Melanoma Institute Australia

RESEARCH RETREAT 2022

RESEARCH PRESENTATIONS

RESEARCH RETREAT 2022

We are delighted to be introducing you to this publication of our research presented at our annual Research Retreat, held at the Reg Richardson Auditorium at The Poche Centre and also online. The Research Retreat is an exciting and thought-provoking day in our annual calendar, where our research leaders, clinical researchers, early career fellows and PhD candidates present their current research to Melanoma Institute Australia staff, academic colleagues and representatives from our consumer advisory panel.

In this publication, we have 42 lay summaries of the research, stretched across all of our five research themes:

- Early Melanoma
- Advanced Melanoma
- Prevention, Risk and Clinical Detection of Melanoma
- Supportive Care and Survivorship
- Society, Policy and Economics

We hope and trust you will enjoy reading what our researchers are up to as we tackle many of the key critical questions that need answering, on our path towards zero deaths from melanoma.

Prof Georgina Long AO
Prof Richard Scolyer AO
Co-medical Directors, Melanoma Institute Australia

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THEME 1
EARLY MELANOMA

THEME LEADERS

Prof Richard Scolyer

Assoc Prof Sydney Ch'ng

This theme aims to:

- identify causes and drivers of melanoma
- determine the best management of early melanoma
- determine accurate prognosis
- improve accuracy of melanoma diagnosis.

Assoc Prof Alex Van Akkooi

International Multicenter Phase 3 Randomized Controlled Trial of NO Re-excision MelanomA (NORMA)

All new detected melanomas are treated by a 2-step procedure, first a narrow excision to find the correct diagnosis and important features, such as the thickness. After this, a second so called “wide local excision (WLE)” with 1 – 2 cm margins is performed. Studies looking at WLE have never shown any impact on survival. This, together with recent advances in drug developments for melanoma, make it that we propose that the ancient practice of WLE is no longer of any benefit for melanoma patients.

The International Multicenter Phase 3 Randomized Controlled Trial of NO Re-excision MelanomA (NORMA) aims to study if this WLE can now safely be abandoned. If successful, this study has the potential to spare thousands of patients unnecessary extra surgery and the associated side effects and save million in health care costs annually, not only in Australia, but worldwide.

Dr James Wilmott

InterMel Update

InterMEL is an international consortium of 12 centres with the goal of improving the accuracy of prognosis predictions for patients with stage II and III melanoma using molecular features of the tumour. Over 1000 primary melanomas have been tested, 43% from the Melanoma Institute Australia. The study has found that profiling the somatic mutations in the patients tumour’s DNA can improve the accuracy of prognostic models which identifies which patients are cured from those that are likely to have their disease return after surgery. Work is ongoing to add more genetic information into these prognostic models to further improve the accuracy of the prediction to better rationalise treatment for melanoma patients.

Dr Peter Ferguson

The ACEMID Cohort Study – refining (or redefining) the diagnosis of early melanocytic neoplasms

The diagnosis of early melanoma can be challenging for general practitioners, dermatologists and pathologists with compelling evidence of increasing rates of overdiagnosis, particularly of melanoma in situ. The NHMRC has awarded a clinical trial and cohort study grant for reconceiving the early detection of melanoma to A/Prof Victoria Mar and colleagues collaborating through the Australian Centre for Excellence in Melanoma Imaging and Diagnosis (ACEMID). This project will recruit 15,000 patients from metropolitan and rural Queensland, New South Wales and Victoria to undergo 3D total body photography and follow-up. The aim of the study is to standardise diagnosis, optimise risk-stratified surveillance strategies and patient outcomes. The pathological analysis will comprise standardised review of a projected 3,000 biopsies (including 2,000 melanomas), with each biopsy digitally scanned and scored by two independent expert dermatopathologists using correlation with the total body imaging to produce the most accurate diagnosis possible. Early results from a pilot study suggest that even in patients at high risk of melanoma, the majority of new and changing pigmented lesions are benign. This project will employ artificial intelligence (AI) to improve the accuracy and standardisation of clinical diagnosis to reduce the number of biopsies performed and to distinguish lesions at high risk of early melanoma. The richly annotated dataset with follow-up data will also enable AI analysis of the scanned histology slides to improve the accuracy and standardisation of the histological diagnosis of early melanoma.

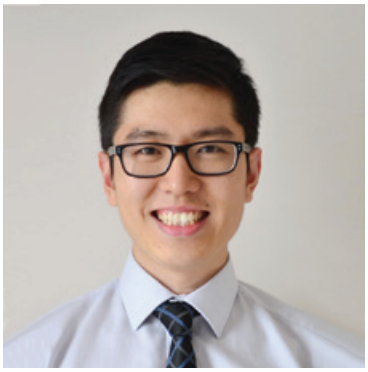
Assoc Prof Alex Varey

Survival calculators for Stage II melanoma

Thicker melanomas have increased risks of recurrence and death associated with them. If these thicker melanomas don't have evidence that they have spread to other sites in the body at the time of diagnosis, then they are classified as 'Stage II', where lower risk thinner ones are 'Stage I'. Recent advances in medical treatment for melanoma have shown that drugs that stimulate the immune system can significantly reduce the risk of recurrence for Stage II melanomas. However, we need to know which of these patients are at highest risk of recurrence and death so that they can decide whether the benefits of taking the drugs outweigh the risks of side effects associated with them. Accordingly, we have developed risk prediction tools that enable us to predict the risks of recurrence and death from any cause up to ten years from diagnosis for individual patients. Importantly, we have also shown that these models are reliable by validating them using two independent data sets from the USA and the Netherlands. Once published, these tools will be freely available on the MIA website for clinicians to use worldwide.

Dr Andrew Li

Clinicopathological comparison of cutaneous head and neck melanoma versus melanoma of other sites in the era of modern systemic therapy



Melanoma is increasingly recognised as a heterogeneous disease, particularly with the advent of immunotherapy and targeted therapy, which have revolutionised the treatment landscape for patients with metastatic disease. There is some evidence to suggest that melanomas arising from the head and neck region may represent a distinct entity compared with melanomas of other sites. Our study aimed to compare the clinical and pathological features and outcomes of head and neck melanoma with melanomas arising from other body sites in order to guide treatment decisions and further research directions. We compared all melanomas treated at MIA between 2000-2018, and additionally compared the subsets that were treated with targeted therapy and immunotherapy. We included approximately 13000 melanoma patients, and found that those with melanomas arising from the head and neck region were older and more likely to be male, and had tumours with worse pathological features at the time of diagnosis. They also had a shorter time to recurrence of their disease and shorter survival. However, amongst the subset of patients who received immunotherapy, the survival outcomes were reversed and head and neck melanoma patients had significantly better survival, even after accounting for other factors that are known to influence prognosis such as age, gender, and pathological features at diagnosis. These results suggest that head and neck melanoma may have unique biological behaviours compared with other melanomas. Further research is needed to elucidate the specific biological mechanisms that contribute to the distinct clinical features and outcomes of head and neck melanoma.

Dr Nigel Maher
Pathology Fellow

Classification and pathological features of melanocytic and non-melanocytic skin tumours

My research projects have included helping to establish a digital pathology workflow with an associated database with catalogued histopathological features. This database forms an easily searchable e-library of slides containing various melanocytic and non-melanocytic tumours, that will promote future research and teaching opportunities. Other projects have included analysing inter-rater reliability of basal cell carcinoma subtype classification and improving clinical information provided on request forms for primary pigmented skin tumours.

Dr Robert Rawson

Diagnostic utility of PRAME, p53 and 5-hmC immunohistochemistry for distinguishing melanoma for its mics

In a proportion of primary melanocytic tumours histopathologist face difficulties distinguishing benign naevi from subtle melanomas. There has been considerable development of ancillary tests to assist pathologists in this task over the last decade including a variety of molecular techniques. Immunohistochemistry offers a cheaper, more widely available and quicker technique to assist pathologists in every day analysis of melanocytic tumours.

This research focuses on the use of two recently described immunohistochemical stains, PRAME and 5-hmC, their diagnostic utility, both in isolation and in combination, to assist in the diagnosis of melanoma and naevi. Appropriate thresholds for a “positive” result were described and an algorithm created using both stains in combination which improves the sensitivity and specificity of the diagnosis of melanoma.

Dr Ismael Vergara

Elucidating the role of aneuploidy in primary cutaneous melanoma

Our previous work has shown that large genomic changes – aneuploidy – are a common feature of lethal melanoma. In fact, these changes are commonly present in primary disease at varying levels. In this work we sought to understand how these changes in primary melanomas can inform on the ability to predict recurrence and to better understand the biology of primary disease. Using a cohort of 100 primary cutaneous melanomas, we find that aneuploidy is higher in more proliferative and invasive disease. Specific genomic changes appear associated with the presence of important immune cells, suggesting these large changes may modulate the immune context. We also find that the presence of specific genomic changes can inform us on the ability of primary melanomas to recur, independently of important factors like thickness. Overall, these results suggest that aneuploidy may be an important mechanism by which tumour-immune interactions are modulated and can predict recurrence of patients with primary disease.

Grace Attrill
PhD Student

Assessing tumour-specific and bystander CD8+ T cells in relation to clinical outcomes in melanoma

CD8+ T cells are immune cells which are responsible for killing tumour cells. They can specifically recognise, target and kill cancer cells, and as such they are vital to the anti-tumour immune response which is boosted by immunotherapy. Recent studies have shown that not all CD8+ T cells in tumours can actually recognise cancerous cells – however, we don't know how to distinguish them from the ones that do.

I have been investigating a population of CD8+ T cells which we think could be the most potent tumour killers, using a technique which makes these cells fluoresce under a microscope. We found that this population is increased in the tumours of adjuvant anti-PD-1-treated stage III melanoma patients who remain recurrence-free after therapy, and that it's also increased in primary melanoma patients whose melanomas never recur following their primary melanoma resection. In our next experiments, we plan to confirm that this population can specifically recognise tumours and investigate its activity in the blood and tumours of melanoma patients.

Prof Omgo Nieweg

Sentinel lymph nodes in minor lymph node fields

Most sentinel lymph nodes are located in the neck, the armpit and the groin. These are the major lymph node regions. But there are also less-known minor nodal regions. Some of these were only discovered through sentinel node biopsy. These nodal regions contain just a few small lymph nodes. Occasionally, such a node is on a direct lymphatic drainage pathway from the melanoma and is then classified as sentinel lymph node. Large numbers of patients are required to assess the relevance of these nodes. So, an ideal project for a student at MIA.

We created two student projects. The first one concerned the popliteal cavity behind the knee joint. Scans showed such a sentinel node in 96 (4.5%) of 3902 patients with a melanoma below the knee. Their surgical removal was attempted in 54% of the cases. The procedure was successful in 82% of the cases but failed in the other 18%. A sentinel node was found to contain spread of melanoma in 14% of the patients in whom the procedure was successful and this was the only involved node in 9%. An involved popliteal sentinel node was associated with a reduction in the chance of a cure.

The other minor node field was the triangular intermuscular space, a wedge-shaped area on the back just on the outside of the shoulder blade. Scans showed a sentinel node here in 259 (12%) of all 2296 patients with a melanoma on the upper back. Biopsy was attempted in 57% of the cases. When pursued, the procedure was successful in 93% of the cases, but failed in 7%. A sentinel node was found to contain melanoma in 12% and was the only involved node in 8%.

Conclusion: Although sentinel nodes in minor nodal regions are uncommon and their removal can be challenging, biopsy is worthwhile, as it improves assessment of the extent of the disease, guiding subsequent management.

Dr Mike Russell

Melanoma and Breast Fellow

Accuracy of PET/CT in assessment of pelvic lymphadenopathy

Mike reported on the preliminary findings of a study looking at the accuracy of PET/CT in the assessment of pelvic lymph node basins. Analysis is still ongoing and is planned for publication at a later date.

Dr Caroline Asirvatham Gjorup

Surgical Oncology Fellow

Lymphoedema and recurrence-free survival

The aim of this retrospective study is to assess if there is an association between lymphoedema and patients' survival and recurrence outcomes. The altered tumour microenvironment and the impaired regional function of the lymphatics in areas of lymphoedema may lead to a different rate of recurrent disease, and pattern of recurrence, in patients with and without lymphoedema following lymph node dissection for metastatic melanoma. Prospectively collected data on patients treated for primary melanoma with axillary and/or inguinal or ilioinguinal lymph node dissection at MIA from 2002-2020 will be analyzed.

Dr Oliver Chow

Synchronous metastasis to two or more node fields confers a worse prognosis compared to N stage-matched single node field controls

The prognosis of metastatic melanoma varies widely in the literature with 5 year survival rates between 39-70% described.(1,2) Lymph node disease is staged by the American Joint Commitee on Cancer according to the number and extent of tumour involved regional nodes as well as the extent of regional metastasis that is non-nodal (satellite or in-transit disease). Presence of lymph node disease represents a key step in the treatment decision making pathway and may guide adjuvant therapies and further surgical intervention.

Our study aims to compare patients with lymph node spread in a single basin, to those patients with spread to two separate nodal basins. Our preliminary findings suggest that those with two basin involvement have more advanced melanoma and a worse prognosis by the metric of Melanoma Specific Survival (MSS). While ongoing, we hope our study can add to existing literature regarding lymph node spread of disease.

THEME 2
ADVANCED MELANOMA

THEME LEADERS

Prof Georgina Long

Prof Helen Rizos

This theme aims to:

- determine how best to treat melanoma that has spread or is locally advanced, for cure or long-term control
- predict treatment response.

Dr Russell Diefenbach

A serum miRNA signature of immunotherapy response

Biomarkers for melanoma patients on immunotherapy are lacking. Liquid biopsy provides a much less invasive tool for monitoring longitudinal response to immunotherapy than tissue biopsies. Profiling of serum miRNAs provides a relatively straightforward approach to identify biomarkers and requires only small quantities of biological material. In this study we have used next generation sequencing to identify serum miRNAs which strongly discriminate response to combination immunotherapy in advanced melanoma. Not only are these miRNAs potential biomarkers they also are likely to have a direct role in melanoma disease progression. Therefore, identification of miRNAs has the potential to drive downstream basic cell biology projects based on elucidating the mechanism of action of such identified miRNAs in the context of melanoma.

Dr Tuba Gide

Personalised Immunotherapy Platform study

While immunotherapies are the most effective therapy for these high mortality cancers, more than 50% of patients develop resistance and die of their disease. These treatments can also cause significant, life-altering side-effects. It is therefore critical to identify patients with low likelihood of response to standard (approved) immunotherapies and efficiently assess alternative novel immunotherapies. The Personalised Immunotherapy Platform (PIP) is designed to address these questions.

The PIP study has two stages: The first is PIP-PREDICT which involves the pilot implementation of a panel of predictive tests utilising clinical factors and different properties of the tumour in a clinical setting in order to identify the patients who will not benefit from the standard-of-care immunotherapies and require a novel clinical trial agent. The data generated will be entered into a biomarker patient report, detailing the likelihood of a patient's response to the standard immunotherapies and the suggested treatment based on their clinical and tumour profiles. A pilot study (open in March 2021) is ongoing in order to prospectively validate PIP-PREDICT model. The second stage of the study is to assess the effectiveness of five novel agents in treatment-naïve pts predicted to be resistant to either anti-PD-1 alone or combined with ipilimumab. A Bayesian adaptive multi-arm multi-stage design using response adaptive randomisation after a burn-in period where pts are randomised to the existing arms with equal probability. From then on, regular interim analyses will be carried out with the objective to either drop poorly performing arms or continue.

The current research program will change the way that cancer patients are treated and selected for clinical trials, by moving away from the one-size-fits-all approach to the use of a precision approach to deliver effective immunotherapies on a personal basis. This platform will increase anti-tumour responses, reduce drug-related side effects, and reduce costs to the health care system.

Assoc Prof Serigne Lo

Rebecca Simpson
PhD Student

Microbiome-immune interactions in checkpoint inhibitor immunotherapy

The microbes in our gut (microbiome) influence immune processes throughout the body. This includes how patients respond to immunotherapies. These therapies aim to reactivate a patient's own immune system to recognise and kill tumour cells. However, still, nearly 50% of patients with advanced melanoma die due to resistance. Furthermore, concurrent inflammatory side effects frequently cause severe morbidities, sometimes resulting in patients having to cease therapy.

My research looks at how diet and intestinal microbes influence the efficacy and safety of treatment. This study broadly breaks down into three overarching themes. First, the impact of the pre-treatment gut microbiome. How a patients microbiome profile prior to treatment influences response and toxicity development. Second, longitudinal changes in the microbiome and circulating immune cells during treatment. How immunotherapy impacts the microbiome and circulating immune profiles, and how these microbiome-immune dynamics influence treatment outcomes. And third, modulating the microbiome with diet to investigate the capacity of short term dietary changes to alter treatment efficacy or toxicity development using a pre-clinical mouse model. Together, understanding the interactions between diet, the microbiome and the immune system will inform the feasibility and design of dietary interventions in the clinic

Biology of Progression and Resistance Mechanisms

Dr Elena Shklovskaya

Durability of immunotherapy response: Lessons from the mouse

Immunotherapy achieves durable responses in advanced melanoma, with 20-50% of patients surviving 5 years or longer. To better understand the mechanisms of immunotherapy response and resistance, we have generated a new mouse model of melanoma responsive to immune checkpoint blockade. In this model, complete responses to single agent immunotherapy ranged from 40% to 60% while combining the two drugs helped achieve an even better response. Immunotherapy prompted the development of anti-melanoma immune memory that prevented disease recurrence, with discrete immune mechanism(s) underlying the protective effect of each drug.

Next, we plan to explore the known and novel mechanisms of immunotherapy resistance, as well as investigate new therapeutic combinations in our immunotherapy-responsive animal model.

For more information, see: Cancers 2022, 14(19), 4830; https://doi.org/10.3390/cancers14194830

Dr Ines Silva

Patterns of progression in immunotherapy

Historically, melanomas that spread to the brain (brain metastases) are associated with a poor prognosis, but advances in drug therapies and increased surveillance have improved the survival of these patients. Nevertheless, melanoma brain metastases are associated with significant emotional burden, and may require specific management and surveillance. We have developed a tool to predict the likelihood of developing brain metastases in patients at the start of drug therapy, and at 3, 6, 9 and 12 months thereafter. While this needs validation, this tool will help guide discussions with patients and may define appropriate surveillance.

Catherine Bai

PhD Student

Single-cell spatial analysis characterising tumour immune architecture of in-transit melanoma

Melanoma in-transit metastasis (ITM) is a type of locoregional metastasis where melanoma cells are deposited between the primary tumour and regional lymph node basin. Patients with ITM melanoma are classified as stage III cancer, where a form of immunotherapy drugs knowns as immune checkpoint inhibitors (ICI) are being increasingly used as a standard treatment.

Recent research shows that the cellular constitution, intercellular interactions and molecular signals within the tumour microenvironment (TME), which describes the local tissue encompassing the tumour and its immediate surroundings, can influence cancer progression and response to therapy. The TME of ITM melanoma is poorly characterised, hence the biology of ITM remains incompletely understood. We performed 40-plex PhenoCycler imaging on whole-tissue slides from 20 ITM melanoma patients treated with ICI, 10 biopsied at baseline and a further 10 biopsies on treatment at the time of progressive disease. Baseline ITMs that responded to treatment (RECIST CR/PR, n=6) had closely associated B cells, cytotoxic T cells and HLA-Ahigh melanoma cells at the invasive margin. Baseline ITMs from patients primarily resistant to ICI (PD, n=4), demonstrated inter- and intra-lesional heterogeneity in tumour phenotype and TME orchestration. Highly proliferative (Ki67+) tumour cells showed high effector cell (T, B and NK cells) exclusion via collagen IV deposition, while lowly proliferative tumour cells showed less immune recruitment. Alternate checkpoint receptors (LAG3, TIM3, ICOS, VISTA) were expressed on T cells in biopsies of progressive disease (PD, n=8), offering the possibility of novel drug combinations. Our results demonstrate patterns of immune cell recruitment, functional phenotypes and cellular neighbourhoods associated with therapy response and tumour progression in ITM melanoma patients treated with ICI immunotherapy.

Jordan Conway
PhD Student

The melanoma or the metastasis: Targeting liver specific immunotherapy resistance

For advanced metastatic melanoma patients, Immunotherapy, which aims to harness the immune system to fight the cancer has become the standard therapy option available. However, not all patients will respond and many will become resistant to treatment. In recent years it has been shown that the response to immunotherapy may be impacted by the organ site the tumour has spread to. Tumours that have spread to the liver in particular have been shown to be associated with a significantly reduced response rate to current treatment options.

Our research focuses on discovering the differences between sites of disease and the biology that underlies organ specific patterns of response and resistance. The aim of this research is to find new and more personalised treatment options for patients who are at risk of developing resistance. So far we have found that liver tumours are less immunogenic in that they have fewer immune T cells and have increased expression of the immune inhibitory marker TIM3. Sites such as the lung and lymph node however were shown to be more immunogenic in that they have an increased infiltration of T cells and have been associated with increased response rates.

We now aim to test some of our findings functionally by targeting TIM3 and other immunosuppressive factors in patient biopsies and other models to see if we can overcome the resistance of liver tumours.

Dr Jorja Braden
PhD Student

Translational Investigations of the NeoTrio Clinical Trial

Initial results of the translational investigations of the NeoTrio clinical trial have demonstrated unique histopathological characteristics of neoadjuvant combination targeted therapy and single agent immunotherapy compared to either modality alone. Such characteristics will be further investigated with a variety of scientific methods to explore such changes and their relationships with response or resistance to treatment.

Dr Camelia Quek

Single cell profiling to dissect novel immunotherapeutic resistance and progression in advanced melanoma

There is a current lack of knowledge in understanding why certain melanoma patients do not benefit from immunotherapy (anti-PD-1 or anti-CTLA-4), and how to extend its benefits to them. Combining anti-PD1 with anti-CTLA-4 has achieved a 58% response rate compared to anti-PD-1 or anti-CTLA-4 alone with respective response rates of 40% and 11%. Despite some success, 50% of patients still die from their disease due to either innate or acquired resistance. This study aims to better understand patients' resistance to treatment by dissecting and tracing individual tumour and immune cell clones. Innovative single-cell and computational methods will be used to identify actionable genes and proteins specific to mechanisms of immune control and escape. The expected outcomes from this project include identifying uncharacterised therapy-resistant clones and novel inhibitory and stimulatory checkpoint molecules. Discovery of such resistance mechanisms will enable therapeutic advancement to improve cancer survivorship and clinical care.

Dr Esther Lim

Single cell sequencing to uncover heterogeneity in melanoma response to treatment

Melanoma patients can be treated with molecular inhibitors and/or immune therapy. The timing of these therapies can influence response to subsequent treatments. In our study, we aimed to understand the features that modulate response to molecular inhibitors.

Tumour biopsies from melanoma patients were excised and processed into cell suspensions, then treated with molecular inhibitors. The cell suspensions were analysed to examine the effects of the molecular inhibitors on the melanoma and immune cell populations. Cell suspensions were also single-cell RNA-sequenced to investigate the effects of treatment in more depth. Several melanoma cell states were identified, with each state showing varying responses to molecular inhibitor treatment. For instance, the proportion of some melanoma cell states reduced while others increased after treatment. Moreover, one distinct melanoma cell state was enriched in a tumour biopsy that did not respond to molecular inhibitors. These findings indicate that melanoma cells show heterogenous responses to treatment, with some more susceptible to treatment while others may be more resistant.

Dr Dario Strbenac

Bioinformatics in the Single Cell Era

Until recently, it has only been possible to measure cancer tissue as a mixture, analogous to fruit smoothie in which the components are ambiguous. But, in the new single cell era, the genes expressed in cancer can be measured at unprecedented resolution of individual cells, analogous to a fruit salad. Researchers at the Sydney Precision Data Science centre, based at University of Sydney, have developed two companion software named scFeatures and ClassifyR to allow researchers to more easily make sense of this newly available level of detail. scFeatures allows comprehensive and efficient summarisation of the data into various biologically-meaningful views, such as genes, gene sets, and cell-cell interaction scores, which may provide better predictions of patient outcome than has traditionally been possible. ClassifyR, a software previously developed for the bulk cell analysis, has been extended with multi-view modelling, allowing researchers to address questions like which data type or combination of data types are most predictive. Future work involves the incorporation of a multi-tiered decision tree algorithm, which will allow the analyst to explore trade-offs between monetary cost of experimental assays and predictive accuracy. In summary, scFeatures and ClassifyR allow researchers to look at melanoma omics data from novel angles and identify novel biomarkers of patient outcomes.

Immunotherapy Toxicity

Dr Piyush Grover

Medical Oncology Fellow

Tik TOX

Immunotherapy drugs activate the immune system to hijack key cellular signalling pathways in melanoma growth. Immunotherapy toxicity is common, significant and impacts anti-cancer treatment (treatment interruption, discontinuation and/or necessitating need of other medicines to treat the toxicity). However, predicting toxicity is an area of unmet need and is the cornerstone of discussion in risk/benefit assessment. We are investigating facets of immunotherapy toxicity.

Assoc Prof Mainthan Palendira

Toxicities in Immunotherapy: lessons from the gut and plans for the future

Immune-related adverse events are a major hurdle to the success of immunotherapy and yet little is known about the mechanisms that cause them. We have examined both systemic and tissue-specific immune changes induced by combination anti-CTLA-4 and anti-PD-1 immunotherapy, to understand the immunological events that are associated with severe colitis. We found distinct changes to patient's immune profile in those who developed moderate-severe colitis irrespective of their anti-tumour response status. We also found significant differences to the innate immune profile of these patients prior to the commencement of immunotherapy. By comparing both endoscopically and histopathologically normal and inflamed regions of colon, we found specific immune cell expansion in areas of inflammation. Together our data shows specific immune populations are associated with the development of combination therapy-induced severe colitis. On-going studies will examine the potential pathways that could be targeted to treat these adverse events without compromising tumour control mechanisms.

Dr Chris Muir

Thyroid irAEs

Thyroiditis (inflammation of the thyroid gland) will affect up to 50% of patients during immune checkpoint inhibitor treatment for melanoma. Risk factors for thyroiditis include younger age, female sex and combination anti-CTLA-4/PD-1 checkpoint inhibitor treatment. Although in most cases there will be no symptoms, 25% of patients who experience checkpoint inhibitor associated thyroiditis will develop permanent hypothyroidism (underactive thyroid) requiring lifelong treatment with thyroid hormone replacement.

Patients who develop thyroiditis are at increased risk for developing checkpoint inhibitor related toxicity in other organs. However, despite increased rates of immune checkpoint related side effects, patients who develop thyroiditis are more likely to respond to immune checkpoint inhibitor treatment and have improved survival compared to patients that do not develop thyroiditis as a side effect of their treatment.

THEME 3
PREVENTION, RISK AND CLINICAL DETECTION

THEME LEADERS

Assoc Prof Linda Martin

Prof Anne Cust

This theme aims to:

- understand the causes of melanoma, and how to better prevent, detect and monitor it.

Kate Dunlop
PhD Student

Acceptability of risk-tailored melanoma screening: qualitative interviews with key informants

There is insufficient evidence to recommend national population melanoma screening. Risk-tailored screening aims to provide personalised screening tailored to individual risk targeting those who benefit most. We aimed to explore the views of key informants on the acceptability of risk-tailored melanoma screening and to identify barriers and facilitators to inform future implementation. Acceptability is crucial, as successful implementation will require those at low risk to screen less frequently or forgo screening altogether. Semi-structured interviews (n=36) were conducted with key informants including consumer advocates; clinical experts; policy makers; and researchers with expertise in this area. Data were analysed using a framework.

Preliminary findings suggest there is broad support for risk-tailored melanomascreening in the population. Clear messaging to the community and cost-benefit analysis were seen as important. However, key informant groups differed in how they felt about the evidence needed, compatibility with current practice and the nature of the intervention. These concerns will need to be addressed to enable successful implementation of a risk-tailored melanoma screening program.

Dr Bruna Gallo
Dermatology Fellow

Changing melanocytic naevus during pregnancy: physiologic or pathologic?

Melanoma is the most common malignancy reported during pregnancy in Australia and some other countries. We conducted this study to analyse the changes on naevus during pregnancy.

We compared all the lesions of the pregnant group with their biologic sisters as control group. The digital images were rated according to various dermoscopic parameters over a period of 3 months.

The conclusion was: naevus change during pregnancy. As expected, most of the changes were seen mainly on the abdomen but all the body parts presented with changes. And most importantly, all the changes were classified as physiologic and no melanoma was found.

Dr Bruna Gouveia
PhD Student

Invasive component on Lentigo Maligna lesions – how can confocal help?

Lentigo maligna is the most common type of Melanoma in Australia and it is crucial to differentiate early from invasive stages to be able to manage the patient properly. In this research project, we use a specific technology called Reflectance Confocal Microscopy. It is an imaging tool with cellular resolution that is now helping to find the areas suspicious for invasion. With it, we will be able to detect earlier the melanoma lesions that are progressing and treat them properly. The study is now on data collection phase so cases suspicious for invasive component are more than welcome for further confocal assessment.

Dr Genevieve Ho

Remote image acquisition and reflectance confocal microscopy an update

Reflectance confocal microscopy (RCM) is a non-invasive diagnostic tool that allows visualisation of the skin at a cellular level. Despite evidence supporting its accuracy, uptake and use in Australia has been relatively slow compared to USA and Europe. Potential barriers to uptake and implementation of reflectance confocal microscopy (RCM) in Australia were first explored. The results of a survey of 14 clinicians with interest and involvement in the field. Perceived barriers ranged from lack of training, few experts, lack of Medicare item number, current deficits in reporting and standardisation and infrastructure limitation. Addressing the issue of geographical barriers and few experts is a model of remote image acquisition where RCM is imaged and read asynchronously. Diagnostic accuracy parameters and implementation outcomes of such a model will be measured, and this study is currently underway and recruiting. Finally, an international expert recommendation has been developed to guide image acquisition in RCM in the hopes of standardising and assuring quality in image acquisition, and to aid future international collaborations

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Gillian Reyes-Marcelino

PhD Student

Incremental value of risk factors identified from 3D total-body imaging on melanoma risk prediction tools

Several risk prediction tools have been developed to estimate risk of developing melanoma, including those for first and subsequent melanoma on the MIA risk tool website. Most risk prediction estimates are based on self-reported risk factors, and do not include objective skin phenotype measures. The aim of this project is to determine the incremental value of risk factors identified from 3D total-body imaging on the performance of melanoma risk prediction tools.

To address this question, I will use data from the Mind Your Moles study and Health Outcomes project led by Professor Soyer and Professor Janda's team at the University of Queensland. Subsequently, I will use data from the ACEMID study and the IMAGE trial, which are running across multiple sites including MIA. I will examine the incremental value of 3D total-body measures on the predictive performance of both the first and subsequent primary melanoma risk tools. I will assess the predictive performance using measures of discriminatory accuracy, such as the area under the curve and net reclassification index, and calibration and net benefit.

The expected outcomes from this project are the availability of new, more accurate risk prediction tools for first and subsequent primary melanoma that incorporate measures from skin imaging technologies. The findings will also be incorporated into a microsimulation model for a national risk-stratified melanoma screening and surveillance program that our team is building (with separate NHMRC funding).

Prof Pascale Guitera

Highlights from New York

I presented 4 studies or future collaborations with the Memorial Sloan Kettering Cancer Centre:

1- Adapting artificial intelligence (AI) to small and new melanoma that are featureless. (recruiting)

2- Ai for triage: models have been developed to help with human error, lack of skills in particular in front of the enormity of the data or lack of availabilities. Most efforts are focusing on lesion-based diagnosis and mostly dermoscopy images (a magnifying glass with polarised light) but it implies someone has the skills to choose the lesion of concern and use specific tools. In order to address this, we will focus on large field images to screen for melanoma, adding patient level context and go all the way to a reliable diagnosis of melanoma based on any mobile photographs. (USA Department of defence grant application)

3- Non-invasive biomarkers: Early diagnosis of melanoma leads to higher patient survival. However, efforts targeted at early diagnosis can also lead to biopsies of millions of benign pigmented lesions and of some in-situ melanomas that may never progress to invasive melanomas. The ultimate outcomes of melanoma depend on growth patterns that are tumor and tumor environment dependent. While the biology associated with invasion and metastasis has been extensively studied, early stages of progression in melanocytic development and transition to invasive disease has not been elucidated. Sequential dynamic studies would help dissect temporal changes associated with early neoplastic progression. (NIH grant application)

4- EX Vivo confocal microscopy is a microscope that allows diagnosing tissue directly in the theatre simplifying and accelerating the pathology diagnosis to help in immediate diagnosis and margins assessments.

Prof H Peter Soyer

ACEMID and related NHMRC projects

The Australian Cancer Research Foundation (ACRF) funded Australian Centre of Excellence in Melanoma Imaging & Diagnosis (ACEMID) is setting up a network of fifteen 3D total body imaging systems in Queensland, New South Wales, and Victoria, with the aim of improving the early detection of melanoma. Eight imaging systems have been installed to date and they will be used to conduct the ACEMID Cohort Study. This research study will collect and link imaging, patient-reported, and clinical data from 15,000 participants over three years, providing a large research database to study the biologic ecosystem of pigmented skin spots over time.

Additional research funding has been obtained by the ACRF ACEMID team to support and expand the project's research activities. This includes the Skin Imaging & Precision Diagnosis research program which will allow the team to explore a range of additional technologies to use with 3D total body imaging. These include non-invasive biopsy methods and next-generation computer algorithms to support clinicians in assessing skin spots and determining the best treatment options. The team also obtained funding for a program of research towards Melanoma Screening which will answer key questions about who needs skin screening and how often people should be screened. This research will work out the best way for a potential National Screening Programme to occur.

More details and full list of investigators in NSW, VIC and QLD can be found here: https://acemid.centre.uq.edu.au

Prof Monika Janda

THEME 4
SUPPORTIVE CARE AND SURVIVORSHIP

THEME LEADERS

Assoc Prof Robyn Saw

Dr Iris Bartula

This theme aims to:

- embed psychosocial support in routine clinical care of melanoma patients and survivors
- increase consideration of caregivers' support needs.

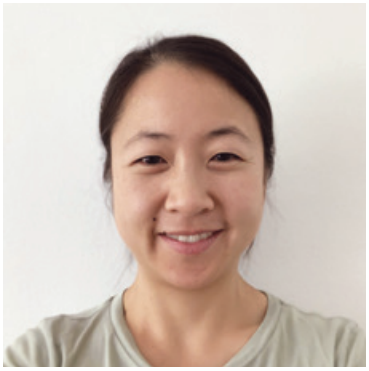
Jake Thompson

Health-Related Quality of Life in Patients with Melanoma Brain Metastases Treated with Immunotherapy

Historically, people whose melanoma had spread to the brain (known as 'brain metastases') only lived 4-6 months after diagnosis, with less than 15% alive at 12 months. However, the development of immunotherapies, such as nivolumab and ipilimumab, to treat advanced melanoma has resulted in more than 50% of patients being alive 5 years after diagnosis. With the effectiveness of these immunotherapies demonstrated in clinical trials, we wanted to examine the impact of these treatments on the quality of life of people with melanoma brain metastases. Using data from a clinical trial evaluating the effectiveness of immunotherapies in people diagnosed with melanoma brain metastases, this study investigated the impact that nivolumab, and nivolumab combined with ipilimumab, has on quality of life. We found that neither nivolumab alone, nor when combined with ipilimumab, had a negative effect on quality of life. Thus, this study provides further support for the use of these immunotherapies as a first-line treatment for melanoma brain metastases.

Dr Julia Lai-Kwon

Feasibility, acceptability and utility of a pilot nurse-led survivorship program for people with metastatic melanoma



People diagnosed with unresectable stage 3 and stage 4 melanoma are living longer because of effective treatments like immunotherapy and targeted therapy. We now know this group of people can face physical, psychological, and social difficulties from the treatment they have had. However, there are no programs to support this group of people. This study tested whether a nurse-led survivorship program (MELCARE) involving two, one hour phone appointments with a specialist melanoma nurse and the creation of a survivorship care plan is appropriate and helpful to people who are doing well on immunotherapy or targeted therapy.

31 people decided to participate. 30/31 people completed MELCARE. The nurse was able to deliver the program, spending around 90 minutes with each participant. The program was shown to be appropriate based on a 4-question survey. Around 80% of participants said MELCARE improved their overall satisfaction with their melanoma care. All the participants said they would recommend MELCARE to other people with melanoma. We also showed people's levels of distress reduced from the 1st appointment to the 2nd appointment.

We showed that MELCARE was appropriate and helpful to patients and may help them feel less distressed over time. We hope to run a larger study to offer MELCARE to more patients. We will also try to understand the best time in a person's melanoma journey to deliver the program, and the resources and costs associated with delivering this program. We shared these results at the European Oncology Nursing Society conference (EONS15), the Australasian Melanoma Conference and the Victorian Cancer Survivorship Conference.

THEME 5
SOCIETY, POLICY AND ECONOMICS

THEME LEADERS

Prof Rachel Morton

Assoc Prof Alex Menzies

This theme aims to:

- determine how health care systems, providers and government can best meet the needs of people with melanoma.

Dr Rashed Mahumud

The Precision Medicine HTA recommendations on melanoma diagnostics

The precision medicine health technologies and health technology assessments (HTA) recommendations on melanoma diagnostics are based on a case study of the ACEMID program.

Precision medicine (PM) technologies in the ACEMID Program

Novel precision medicine (PM) technologies for melanoma diagnosis in ACEMID programs are three-dimensional (3D) total body skin surface macro imaging; teledermoscopy (the patient photographs suspicious lesions using a smartphone dermatoscope attachment and sends the images to the clinician for remote diagnosis); scarless biopsy (tape stripping) reduces unnecessary excisions; and artificial intelligence (AI)-driven algorithms are used for lesion recognition and support for clinical decision making.

Evaluation of PM technologies by HTA agencies

The new PM technologies do not neatly fit into existing HTA frameworks. These PM technologies are adaptive and complex, continually building on new datasets to improve diagnostic sensitivity and specificity; they can stratify people into very small groups based on genetic or protein signatures, with potentially uncertain estimates of effect and wide confidence intervals.

Challenges in assessing value of new PM technologies

Challenges include the place of the new technology on the diagnostic pathway, the certainty of effectiveness and cost-effectiveness data, equity considerations, and the shelf-life of the evidence.

Recommendations for Australian Health Technology Assessment (HTA) agencies.

Six possible recommendations could be considered for HTA of PM technologies, including those advanced by the ACEMID consortium to deal with specific issues:

i) clarification of the intended position (or positions) of the diagnostic test in the clinical pathway, and assessment of the cost-effectiveness of each position (eg, triage, add-on, replacement), with estimates of the proportionate use in each position;

ii) Use of “base case” models that are updated with test performance characteristics (eg, sensitivity and specificity) as they learn and develop. These models could be created during AI algorithm testing, with preliminary inputs from software developers;

iii) Use of value of information analysis to determine whether meta-analyses could reduce the uncertainty in economic models associated with small denominators of subpopulations;

iv) Use of observational cohorts, indirect evidence comparisons, and registry data to assess comparative effectiveness where randomised trials are not possible;

v) Consideration of distributional cost-effectiveness analysis to provide an equity weighting, with a higher willingness to pay threshold if the technology can reduce inequities in access to dermatology or other specialist services and improve early detection among disadvantaged populations;

vi) Incorporation of patient and clinician preferences for imaging, biomarker or AI-assisted diagnoses, assessed through quantitative methods such as discrete choice experiments

This paper has already been published in the Medical Journal of Australia. https://doi.org/10.5694/mja2.51696

Dr Stephen Law

Long-term cost cost-effectiveness of a melanoma prevention program using genomic risk information compared with standard prevention advice in Australia

This study aimed to determine the lifetime cost-effectiveness of the program through a Markov model to prevent melanoma and keratinocyte carcinoma. Many melanomas and keratinocyte carcinomas are preventable by reducing sun exposure and improving sun protection behaviors. Recent evidence indicates a melanoma prevention program involving personalized genomic risk provision can reduce self-reported sunburns at 12 months in Australian adults with no history of melanoma. This was alongside genetic counselling and educational materials on skin cancer prevention and early detection. However, the economic impact of this approach remained unclear. We used data from the Melanoma Genomics Managing Your Risk Study Randomized Control Trial. Traditional risk was measured by a validated melanoma risk prediction model involving hair color, nevus density, history of non-melanoma skin cancer, family history of melanoma, level of sunbed sessions. Quality-adjusted life years (QALY) gained was used to estimate the incremental cost-effectiveness ratio (ICER) for a hypothetical cohort of 18-year-old adults. To test robustness of results, sensitivity analyses were taken.

Genomic risk provision targeting high-traditional risk individuals was a cost-effective strategy with an ICER of around AUD$35,000 per QALY gained , compared with standard preventive advice. A targeted genomic risk provision strategy to high-traditional risk individuals may be more cost-effective than promotion of daily sunscreen uses via generic public health messaging (ICER at AUD$40,890). The enduring effect of the intervention on sun protection behaviors should be investigated.

Ann Livingstone
PhD Student

Preferences for Adjuvant Immunotherapy in Patients with Resected Stage III Melanoma - A Discrete Choice Experiment

Ann reported on the preliminary findings of a study looking at preferences for adjuvant immunotherapy in patients with resected stage III melanoma. Analysis has been finalised, with publication in progress.

Notes

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