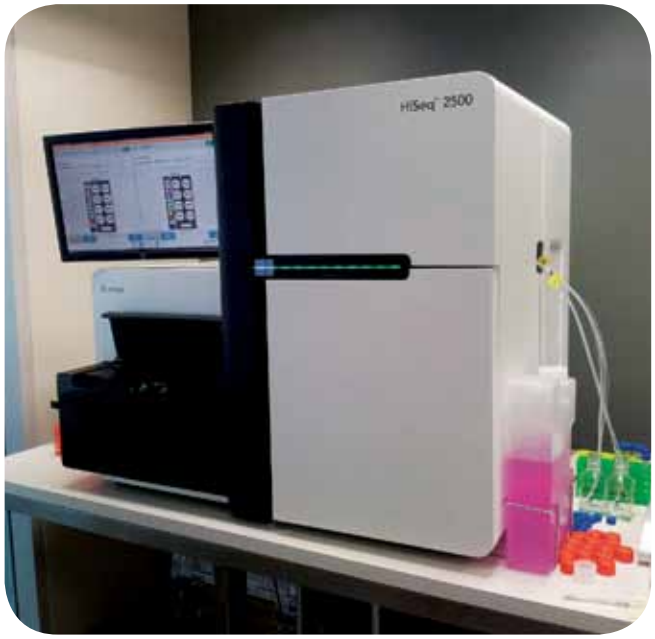


HiSeq2000 used to sequence genes from melanoma tissue samples

Melanoma Genomics

BRAF and NRAS are the most commonly mutated genes in melanoma, occurring in approximately 50% and 20% of melanomas respectively. Treatments targeting BRAF mutations within a melanoma have significantly improved patient outcome in recent years. Drugs targeting NRAS-mutant melanoma are also currently under investigation. By profiling the genetic landscape in a large number of melanoma tumours we show that melanomas that do not have a BRAF or NRAS mutations are a complex group, more commonly arising in sun-exposed sites and associated with severe sun exposure. Compared to tumours with BRAF or NRAS mutations, they have a high burden of mutations due to ultraviolet radiation-induced damage. It is likely that a number of genomic alterations are required for melanoma progression in this group. Drs Victoria Mar and Stephen Wong have described a number of genetic mutations in this group which may be suitable targets for new drugs and treatment approaches in the future.

Fast Facts

- Project began in 2009
- Major scientific collaboration
- Metropolitan and rural collection sites
- 1200 melanoma samples
- Oldest participant is 100 years
- Youngest participant is 18 years
- 63% participants are from Melbourne
- 33% participants are from rural Victoria
- 4% participants are from interstate
- 46% have blue eyes
- 55% have blonde or fair hair
- 52% have experienced severe sunburn
- 8% have used solaria
- 60 research publications
- 124 scientific presentations
- Linked to 9 clinical trials
- 1 public forum on tissue collection

The Melbourne Melanoma Project is supported by the Victorian Government through the Victorian Cancer Agency Translational Research Program

Peter Mac

Victorian Cancer Biobank

Victorian Cancer Agency

VMS Victorian Melanoma Service

LUDWIG INSTITUTE FOR CANCER RESEARCH

MELBOURNE MELANOMA PROJECT

March 2013

MMP Overview

Professor Grant McArthur (left) is the Chief Investigator of the Victorian Cancer Agency funded Melbourne Melanoma Project (MMP).

MMP is a collaboration of Melbourne's major metropolitan melanoma centres and one regional Victorian centre. The Victorian Melanoma Service at the Alfred Hospital, the Peter MacCallum Cancer Centre, the Ludwig Institute for Cancer Research at Austin Health and Border Oncology have collected 1200 primary melanoma specimens and associated clinical data to create an incredibly valuable research tool.

Scientists have been able to ask specific research questions regarding first time melanomas. MMP tissue samples have been interrogated under the microscope and tested for genetic changes. Some have been stained with dyes that reveal the presence of proteins that could be used as targets in future therapeutics. All of MMP's scientific data can be aligned to patient clinical information, such as eye colour and sunburn incidents, that is collected when people agree to donate their melanoma tissue to research.

MMP research has been widely reported in Australia and overseas and has made significant contributions to the understanding of this disease. From a research perspective it is a very exciting time to be working on melanoma.

Photo courtesy of Jerry Gallea Photography

Evaluating Genetic Instability

Dr Mark Shackleton (left) was awarded the 2012 ScienceMinister's prize for Life Scientist of the Year. The award was presented by the Prime Minister and Senator Chris Evans at Parliament House in October 2013.

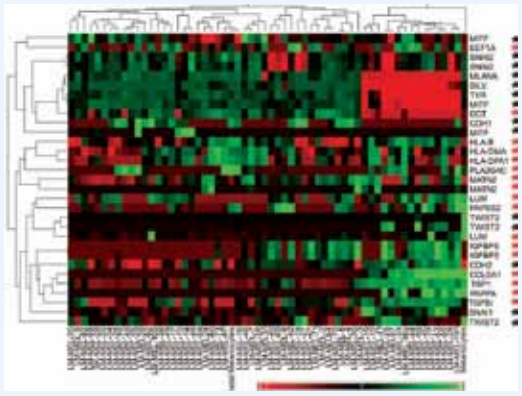
Tissue access via MMP has enabled the Melanoma Research Laboratory at Peter Mac, led by Dr Shackleton, to study fundamental mechanisms of melanoma progression in patients. Such studies lead to the discovery of new way of treating melanoma. For example, Dr Shackleton and colleagues discovered that one of the most important cancer-preventing proteins, p53, malfunctions in melanoma as a result of being inhibited by another protein, MDM4, which is expressed at high levels in most melanomas. Excitingly, it is possible to interfere with MDM4 using targeted drugs that should have the effect of re-activating p53 to stop melanoma growth – which is exactly what was seen.

Another aspect of MMP-enabled research in Dr Shackleton's lab is seeking to understand why melanomas frequently become resistant to drugs after a short period of time. The important findings are that a major hurdle to melanoma therapy is the ever-changing nature of this cancer, in which new gene mutations appear at an alarmingly high rate, even as melanomas are spreading or being treated. This work is now focused on understanding the basis of melanoma dynamism with a view to halting it so that other targeted therapies have a better chance of working.

Melanoma Consumer Reference Group

The Melbourne Melanoma Project has benefitted hugely from the involvement of a Consumer Reference Group (CRG). The CRG is a mixture of melanoma survivors, carers and those what have been impacted by a loved ones' melanoma journey. The CRG have volunteered their time to facilitate patient participation in melanoma research at every level. The group chaired by Mr Paul White (left) have contributed significantly to MMP research planning and strategies. They have undertaken to report MMP and other scientific findings to the MMP community via newsletters, the MMP website, public forums and social media platforms (as they are developed). The consent of the 1000th patient, Mr Jason Nielson, was deemed a significant achievement worthy of a celebration of all parties in this collaboration.

The MMP CRG can also report success on a national front. Mr Campbell Rose has led the development of the Australian Melanoma Consumer Alliance (AMCA) via a close collaboration with MMP CRG. The AMCA is a neutral body hoping to become a national voice for all melanoma groups. The group have already been called upon numerous times to speak at conferences and review potential melanoma research projects across Australia.



Sixty melanoma cell lines grown from patient tumours (columns) display different target molecules (rows)

Melanoma Immunology

At the Ludwig Institute for Cancer Research Professor Jonathan Cebon and his team has been investigating melanoma from an immunological perspective. The immune system is able to recognise and eradicate melanoma cells and this has led to some exciting new treatments for melanoma. Many of the MMP tissue and blood samples are being screened for a set of immune targets and this is being correlated with clinical information. MMP has enabled the researchers to test significant numbers of samples that allow accurate definition of the role of these target molecules.

Interestingly some of the new melanoma treatments have been shown to alter the targets that melanomas display. Heat maps, such as the one left, can be used to identify genetic differences and similarities in laboratory melanoma cells that have been exposed to different treatments. These studies will help identify the best strategies for immune therapy in patients whose disease becomes resistant to new drugs such as BRAF inhibitor treatments.