among those reporting no prior history of skin cancer, a model with 10 factors (including age, sex, ethnicity and phenotypic factors) predicted KC events with reasonable discrimination (AUROC 0.72, 95% CI 0.70-0.75). The tool is undergoing external validation in primary care skin cancer clinics.

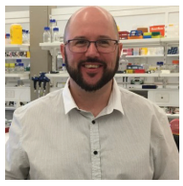
Professor Nikolas Haass MD, PhD, FACD

Head, Experimental Melanoma Therapy Group, President of the Australasian Society of Dermatology Research (ASDR), The University of Queensland Diamantina Institute

Title: Cell cycle-tailored targeting of metastatic melanoma: challenges & opportunities
Authors: Loredana Spoerri, Crystal A. Tonnessen, Kimberley A. Beaumont, David S. Hill, Russell J. Jurek, Sheena M. Daignault, Farzana Ahmed, Glen Boyle, Aaron G. Smith, Wolfgang Weninger, Nikolas K. Haass

Significance: Dynamic melanoma heterogeneity is defined by the co-occurrence of cancer cell sub-populations with distinct proliferative and invasive capabilities, which in turn reflect variable drug sensitivities, making their identification and characterisation crucial for the design of effective therapies.

Content: To better understand tumor heterogeneity within melanoma, cutting edge imaging technology and the fluorescence ubiquitination cell cycle indicator (FUCCI) system were employed to observe different phases of the cell cycle in real-time. Our data reveal that MITF is the key regulator of the dynamic proliferative and invasive behaviour of melanoma cell sub-populations and could therefore be utilised as a marker for tumour subpopulations that respond differentially to drug therapy.



Dr Matthew Law

Research Officer,
QIMR Berghofer Medical
Research Institute

Associate Professor Stuart MacGregor

Team Head, Statistical Genetics,
QIMR Berghofer Medical Research Institute

Title: Statistical genetics: A Swiss army tool for understanding melanoma risk and outcome

Significance: Whilst some melanoma risk factors are well understood, more needs to be uncovered, and gene mapping approaches will enable us to better understand the molecular aetiology of risk and outcome.

Content: We will discuss work we are undertaking to identify the germline contributions to melanoma risk through GWAS, prioritization of high risk families for sequencing, and functional characterisation of risk loci. We will also report on work identifying heritable contributions to melanoma survival, Breslow thickness, and treatment response. Finally we will explore how genetic data can help to determine which modifiable risk factors cause melanoma (mendelian randomisation).