ACRF ACCELERATE
An Impact Philanthropy Initiative

AUSTRALIAN CANCER RESEARCH FOUNDATION

# Unlocking the potential of immunotherapies for childhood cancer

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| Project Title | ACRF Spatial Immune-oncology Research Program |
| Lead Institute | Children's Cancer Institute, Sydney |
| Focus Area | Immunotherapy, Spatial Multiomics, Biomarker and Drug Discovery |
| Cancer Types | Childhood cancers |

## Challenge and Opportunity

Immunotherapy is the most appealing anti-cancer approach of the modern era but despite the success in treating several adult cancers, these immunotherapy treatments are yet to show benefit in childhood cancers. Childhood cancers are very different from adult cancers, and it is known that interactions between cancer cells and the tumour immune microenvironment (TIME), the ecosystem that surrounds the tumour, play an important role.

Until recently technologies have not been available to allow researchers to study the complex interactions in the TIME. The ACRF Spatial Immune-oncology Research (ASpIRe) Program for Childhood Cancer, led by the Children's Cancer Institute (CCI), will change that. Leveraging novel technologies, some of which will be available in Australia for the first time, the research team will be able to cast light on the complex interactions between cancer cells and immune cells in cancers affecting children.

Research generated through ACRF ASpIRe will accelerate the discovery, development, and deployment of new and effective immune-based therapeutic strategies for children with cancer.

# Project in Brief

- It is not yet well understood why immunotherapy is ineffective in children with cancer but the interactions between cancer cells and the surrounding environment including the immune cells are likely to be important.
- Understanding more about how cancer cells and immune cells interact throughout disease development and progression are critical in advancing the development of immunotherapies for children.
- ACRF ASpIRe brings together a leading team of childhood cancer researchers and technology experts, with the latest technologies, to investigate the complex and dynamic interactions in the TIME .
- New knowledge will lead to the development of new and better ways to identify which children with a cancer can most benefit from existing immunotherapies and drive the discovery of new ways for the immune system to be modified in children to treat their cancers.

# Project Detail

## Introduction

Immunotherapy, in which the bodies' own immune system fights cancer, has become a standard treatment for several adult cancers and has radically improved the outlook for a number of common adult cancers. Despite these advances, the immunotherapy treatments that have been developed for adults have shown little benefit for childhood cancers[1].

Childhood cancers are very different from adult cancers, and it has been suggested that the TIME of childhood cancers are different to adult cancers and may be a factor in why immunotherapy is not effective. The future success of cancer immunotherapy in children relies on an improved understanding of the how the elements of the TIME (e.g. immune cells, blood vessels) interact with the tumour[2]. Understanding more about this could be the key to unlocking the potential of immunotherapy to effectively treat childhood cancers.

## The Unique Approach

The ACRF ASpIRe Program will capitalise on Australia's largest and most comprehensive precision medicine program - Zero childhood cancer (ZERO) – where ACRF was a founding partner with a grant awarded in 2014 (ACRF Child Cancer Precision Medicine Centre ) – as well as technologies and methods developed from the grant awarded in 2019 to establish the ACRF Child Cancer Liquid Biopsy Program. ZERO has been open to Australian children with high-risk cancer since 2017 and in 2023 was expanded to include all children in Australia diagnosed with cancer. ZERO is now a rich resource of molecular data and matched biological samples from over 1,000 paediatric cancer patients. Access to this resource provides the ACRF ASpIRe Program with a unique and unparalleled opportunity to investigate the TIME in the deadliest paediatric cancers.

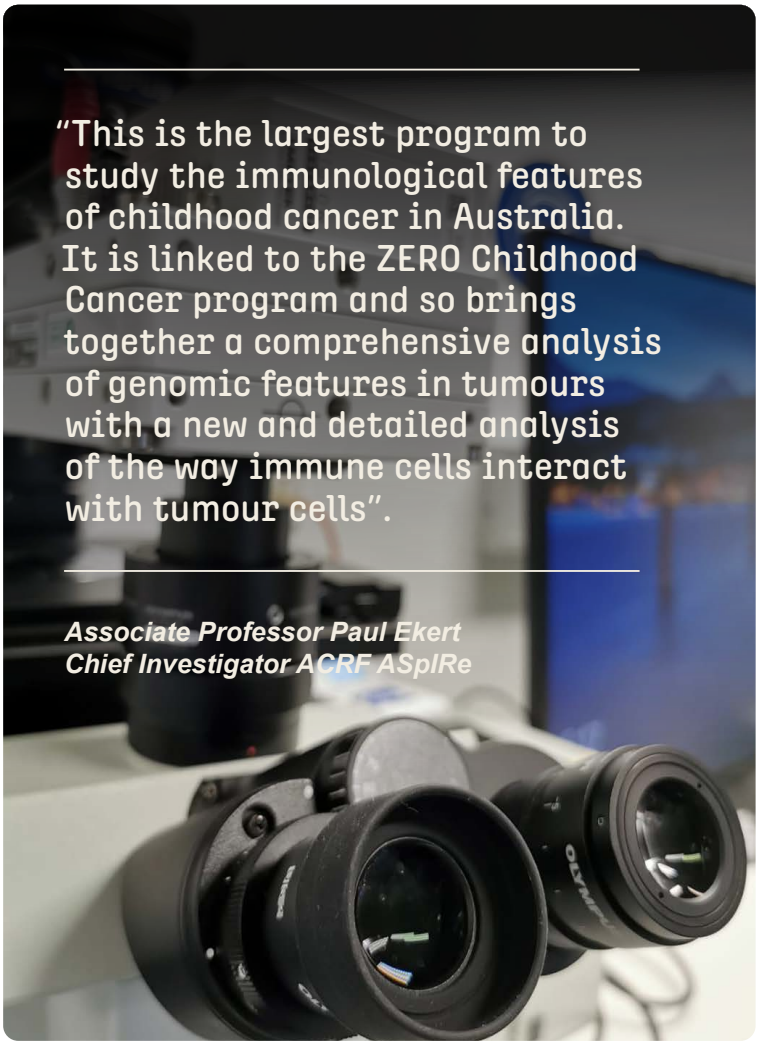
Conventional technologies have been instrumental in providing the global picture of the immune landscape of tumours but are not effective in capturing the complexity and depth of immune phenotypes and potential functional cues in a dynamic system within the TIME. Advances in technologies such as spatial multiomics, cytometry and plasma proteomics will allow researchers to directly examine the complex and dynamic interactions between cancer cells and the TIME. The ACRF ASpIRe Program will leverage these new technologies to develop high-resolution, low-cost analyses of the TIME of childhood cancers. This includes a new, innovative platform – the MACSima as well as the Olink system – which will position Australia at the forefront of delivering the first specialised translational TIME profiling program for paediatric cancers.

## Research Program

The ACRF Spatial Immune-oncology Research Program will address three central themes:

**1. Identifying mechanisms in the TIME associated with high-risk paediatric cancer**

The TIME of childhood cancers is largely unexplored. Members of the ACRF ASpIRe research team have recently developed a unique gene signature, the Immune Paediatric Signature Score (IPASS), which provides some insights into how the immune response in some childhood cancers is affected[3]. The identification of IPASS is an important step towards developing immunotherapy in children's cancer but is not the full picture. Using samples from ZERO and the new technology available, namely the MACSima platform, will allow ASpIRe researchers to characterize, for the first time, the immune cells and associated environment in over 600 children with high-risk cancer. In addition, the Olink system will profile the proteome of plasma samples to investigate mechanisms such as immune cell recruitment, activation and inhibition which could inform the development of a range of novel therapies.




**2. Immunotherapy biomarkers for prognosis and molecular monitoring**

Many studies of the immune system in cancer focus on understanding interactions between cancer cells and the immune cells in the TIME. Investigations of a range of adult cancers have highlighted that analysing immune cells in the peripheral blood can predict clinical outcomes of the effectiveness of immunotherapy. The profiling of this peripheral blood has been suggested as a way to identify who would benefit from increased monitoring during treatment. Currently this is not well studied in children but using technology previously provided through the ACRF Child Cancer Liquid Biopsy program along with the Olink system will allow characterisation and tracking of changes in circulating cells and potentially useful biomarkers. From this a less invasive type of test called liquid biopsy can be developed to identify those paediatric cancer patients who are likely to respond to immune treatments and to track how effective the treatments are.

**3. Modification of the TIME to improve the effect of immunotherapy in high-risk childhood cancers**

Many solid paediatric tumours have a TIME that evades or suppresses immune responses which can limit the effectiveness of immunotherapies. Members of the ACRF ASpIRe research team have identified some novel anticancer drugs that could 'rewire' the TIME and improve a response to immunotherapy. Detailed immunoprofiling of tumours will be made possible in the ACRF ASpIRe program using the MACSima platform and Olink system to dramatically increase understanding of how this rewiring takes place. This can then enable the identification of new biomarkers to track responses and accelerate the progression of much needed immunotherapies.

## The Benefit

Personalised cancer treatment is based on an understanding that the genetic profile of a tumour will vary between patients and this information can be used to guide more effective therapy selection. This principle can also be applied to the TIME, as each tumour harbours a unique immune profile. The ACRF ASpIRe Program offers a unique opportunity to validate and translate novel biomarkers of response, develop new non-invasive diagnostic applications and new treatment strategies into an active precision medicine program for children with cancer, which includes immunotherapy. In addition to providing new life-saving drugs, advancing the use of immunotherapy for children with cancer could offer a unique opportunity to reduce the side effects and long-lasting chronic health conditions that can be associated with standard treatments.

## Use of Funds

The $2 million investment will support the development of the ACRF Spatial Immune-oncology Research Program for Childhood Cancer by providing the novel technology and associated support to identify new diagnostic tools and immunotherapeutic approaches to childhood cancer.

| Technology | Cost |
|---|---|
| Tissue microarray (TMA Master II) and general lab equipment | $150,000 |
| MACSima (Miltenyi Biotech) | $690,000 |
| Olink System – to be based in Melbourne at Australian Genome Research Facility | $225,000 |
| Specialised Reagents | |
| - Spatial multiomics | $205,000 |
| - MACSima | $150,000 |
| - Olink | $130,000 |
| Assistant Manager (over 3 years) | $300,000 |
| Computing and data storage | $150,000 |
| Total | $2,000,000 |

## Meet the Team

The ACRF ASpIRe Program for Childhood Cancer will include a team of 10 Chief Investigators and 20 scientists and research specialists, representing a truly national collaborative network with a well-established track record of research excellence from Australian and International organisations such as St Jude Children's Research Hospital (US). This brings together an outstanding and diverse team of early, mid and established career childhood cancer researchers, immunologists, clinician scientists, and technology experts to deliver what will be Australia's first specialised translational TIME profiling program for paediatric cancer patients.

**Chief Investigator Paul Ekert**
Co-Head of Theme Personalised Medicine, Group Leader Translational Tumour Biology, Children's Cancer Institute

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

**Chief Investigator Michelle Haber AM**
Director, Children's Cancer Institute

**Chief Investigator Mark Cowley**
Group Leader Computational Biology, Children's Cancer Institute

**Chief Investigator Klaartje Somers**
Senior Scientist, Molecular Oncology Group, Children's Cancer Institute

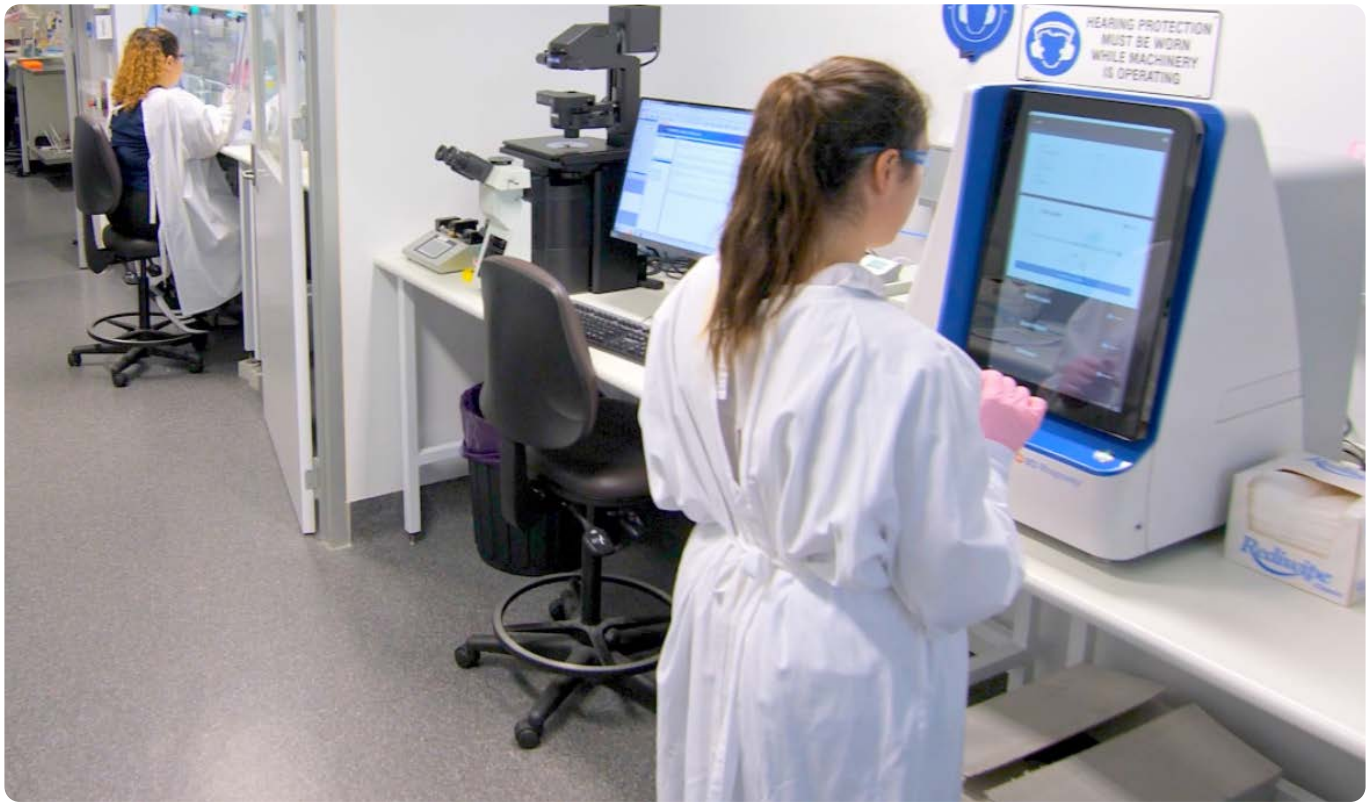
**Chief Investigator Orazio Vittorio**
Team Leader, Children's Cancer Institute

**Chief Investigator Raelene Endersby**
Co-Head, Brain Tumour Research, Telethon Kids Institute

**Chief Investigator Andrew Gifford**
Paediatric Pathologist, Sydney Children's Hospital Network, Randwick Campus, Clinical Research Fellow, Children's Cancer Institute

**Chief Investigator Robert Salomon**
Operations and Technology Manager, ACRF Child Cancer Liquid Biopsy Program, Children's Cancer Institute

**Chief Investigator Chelsea Mayoh,**
Senior Scientist, Head of Bioinformatics Core, Children's Cancer Institute




Researcher at Children's Cancer Institute's laboratory in Sydney

# ACRF Model for Impact

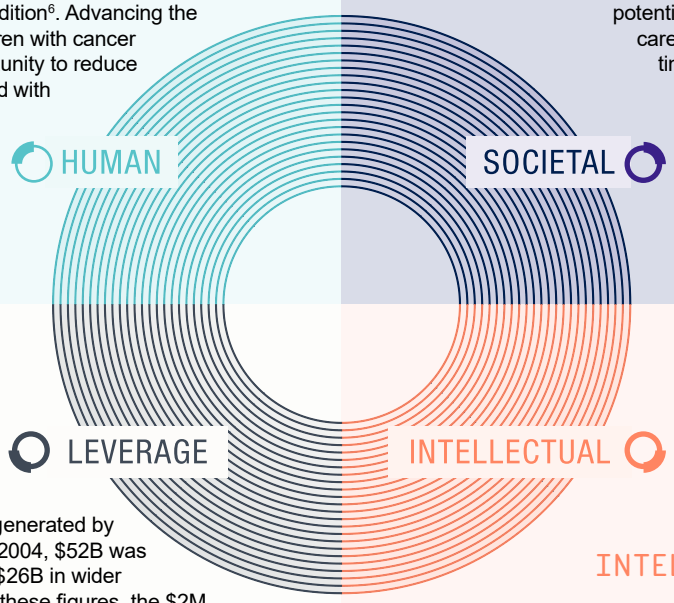
With input from health economic specialists, ACRF has developed a framework to articulate the anticipated future impact of projects that receive ACRF funding. Below is an overview of the outcomes the ACRF ASpIRe program has the potential to achieve:

## HUMAN

- Immunotherapy holds significant promise for childhood cancers – the introduction of an immunotherapy (anti-GD2) for children with high-risk neuroblastoma alongside standard therapy has significantly improved survival rates but this is not without toxic side effects[4,5]. The ACRF ASpIRe Program has the potential to develop new immunotherapies for children that will improve outcomes and reduce toxic side effects.
- Studies on survivors of childhood cancer have shown that at least 60% of young adults develop chronic health conditions, and by age 45 years, 80% experience at least one serious disabling or life-threatening condition[6]. Advancing the use of immunotherapy for children with cancer could also offer a unique opportunity to reduce the high co-morbidity associated with standard therapies.

## SOCIETAL

- Adult survivors of childhood cancers are more likely to be in poorer health, need assistance with personal care and routine needs, have work limitations, be unable to work because of health, miss more days of work, and have greater household productivity. The annual productivity loss for adult survivors of childhood cancer is estimated to be $12,000 per person compared with $4,800 per person for individuals without a history of cancer[8]. The ACRF ASpIRe Program has the potential to greatly enhance the long-term outcomes for childhood cancer survivors thereby reducing productivity losses.
- The ACRF ASpIRe Program 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[9,10]. Based on the average Australian wage, this accounts for an annual productivity loss of $13,916 per caregiver annually.




## LEVERAGE

- 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[7]. Extrapolating these figures, the $2M invested by the ACRF has a potential return of $7.8M - $5.23M in the form of health gains and $2.57M in the form of wider economic gains.
- Leveraged funding totalling $2M will be provided by the Australian Genome Research Facility Limited ($250,000 cash plus $543,000 in kind); the University of New South Wales ($915,000) and the Cancer Institute NSW ($500,000) to support the development of the ACRF ASpIRe Program.

## 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 $938,000 in value added gain[7].
- One of the most important outputs of the ACRF ASpIRe Program will be publications to inform future research. The $2M invested by ACRF alone has a potential return of 23 publications[11].

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

BACKING BRILLIANT

AUSTRALIAN CANCER RESEARCH FOUNDATION

## Contact Information

To find out more about ACRF Accelerate and this exciting project please contact:
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