ACRF ACCELERATE
An Impact Philanthropy Initiative

AUSTRALIAN CANCER RESEARCH FOUNDATION

Improving immunotherapy effectiveness and reducing its toxicity

Project Title	The ACRF Centre for Dynamic Immuno-Oncology
Lead Institute	Alfred Health and Monash University
Focus Area	Personalise immunotherapy so it works consistently, safely and more effectively
Cancer Types	All cancers

Challenge and Opportunity

Despite remarkable advances in cancer treatment, via the development of immunotherapies, personalised immunotherapy is still in its infancy; we do not yet know how to tailor immunotherapy regimens to the unique cancer and immune biology of each patient. This is due to a limited understanding of how immunotherapies trigger and sustain immune responses that result in profound anti-tumour effects as well as serious and sometimes fatal toxicities.

While immunotherapy approaches like immune checkpoint blockade, CAR-T, and BiTE therapies are revolutionising cancer care, their effectiveness is often unpredictable, and many patients (10-30%) experience severe side effects. This variability highlights an urgent need to better understand how these therapies interact with the immune system in patients and in real-time.

As immunotherapy can cause severe complications, it is crucial to predict which patients will benefit from treatment and which might develop toxicities. Current methods for predicting and monitoring tumour response are limited, often relying on fractionally sampled tissues from a single biopsy site at a single point in time, or blood-based biomarkers that provide an incomplete picture of the disease and immune activity.

Moreover, screening for immunotherapy toxicities typically depends on delayed symptom reporting, increasing the risk and severity of toxicities and reducing opportunities for preventive intervention.

TECH TALK

Understanding the mechanisms of immune response

Immune checkpoint inhibitors like anti-PD-1, anti-PDL-1, CTLA-4, and anti-LAG3 antibodies (2) activate T-cells, but how these cells are activated and travel through tissues to exert their effects remains poorly understood. Similarly, cell-based therapies like CAR-T cells and Bi-specific T-Cell Engagers (BiTEs), which are transforming the treatment of blood cancers but can cause severe toxicities such as Immune effector Cell Associated Neurotoxicity Syndrome (ICANS), have largely unknown mechanisms of tissue infiltration and immune activation.

"Cancer cells, although they're more similar to normal cells than are bacteria or viruses, they're still actually quite different.
This research is bringing together human patients with the latest technologies to enable researchers to see the abnormal parts of the cancer cell in an person who's going through the cancer treatment.
That's never been done before."

Associate Professor Vivek Naranbhai, Chief Investigator

Project in Brief

The ACRF Centre for Dynamic Immuno-Oncology (ACRF CDIO), to be based at the Paula Fox Melanoma and Cancer Centre within The Alfred in Melbourne, will be equipped with the highest sensitivity PET scanner available – the Quadra PET-CT - which offers unprecedented scanning speeds and body scanning capabilities.

Monitoring immune and cancer responses in cancer patients receiving immunotherapy will provide an insight into the nature of immune responses and patterns that indicate anti-cancer benefits or toxicity. This is possible because of advances in the sensitivity of scanning systems and radiotracers.

To realise the full research potential of Quadra, safely, the Centre will deploy cutting-edge technology with existing and new radiotracers that will enable immune monitoring in patients and correlate this with various biomarkers.

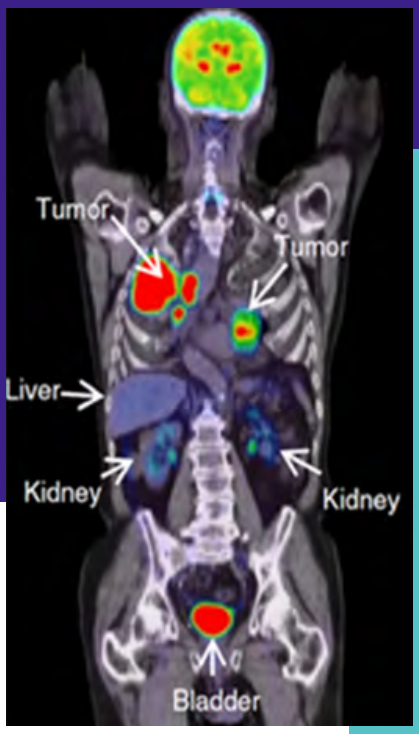
To address the complex challenges of immunotherapy treatment and side-effects, the ACRF CDIO will focus on two key research objectives:

- understanding the nature of immune responses, and
- discovering patterns of immune and tumour response that predict anti-cancer benefits and organ-specific toxicities in these patients.

ACRF CDIO will achieve its objectives through three pillars of excellence:

- technological innovation (using existing PET radiotracers in novel ways),
- developing new radiotracers, whole-body and serial PET-CT imaging, and advanced data analysis, and
- integrate imaging with histological, blood-based, and other measures, ensuring immediate clinical relevance and overcoming the limitations of model systems (3).

The vision is that ACRF CDIO will be a globally leading programme of dynamic immune monitoring to augment the anti-cancer benefits and minimise the toxicity of immunotherapy.



The ACRF CDIO will focus on fundamental discovery and translation of the biology of immune checkpoint blockade (ICB), CAR-T, and Bi-specific T-Cell Engagers (BiTE) immunotherapies.

Patients will donate their clinical data, archived and/or fresh tissues (via biopsies), blood or cerebrospinal fluid (CSF) relevant to the specific aims. Serial collections will be obtained from timepoints before and after immunotherapy administration, depending on the specific aim in question and linked where appropriate to imaging studies.

It will leverage flagship technology in the form of the Biograph Visiona Quadra PET-CT, developing novel methods and tracers.

Blood, CSF and other samples will be analysed by multiparametric flow cytometry on the Cytek Aurora.

The Benefit

In collaboration with leading experts in immunology, oncology, radiology, and artificial intelligence, the ACRF CDIO will substantially bypass the need for surrogate models, generating data directly from cancer patients to pioneer new ways of optimising immunotherapy. This approach will reshape cancer treatment by making it more effective and adaptable to the unique biology and immune ecosystem of each patient.

These discoveries will

- have substantial potential to advance this exciting field by revealing ways in which current immunotherapies such as ICB, CAR-T cells and BiTEs (and future innovations currently unknown) may be improved and adapted in real-time by modifying treatment schedules or combining with other therapies.
- uncover novel insights into mechanisms of immunotherapy associated toxicity and illuminate potential approaches to nullify these

This unique research endeavour combines 1) access to high patient volumes via a public hospital, 2) leaders in immuno-oncology, haematology, nuclear medicine, and pathology, and 3) the advanced technologies of ACRF CDIO.

The Quadra PET-CT, the highest sensitivity PET scanner available, offers unprecedented scanning speed and whole-body capabilities. Additionally, few countries have a regulatory framework like Australia's, which allows rapid evaluation of novel radiotracers. This combination of cutting-edge PET technology with both existing and novel radiotracers enables dynamic immune monitoring and correlation with blood and tissue biomarkers.

The ACRF CDIO will be unique, transforming cancer immunotherapy in Australia and globally.

"The ACRF CDIO will place Australia at the forefront of global cancer immunology research. By combining advanced imaging technology with cutting-edge tools to study cancer immunology, we will gain unprecedented insights into how immunotherapies work, ushering innovations and a new era in cancer treatment."

Professor Mark Shackleton, Chief Investigator

Use of Funds

The $2M investment will support the development of The ACRF Centre for Dynamic Immuno-Oncology, which will be a flagship program within the newly built Paula Fox Melanoma and Cancer Centre in Melbourne, Australia. This $150+M facility, co-funded by Federal/State Governments and philanthropy, will be a national node for innovation in cancer diagnostics and therapeutics, all under co-governance of Australia's largest tertiary institution, Monash University, and one of Australia's leading academic hospitals, The Alfred.

Technology	Cost
Siemens Quadra PET Data/Storage system	$300,000
MIMS PET research imaging software licences	$260,000
Standalone Radiopharmaceutical Hot Cell	$100,000
Automated Patient FDG Injector	$175,000
Radiotracer Gamma Counter	$100,000
Handheld Radiation Monitoring Equipment	$30,000
Radinject Manual Radiotracer injectors	$60,000
Mobile Radiation Shields	$60,000
Olympus VS200 Slide Scanner	$240,000
Cytek Aurora Flow cytometer	$430,000
Quadra PET reagents such as radiolabelled anti-CD8 and abti-PD-L1 antibodies	$245,000
Total	**$2,000,000**

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 ten Chief Investigators (listed below) and 18 collaborators.

Chief Investigator Mark Shackleton
Director of Oncology, Alfred Health
Laboratory Head and Professor of Oncology, Monash University
Director, Cancer Trials Australia
CoDirector, Monash Partners Comprehensive Cancer Consortium
Chair, Melanoma and Skin Cancer Trials

Chief Investigator Martin Cherk
Nuclear Medicine Physician and Medical Oncologist, Alfred Health
Head of Clinical Services and Head of Training Department of Nuclear Medicine and PET, Alfred Health

Chief Investigator Vivek Naranbhai
Consultant Medical Oncologist, Alfred Health
Laboratory Head and Associate Professor of Oncology, Monash University

Chief Investigator Catriona McLean AO
Head of Department, Anatomical Pathology, Alfred Health
Head of Solid Cancer Molecular Pathology Unit, Alfred Health
Director Victorian Neuromuscular Laboratory Service, Alfred Health
Director Victorian Brain Bank, Florey Institute

Chief Investigator Mastura Monif
Consultant Neurologist, Alfred Health
Laboratory Head and Senior Research Fellow, Monash University

Chief Investigator Constantine Tam
Head of Lymphoma Service, Alfred Health
Laboratory Head and Professor of Haematology, Monash University

Chief Investigator Anna Kalff
Consultant Clinical and Laboratory Haematologist, Malignant Haematology and Stem Cell Transplantation Service, Alfred Health Adjunct Senior Research Fellow, The Australian Centre for Blood Diseases, Monash University

Chief Investigator Shaun Fleming
Head of Myeloid Disease Service, Alfred Health
A/Professor Australian Centre for Blood Disease, Monash University

Chief Investigator Victoria Mar
Director, Victorian Melanoma Service, Alfred Health
Adjunct Professor, School of Public Health and Preventive Medicine, Monash University

Chief Investigator Zongyuan Ge
Founding Director, Monash Medical AI group
Chief Scientist, Monash Airdoc Research Centre
Associate Professor, Department of Data Science and AI, Monash Data Futures Institute

ACRF Model for Impact

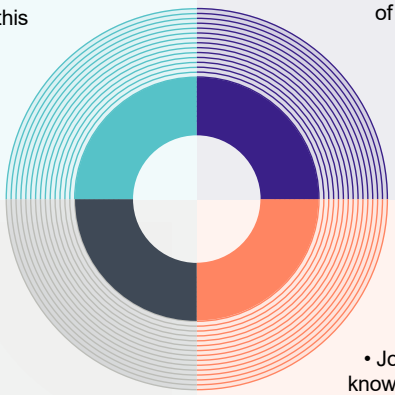
With input from health economic specialists, ACRF has developed a framework to articulate the anticipated future impact of projects that receive ACRF funding. Below is an overview of the outcomes the ACRF Centre for Dynamic Immuno-Oncology has the potential to achieve:

HUMAN

- In 2024, it is estimated 169,500 Australians will be diagnosed with cancer and 53,000 will die[1]. The application of imaging technology to predict and monitor responses to immunotherapy is expected to rapidly increase over the next decade and will pave the way to improve outcomes for people with cancer[2].
- 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[3,4]. Research conducted in the ACRF Centre for Dynamic Immuno-Oncology 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 Dynamic Immuno-Oncology has the potential to reduce the burden on caregivers who, when considering time spent caregiving for loved ones, work absenteeism and presenteeism, experience a 23% work productivity loss because of caregiving[6,7]. 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 has been an effective treatment for certain cancers, but 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 adverse effects[8]. Research undertaken in the ACRF Centre For Dynamic Immuno-Oncology to predict which people will respond thereby reducing harmful side effects and hospitalisations.



LEVERAGE

- This research team have previously secured over $57 million in competitive grant funding. The investment in the ACRF Centre for Dynamic Immuno-Oncology 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[5]. 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.
- Additional funding totalling $21.5 million to support the development of the ACRF Centre for Dynamic Immuno-Oncology has been secured. This includes $19 million from the Commonwealth and Victorian State Government.

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 $375,200 in value added gain[5].
- 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