ACRF ACCELERATE
An Impact Philanthropy Initiative

AUSTRALIAN CANCER RESEARCH FOUNDATION

Cracking the immunotherapy effectiveness code for the 80% who currently have a poor response

Project Title	ACRF Centre for Cellular Imaging of Precision Immunotherapy
Lead Institute	Peter MacCallum Cancer Centre, Melbourne
Focus Area	Understanding and improving outcomes for patients receiving immunotherapy
Cancer Types	Initial focus on haematological, breast, prostate, lung cancers and melanoma; leading to all cancers

Challenge and Opportunity

Macfarlane Burnet proposed the concept of cancer immune surveillance almost 70 years ago. However, it is only over the past decade that this visionary concept has been validated, and its power manifested through immune-based therapies that have revolutionised cancer treatment. The idea of **cytotoxic** (*causes cells to die*) **lymphocytes** (*immune cells made in bone marrow, found in blood and lymph*) seeking out and destroying rogue cells has now come to fruition, with immunotherapy – in its various forms - being widely considered the "fifth pillar" of cancer therapy.

Immunotherapy stands as the single most exciting development in cancer treatment this century. Having become a standard of care for such cancers as melanoma, NSCLC (non-small cell lung cancer), acute lymphocytic leukaemia and various subtypes of breast cancer.

However, despite many spectacular successes that result in durable and "curative" patient responses, and for reasons that are currently unknown, immunotherapy fails to deliver a significant therapeutic benefit to a high proportion of patients (as high as 80%), who instead show an incomplete or poor treatment response.

Immune oncology is a new and cutting-edge area of research that is beginning to revolutionise cancer care.

Professor Belinda Parker, Chief Investigator

"The problem is immunotherapy only works for some patients. We don't know why, we don't know who. So what we're hoping with this Centre is that we can actually change that and look deeper into cancers and see why this is happening. The potential impact is huge."

Currently, no one knows why this discrepancy exists. Consequently, immunotherapy is largely prescribed to patients entirely empirically, often incurring great financial costs and potentially leading to severe side-effects in patients that may not achieve benefit. Understanding mechanisms of response and resistance will allow informed and individualised design of combination therapeutic strategies to expand the proportion of patients that respond to immunotherapy — arguably the most promising avenue for aggressive cancers.

Overall, predicting the response and applying immunotherapy rationally would be a critically important advance for patients. Apart from maximising efficacy, avoiding debilitating side effects is also an extremely worthwhile aim. Currently, a major gap in our ability to model and understand cellular mechanisms of immunotherapy and resistance to it arises from our inability to directly image and observe these processes in action in human tissues during either successful treatment or in cancer that fails to respond to medical treatment.

TECH TALK

Different cancer types, different codes

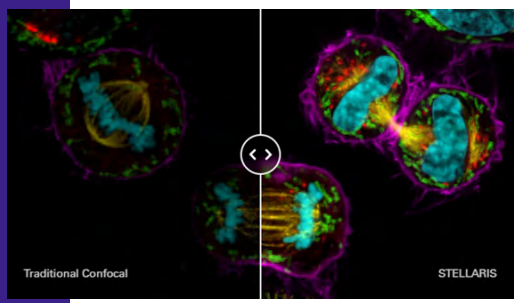
This issue is starkly illustrated by the fact that while refractory childhood acute lymphocytic leukaemia almost invariably responds to anti-CD19 CAR T cells, only a small proportion of patients with chronic lymphocytic leukaemia respond, even though both cancers express very high levels of the target antigen, CD19. This is also evident using the immune checkpoint inhibitors that target PD1/PDL1 and CTLA4, where approximately 50% of patients with metastatic melanoma (one of the most responsive cancers) achieve a complete and sustained response to immunotherapy, while others go on to progressive disease despite treatment.

Project in Brief

The ACRF Centre for Cellular Imaging of Precision Immunotherapy will address this problem by bringing together an expert team whose research collectively addresses the central mission: understanding and improving outcomes for patients receiving immunotherapy. This world-class cancer imaging initiative based at the Peter MacCallum Cancer Centre (PMCC) in Melbourne will be made available to the whole cancer community.

This unique, tightly integrated collaborative program will bring together tumour immunologists from the largest such program in Australia, clinicians leading international immunotherapy trials, and experts in biochemistry and cellular imaging all, working together under the same roof. This collaboration will enable the study of immunotherapy of cancer at multiple scales – from single molecules to single cells and various tissue preparations, from biospecimens derived from the 1000s of cancer patients undergoing immunotherapy at Peter Mac per year. Through tightly entwined discovery and clinical research programs, they will generate a deeper understanding of the mechanisms of resistance to immunotherapy and develop a pipeline using patient-derived/humanised models that will predict and enhance patient response to treatment.

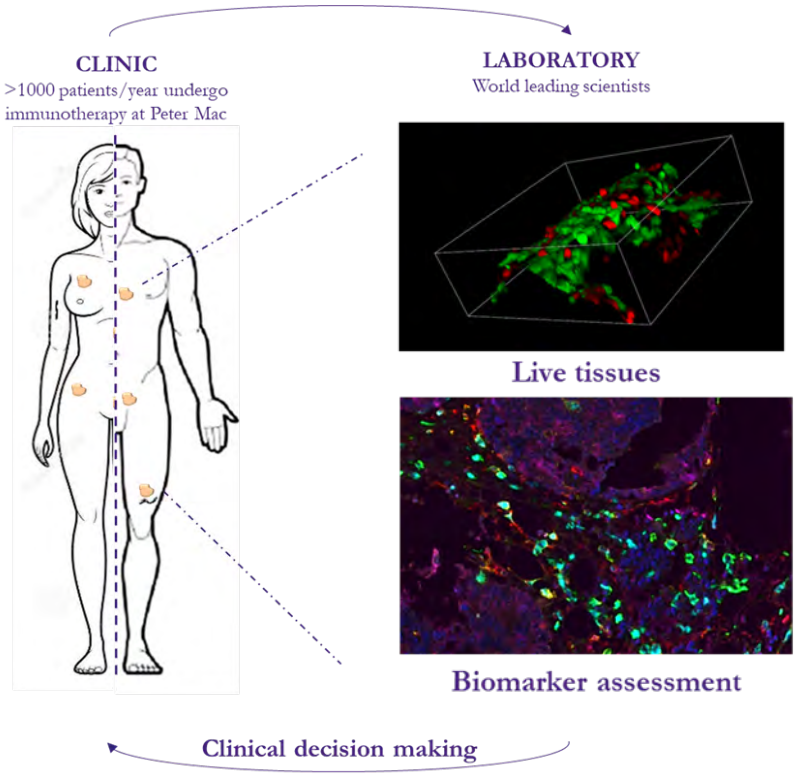
The initiative will provide researchers and clinicians with world-class imaging infrastructure to allow parallel assessment of patient-derived tissue models and matched clinical response data. While suitable for the study of any cancer, the initial focus will be on: haematological, breast, prostate, lung cancers and melanoma, which are among the most common cancer types in Australia.



The Benefit

Both in Australia and worldwide, the ACRF Centre for Cellular Imaging of Precision Immunotherapy will be unique at three main levels impacting cancer control, it will:

- Offer a new and innovative technology pipeline not currently available in Australia.
- Support a conceptually novel approach to investigate the molecular drivers of cancer therapy resistance across multiple scales from single molecules through to patients, and with unprecedented resolution.
- Enhance the research efforts of the most concentrated collection of world-class cancer immunotherapy researchers and clinicians in Australia, by integrating complementary skill sets to address therapy resistance.

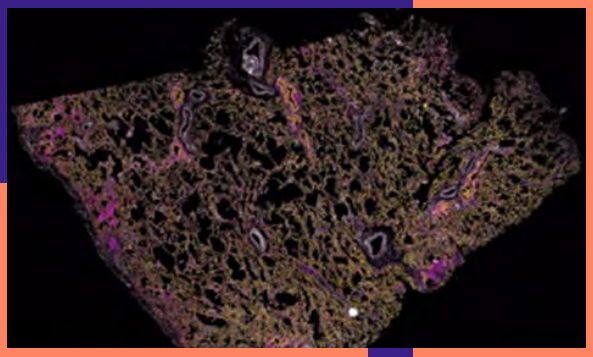


Results of the proposed research can be rapidly translated into clinical practice, leading to predictive and personalised immunotherapy for cancer patients.

Use of Funds

The $3M investment will support the development of the ACRF Centre for Cellular Imaging of Precision Immunotherapy and provide the ability to image cancer at multiple scales.

Technology For live imaging across scales: molecules, organelles, cells and tissues.	**Cost**
Leica Stellaris 8 DIVE multiphoton – for live imaging across scales: molecules, organelles, cells and tissues.	$1,760,000
Zeiss Elyra 7 with Lattice SIM Rarecyte, Orion – for spatial multi-omics in 2D and 3D	$1,240,000 $680,000
Aquifer Hive Systems (computing)	$560,000
Total	$3,000,000



TECHTALK

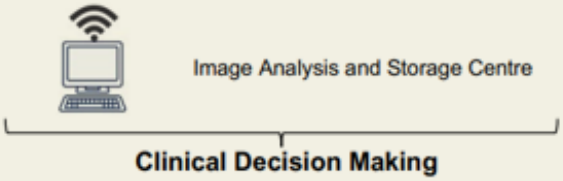
Understanding the equipment

Leica Stellaris 8 DIVE

- Live tissue assessment
- Predicting response to immunotherapy
- Sequential biopsies
- Spatial analysis of immune cell

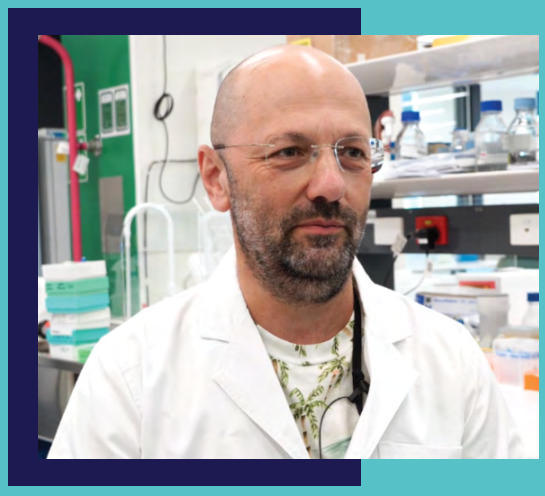
RareCyte Orion

- Spatial immune cell characterisation
- Biomarker validation/assessment
- Pathology-ready mIHC
- 17 marker assessments in a single scan
- Thousands of bio-banked samples.



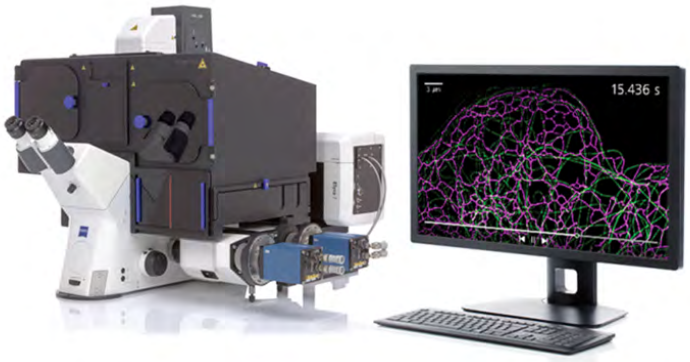
Zeiss Elyra 7 with Lattice SIM

- Tracking cellular interactions
- T cell cytotoxicity
- Effector molecule assessment



"We expect especially high uptake of our new capabilities from neighbouring and collaborating organisations such as WEHI, Murdoch Children's Research Institute and ONJCRI."

Professor Ilia Voskoboinik, Chief Investigator

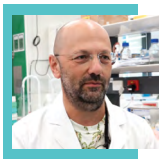


Meet the Team

The proposed teams consist of clinical and laboratory researchers working together to establish a pipeline that will lead to precision immunotherapy.

ACRF Centre for Cellular Imaging of Precision Immunotherapy will include a team of 14 Chief Investigators (listed below) and 12 collaborators. The Chief Investigators are international experts in their respective disciplines of cancer and/or have expertise in cellular and tissue imaging. As such, the CI team is ideally aligned with the research goals that will be made possible by the ACRF CIMPRIM.

Chief Investigator
Belinda Parker
Co-Head, Cancer Evolution and Metastasis Program, Peter MacCallum Cancer Centre



Chief Investigator
Ilia Voskoboinik
Head, Killer Cell Biology Laboratory, Peter MacCallum Cancer Centre

Chief Investigator Sherene Loi
Medical Oncologist; Head, Translational Breast Cancer Genomics and Therapeutics, Peter MacCallum Cancer Centre

Chief Investigator Shahneen Sandhu
Medical Oncologist, Peter MacCallum Cancer Centre

Chief Investigator Joseph Trapani
Director, Cancer Immunology Program and Centre for Cancer Immunotherapy; Head, Cancer Cell Death, Peter MacCallum Cancer Centre

Chief Investigator Clare Slaney
Senior Research Fellow, Cancer Immunology, Peter MacCallum Cancer Centre

Chief Investigator Prof Paul Beavis
Group Leader, Peter MacCallum Cancer Centre

Chief Investigator Paul Neeson
Head, Human Immunology Translational Research, Peter MacCallum Cancer Centre

Chief Investigator Elizabeth Christie
Head, Cancer Evolution and Metastasis, Peter MacCallum Cancer Centre

Chief Investigator Anna Trigos
Head, Computational Biology, Peter MacCallum Cancer Centre

Chief Investigator Thomas John
Medical Oncologist, Peter MacCallum Cancer Centre

Chief Investigator Grant McArthur
Executive Director, Victorian Comprehensive Cancer Centre Head, Molecular Oncology, Peter MacCallum Cancer Centre

Chief Investigator Jane Oliaro
Chief Scientist, the Centre of Excellence in Cellular Immunotherapy Translation Laboratory; Head, Immune Defence, Peter MacCallum Cancer Centre

Chief Investigator Simon Harrison
Haematologist; Director, Centre of Excellence for Cellular Immunotherapy, Peter MacCallum Cancer Centre.

> "Peter MacCallum Cancer Centre is a national centre for immune oncology and this team is outstanding on an international level."
>
> ***Kerry Strydom , ACRF CEO***

ACRF Model for Impact

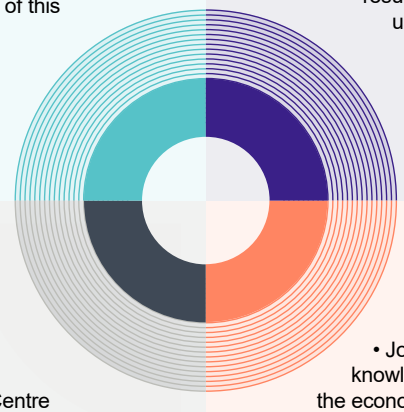
With input from health economic specialists, ACRF has developed a framework to articulate the anticipated future impact of projects that receive ACRF funding. Below is an overview of the outcomes the ACRF Centre For Cellular Imaging of Precision Immunotherapy has the potential to achieve:

HUMAN

- In 2024, it is estimated 169,500 Australians will be diagnosed with cancer and 53,000 will die[1]. Immunotherapy has revolutionised cancer treatment and has already changed the management of certain cancers including melanoma, lung and breast. The predictive approach that will be developed in the ACRF Centre For Cellular Imaging of Precision Immunotherapy will lead to better outcomes for those who will respond to immunotherapy and avoid severe side effects for those people who don't.
- Immune checkpoint inhibitors, the most widely used immunotherapy, is now an option for over 40% of people with cancer but may only be effective in around 12.5% of cancer patients[2,3]. Research conducted in the ACRF Centre For Cellular Imaging of Precision Immunotherapy will develop a rapid and efficient way to identify who is likely to respond to immunotherapy and increase the potential of this treatment.

SOCIETAL

- The ACRF Centre For Cellular Imaging of Precision Immunotherapy has the potential to reduce the burden on caregivers who, on average, experience a 23% work productivity loss because of caregiving[5,6]. Based on the average Australian wage, and taking into consideration the labour force participation and unemployment rate, this accounts for an annual productivity loss of $14,467 per caregiver annually.
- Immunotherapy often incurs great financial costs and potentially leading to severe side-effects in. Understanding mechanisms of response and resistance will allow informed and individualised design of combination therapeutic strategies to expand the proportion of patients that respond to immunotherapy[7].
- Immunotherapy has been an effective treatment for certain cancers; however, it is not effective for everyone and can result in toxicity and complications – the increased use of immunotherapies has seen an increase in hospitalisations because of the severe side effects[8]. Research undertaken in the Centre to predict which people will respond thereby reducing harmful side effects and hospitalisations.



LEVERAGE

- Over the last five years, the research team have secured over $75 million in competitive grant funding. The investment in the ACRF Centre For Cellular Imaging of Precision Immunotherapy would significantly strengthen future grant applications and secure additional funding.
- Of the $78B net present gains generated by medical research from 1990 to 2004, $52B was in the form of health gains and $26B in wider economic gains[4]. Extrapolating these figures, the $4.5M invested by the ACRF has a potential return of $17.5M - $11.7M in the form of health gains and $5.8M in the form of wider economic gains.
- Close to $4 M of in-kind funding is being provided by PMCC for technical and operational support, data storage and research infrastructure.

INTELLECTUAL

- Jobs in medical research are high value and knowledge-based jobs that contribute substantially to the economy. The core team alone (excluding the CI's) has the potential to generate $1.27M in value added gain[4].
- One of the most important outputs of the ACRF Centre For Cellular Imaging of Precision Immunotherapy will be publications to inform future research. The $4.5M invested by ACRF alone has a potential return of 52 publications[9].

For references, please visit acrf.com.au/philanthropy-accelerate-references

BACKING BRILLIANT

To find out more about ACRF Accelerate and this exciting project please contact philanthropy@acrf.com.au **1300 884 988**

AUSTRALIAN CANCER RESEARCH FOUNDATION
www.acrf.com.au