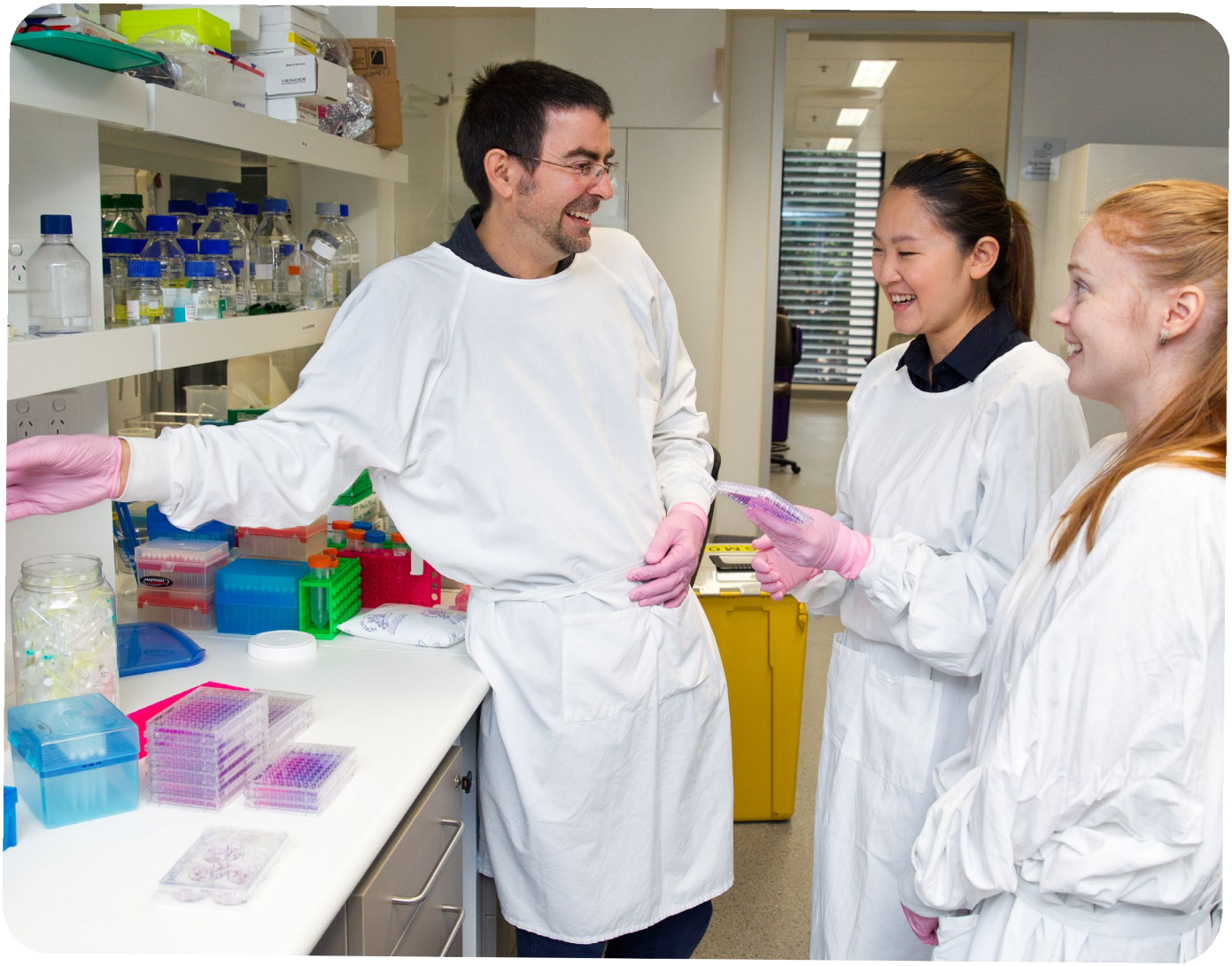
STUDENT PROJECTS 2024

Children's Cancer Institute



Children's Cancer Institute

Curing childhood cancer. It's not if. It's **when**.

CHILDREN'S CANCER INSTITUTE

A MESSAGE FROM EXECUTIVE DIRECTOR PROFESSOR MICHELLE HABER, AM

Today, as a result of medical research, eight out of ten children will survive their cancer. But, unfortunately, nearly three children in Australia are still dying from this disease every week.

We believe this is three too many.

From the very beginning, our focus has been to cure all children with cancer and eliminate their suffering. While we are getting closer to this aim, there is so much more to do.

Children's Cancer Institute is the only independent medical research institute in Australia wholly dedicated to putting an end to childhood cancer.

Based at the Lowy Cancer Research Centre, UNSW, we have world-class facilities and global collaborations with researchers and doctors, we drive discoveries into improved treatments as quickly as possible.

Children's Cancer Institute nurtures an environment of innovation, collaboration and learning. We are committed to fostering the next generation of research leaders. As one of our students, you will be provided with personalised training in state-of-the-art facilities to bring out your best.

Student opportunities at the institute are listed in the following pages, if you are interested in exploring these further please get in touch with the listed supervisor.

If you are interested in a particular area of research but do not find a project that appeals to you listed here, we encourage you to contact these programs directly to discuss a project to best suit both you and the research team.

STUDENT SUPPORT

Our students bring great energy and enthusiasm, providing fresh ideas and perspectives to tackle the complex challenges faced in childhood cancer research today. As a student, you will be guided and mentored by a dynamic team of world class researchers who have strong collaborative links with research and clinical teams throughout the world. In addition to this, you will have access to a comprehensive professional development program run by a dedicated team focussed on career development, state-of-the-art equipment and facilities, professional support staff, access to a full range of laboratory services and opportunities for overseas travel to present at conferences and work with collaborators. You will also receive the support of your peers through the Children's Cancer Institute Student Association (CCIStA) that runs activities throughout the year, including an annual student retreat.

POSTGRADUATE TOP UP SCHOLARSHIP

We offer a Top Up Scholarship for up to 4 years to students who have been awarded a competitive scholarship, eg. a Research Training Program Scholarship or similar. The value of the scholarship is dependent on the base award of the individual's stipend, students will be topped up to a total of $40 000 P/A, eg. current UNSW RTP rate is $35 000, so the Top Up received would be $5000.

JOSEE HILTON EXCELLENCE AWARD

These tax-free, competitive awards will be offered to a value of up to $10,000 AUD per annum and are offered to students demonstrating exceptionally high potential who have succeeded in attracting a primary competitive scholarship such as an APA. This Excellence Award is in addition to the top-up scholarship.

HONOURS SCHOLARSHIP

We offer two honours year scholarships of $5,000 tax free annually. Selection is based on academic achievement throughout the undergraduate degree, interest in cancer research, personal qualities, as well as other evidence as may be deemed relevant to future success in the area of biomedical research. Scholarships are awarded for one year and are not deferrable.

Applications for honours year scholarships will be open in July each year and close in early-November.

HOW TO BECOME A STUDENT

1. Browse the information and lists of student projects in this booklet.
2. Identify an area of interest, contact a potential supervisor and arrange a suitable project. When you contact potential supervisors, please include a CV and your most recent academic transcript.
3. Submit an admissions application to the University of New South Wales (UNSW). Honours students must be accepted into an Honours program in an appropriate UNSW Faculty. PhD students should successfully fulfil the requirements for admissions through UNSW.
4. Coordinate with your supervisor to obtain clearances from the appropriate Ethics Committees.
5. Begin your research program.

HONOURS

The standard duration of enrolment for an Honours degree is one academic year, actual dates for the honours programs you may enrol in can vary, so please consult the websites below for more detailed information.

When you undertake an Honours project at Children's Cancer Institute you will be enrolled in a UNSW Honours program. Therefore, you need to meet the UNSW Honours entry criteria. For information regarding the Honours Programs at UNSW that students may be enrolled in, please visit the following websites:

- https://www.unsw.edu.au/science/student-life-resources/honours-how-apply
- https://www.unsw.edu.au/science/our-schools/babs/student-life-resources/student-resources/honours
- https://www.unsw.edu.au/medicine-health/our-schools/biomedical-sciences/student-life-resources/honours/soms-honours

POSTGRADUATE STUDIES

The majority of PhD students at the Institute are enrolled through the Faculty of Medicine, School of Clinical Medicine, Paediatrics, Course Code 1825 Child Cancer Research. Professor Richard Lock is the School's Postgraduate Coordinator and is responsible for advising supervisors and Higher Degree Research (HDR) candidates on all academic and administrative matters relating to their candidature.

UNSW Graduate Research School

The UNSW Graduate Research School is the central administrative and support unit for all higher degree research students and their supervisors at UNSW. The website below will direct you to information on admissions requirements and enrolment procedures to undertake postgraduate study at UNSW together with links to scholarship application forms for both local and international students.

https://research.unsw.edu.au/graduate-research

CHILDREN'S CANCER INSTITUTE
RESEARCH GROUPS

Listed below are our 17 Research Groups and their Leaders. Please take a look at our website for more information on their areas of research focus. We are always looking for enthusiastic students interested in our research so even if they don't have projects listed on the following pages.

BRAIN TUMOURS GROUP

Group Leader

Prof David Ziegler ✉ DZiegler@ccia.org.au

Dr Maria Tsoli

Dr Ben Rayner

CANCER EPIGENETIC BIOLOGY AND THERAPEUTICS GROUP

Team Leader and Theme Head (Therapeutic Discovery)

Dr Fa Valdes Mora ✉ FValdesMora@ccia.org.au

CHEMICAL BIOLOGY AND TARGET BASED THERAPIES GROUP

Team Leader Dr

Jean Bertoldo ✉ JBertoldo@ccia.org.au

COMPUTATIONAL BIOLOGY GROUP

Group Leader and Deputy Director (Enabling Platforms and Collaboration)

A/Prof Mark Cowley ✉ MCowley@ccia.org.au

COMPUTATIONAL DRUG DISCOVERY BIOLOGY GROUP

Group Leader

A/Prof Antoine de Weck ✉ ADeWeck@ccia.org.au

EMBRYONAL CANCER THERAPY AND PREVENTION GROUP

Group Leader

Prof Glenn Marshall ✉ GMarshall@ccia.org.au

A/Prof Belamy Cheung

CHILDREN'S CANCER INSTITUTE
RESEARCH GROUPS

EXPERIMENTAL THERAPEUTICS GROUP

Group Leader and Executive Director

Prof Michelle Haber ✉ MHaber@ccia.org.au

A/ Prof. Jamie Fletcher

FUNCTIONAL GENOMICS OF LEUKAEMIA GROUP

Team Leader

Dr Charles de Bock ✉ CDeBock@ccia.org.au

GENE DYSREGULATION GROUP

Group Leader

A/Prof Tao Liu ✉ TLiu@ccia.org.au

GENE THERAPEUTICS AND DRUG DELIVERY GROUP

Team Leader

A/Prof Joshua McCarroll ✉ JMccarroll@ccia.org.au

GENOMIC CHILDHOOD CANCER RISK GROUP

Team Leader

Dr Mark Pinese ✉ MPinese@ccia.org.au

LEUKAEMIA BIOLOGY GROUP

Group Leader and Theme Head (Cancer Biology)

Prof Richard Lock ✉ RLock@ccia.org.au

Dr Patrick Connerty

METAL-TARGETED THERAPY AND IMMUNOLOGY GROUP

Team Leader

A/Prof Orazio Vittorio ✉ OVittorio@ccia.org.au

CHILDREN'S CANCER INSTITUTE
RESEARCH GROUPS

MOLECULAR DIAGNOSTICS GROUP

Principal Scientist

Dr Michelle Henderson ✉ MHenderson@ccia.org.au

MOLECULAR ONCOLOGY GROUP

Group Leader

Prof Murray Norris ✉ MNorris@ccia.org.au

SARCOMA BIOLOGY GROUP

Team Leader

Dr Emmy Fleuren ✉ EFleuren@ccia.org.au

TRANSLATIONAL TUMOUR BIOLOGY GROUP

Group Leader and Deputy Director (Research Themes)

A/Prof Paul Ekert ✉ PEkert@ccia.org.au

Dr Emmy Dolman

TUMOUR BIOLOGY AND TARGETING GROUP

Group Leader

Prof Maria Kavallaris ✉ MKavallaris@ccia.org.au

CHILDREN'S CANCER INSTITUTE
STUDENT PROJECTS

BRAIN TUMOURS GROUP STUDENT PROJECT

Project Title: **Targeting drug resistance in paediatric high-grade glioma**
Supervisor: Prof David Ziegler DZiegler@ccia.org.au and Dr Rebecca Lehmann RLehmann@ccia.org.au
Suitable for: Honours Students
Project outline:

Paediatric high-grade glioma (pHGG) is a devastating form of brain cancer with an extremely poor prognosis. The BRAFV600E mutation has recently been discovered as a driver mutation in a subset of pHGGs, with tumours driven by this mutation responding to targeted BRAF and MEK inhibitors. Unfortunately, resistance inevitably develops, resulting in disease progression. Our laboratory has derived several drug-resistant BRAFV600E mutant pHGG cultures, which display resistance to the drugs commonly used in the clinic. This project will involve identifying potential therapeutic targets in these in vitro models of drug resistance, and subsequently determining the efficacy of novel therapies. A wide range of in vitro techniques will be used and if interested, students can use this project to develop skills in bioinformatics.

LEUKAEMIA BIOLOGY STUDENT PROJECTS

Project Title: **Nanomedicine for the targeted treatment of childhood leukaemia**
Supervisor: Prof Richard Lock RLock@ccia.org.au, Dr Narges Bayat NBayat@ccia.org.au and Dr Sara Mohamed smohamed@ccia.org.au
Suitable for: Honours, ILP, Masters or PhD Students
Project outline:

Acute lymphoblastic leukaemia (ALL) is the most common paediatric malignancy, and is one of the leading causes of death from disease in childhood. Progress in chemotherapy treatment has dramatically improved the survival rates of children with leukaemia. However, conventional therapeutic agents have inherent limitations such as low solubility, limited diffusion across cancer cell membranes, and low therapeutic index which leads to lower treatment efficiency. Moreover, the lack of target specificity of chemotherapy drugs leads to debilitating side effects in >60% of childhood cancer survivors. This highlights the importance of targeted delivery of drugs to cancer cells to ensure reduced toxicity on normal cells and a more efficient treatment. In this project we aim to integrate cancer biology and nanotechnology in order to develop a novel targeted diagnostic and therapeutic system to improve the efficacy, as well as to reduce side effects of chemotherapy treatment in childhood ALL.

Students will have access to the exceptional technical resources, equipment and facilities of the laboratories of Children's Cancer Institute. Some of the techniques and resources involved in this project may include molecular biology, conducting cytotoxicity and cell viability assays, studying cellular interactions of antibodies with their specific targets and preclinical testing of novel therapeutics in orthotopic patient derived xenograft mouse models of childhood ALL.

CHILDREN'S CANCER INSTITUTE
STUDENT PROJECTS

Project Title: **Liquid biopsy for monitoring of minimal residual disease in childhood acute leukaemia**

Supervisor: Prof Richard Lock ✉ rlock@ccia.org.au, Dr Narges Bayat ✉ NBayat@ccia.org.au

Suitable for: Honours, ILP, Masters or PhD Students

Project outline:

Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer. Around 20% of ALL patients will eventually relapse and the prognosis for these patients remains as low as 30%. The strongest prognostic factor for relapse and poor prognosis in childhood ALL is the persistence of minimal residual disease (MRD) in the bone marrow throughout therapy. The current gold standard for detecting MRD and early relapse in high-risk childhood leukaemia are patient- specific tests performed on bone marrow samples collected from the patient. We aim to develop less invasive, but equally sensitive, methods to detect MRD in the peripheral blood called "liquid biopsy". Liquid biopsy is the detection of DNA or microRNA (miRNA) fragments released into the blood and bone marrow by cancer cells (circulating tumour DNA [ctDNA] or ct-miRNA). However, there is limited information about liquid biopsy in childhood leukaemia. Therefore, this project aims to investigate if liquid biopsy can be used for the sensitive detection of residual leukaemia and whether it can be used for ALL risk stratification analogous to conventional MRD assays. Some of the techniques and resources involved in this project may include: Orthotopic patient derived xenograft mouse model of childhood ALL which is considered to be the most clinically relevant model to assess novel therapeutics and diagnostic approaches for childhood leukaemia.

Project Title: **Therapeutic targeting of T-cell acute lymphoblastic leukemia using an AKR1C3 activated prodrug**

Supervisor: Prof Richard Lock ✉ rlock@ccia.org.au, Dr Charles de Bock ✉ CDeBock@ccia.org.au

Suitable for: Honours, Masters or PhD Students

Project outline:

Acute lymphoblastic leukaemia (ALL) is the most common paediatric malignancy and can be broadly divided into B-lineage (B-ALL) and T-lineage (T-ALL). T-ALL is an aggressive malignancy that is exceptionally difficult to cure after relapse. We have recently shown that T-ALL expresses significantly higher levels of the enzyme AKR1C3 compared with B-ALL. These findings were exploited using a first-generation AKR1C3-activated prodrug, OBI-3424, now in a clinical trial.

Our initial testing of the second-generation AKR1C3-activated prodrug, ACHM-025, has shown greater selectivity for activation by AKR1C3 and superior antileukemic efficacy compared with OBI-3424. Moreover, we have identified two active downstream AKR1C3 enhancer regions in T-ALL versus B-ALL cells. In this project we aim to understand the mechanism of AKR1C3 regulation in T-ALL versus B-ALL, and test the efficacy of ACHM-025. This work will facilitate the development of ACHM-025 and will lead to personalised approaches to improve the outcome for patients with T-ALL.

Aims of the project:

1. Define the determinants of response to AKR1C3-activated prodrugs.
2. Define the mechanism of AKR1C3 gene regulation in T-ALL versus B-ALL.
3. Test the in vivo efficacy of ACHM-025 alone and in combination with standard-of-care drugs.

This research project incorporates both discovery science and preclinical studies and will involve molecular biology, epigenetics, genomics and in vivo preclinical testing in our patient-derived xenograft model of paediatric ALL.

CHILDREN'S CANCER INSTITUTE
STUDENT PROJECTS

Project Title: **Targeted treatments for high-risk acute lymphoblastic leukaemia in children**
Supervisor: Prof Richard Lock ✉ RLock@ccia.org.au, Dr Patrick Connerty ✉ PConnerty@ccia.org.au
Suitable for: Honours, Masters or PhD Students
Project outline:

Acute lymphoblastic leukaemia (ALL) is the most common paediatric malignancy and, despite marked improvements in treatment over the past 60 years, it remains one of the most common causes of death from disease in children. While most children will experience good outcomes, several high-risk ALL subtypes, as well as children who experience relapse from their disease, require the development and testing of novel targeted treatments to facilitate cure.

This student project is part of a larger preclinical drug testing endeavor funded in the Primary Supervisor's lab by the US National Cancer Institute continuously for 21 years. Novel targeted drugs are selected for testing in patient-derived xenograft models of paediatric ALL, in collaboration with industry partners. The most active agents are then prioritised for advanced testing and for progression into clinical trials. Several opportunities exist to further elucidate the mechanisms of action of these active drugs, and the molecular determinants of sensitivity or resistance, using cutting edge cell and molecular techniques.

Techniques and key outcomes /learnings:

The Higher Degree Research Candidate will master cutting edge cell and molecular techniques to test hypotheses relating to anti-leukaemic drug mechanism of action and determinants of in vivo sensitivity or resistance, some of which will include:

1. Forward genetics using gene overexpression, knockdown and knockout
2. Genome-wide and small library CRISPR/Cas screening in vitro and in vivo
3. Cell and molecular techniques including flow cytometry, RT-PCR and immunoblotting
4. Experience in working with patient-derived xenograft models of acute leukaemia

Project Title: **Identifying novel long non-coding RNAs vital for paediatric acute myeloid leukemia**
Supervisor: Dr Patrick Connerty ✉ PConnerty@ccia.org.au, Prof Richard Lock ✉ RLock@ccia.org.au
Suitable for: PhD Students
Project outline:

Acute myeloid leukaemia (AML) is a haematological cancer with dismal survival rates in children. A major limitation of AML treatment is the off-target toxicity of current chemotherapies. Consequently, there is a need to identify molecular targets which are specific to AML and absent in healthy cells, allowing for a precision medicine approach to treat the disease. Long non-coding RNAs (lncRNAs) are a class of RNAs which have unique expression profiles in multiple cancers, including AML. Targeting lncRNAs therapeutically is a rapidly emerging field and presents an opportunity to specifically eradicate AML cells. Therefore, the aims of this project are to identify lncRNAs that are both specific and vital for AML cells and explore their potential as therapeutic targets.

Techniques and key outcomes /learnings:

- Tissue culture
- RNA extraction
- qPCR
- Flow cytometry
- Transfection
- Viral transduction
- CRISPR-Cas9 screening
- Bioinformatic analysis
- Animal studies (mice)
- Project design
- Manuscript writing

CHILDREN'S CANCER INSTITUTE
STUDENT PROJECTS

EMBRYONAL CANCER THERAPY & PREVENTION STUDENT PROJECTS

Project Title: **Effective targeting of chemoresistant subclones identified by single cell transcriptomics for the treatment of sarcomas**

Supervisor: A/Prof Belamy Cheung BCheung@ccia.org.au, Dr Parisa Ferdowsi PVahidi@ccia.org.au

Suitable for: Honours, Masters or PhD Students

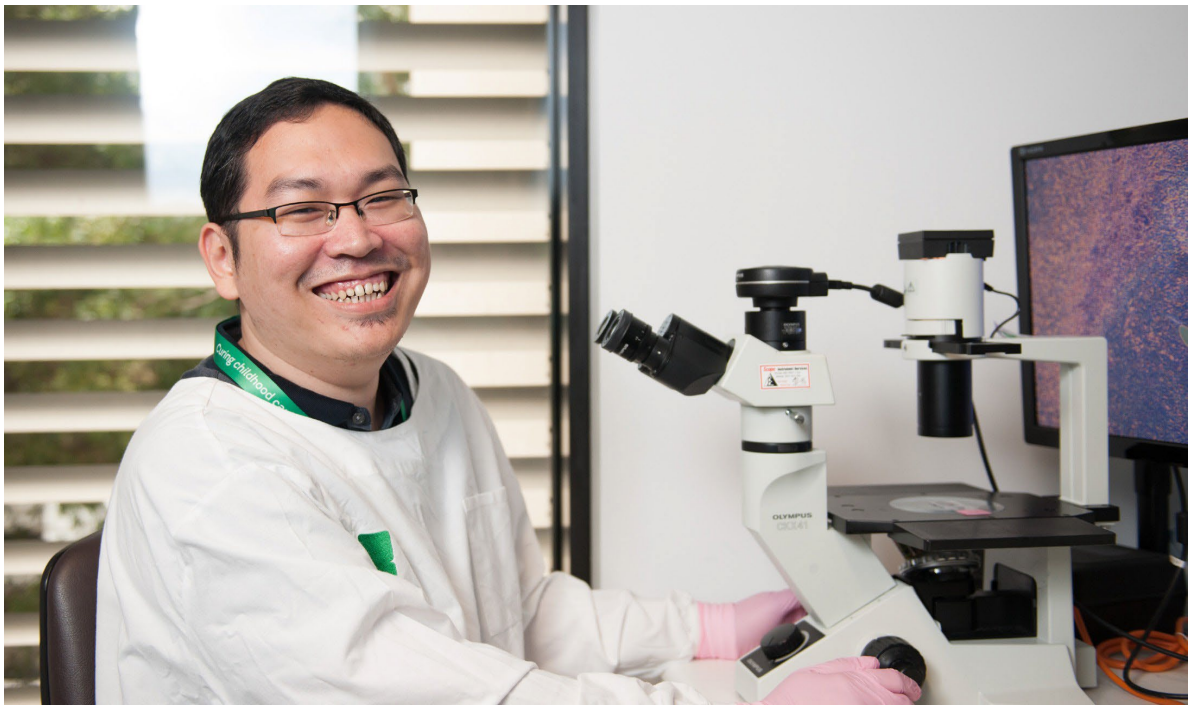
Project outline:

Most child, adolescent and young adult (AYA) sarcoma patients achieve clinical remission with a "one-size-fits-all" chemotherapy approach based on histo-type. Almost one third will relapse and most will die of cancer. There is an urgent need for accurate assays which predict relapse. Longitudinal studies reveal minor cancer subclones at diagnosis which survive early chemotherapy, later leading to relapse. The precision of single cancer cell RNA sequencing (scRNA-seq) has provided unprecedented resolution to uncover the transcriptomic features of these minor subclones. At Children's Cancer Institute we have established the high-throughput droplet-single cell sequencing platform and have performed proof-of-principle experiments comparing osteosarcoma samples before and after chemotherapy, which indeed revealed enrichment of chemoresistant clones with sensitivities to drugs not normally used in that disease. Our study combines cutting edge scRNA-seq and whole exome sequencing (WES), advanced bioinformatics, large public datasets, and unique clinical resources to address fundamental questions about the impact of chemotherapy-resistant subclones on individual patient outcomes.

Techniques and key outcomes /learnings:

The Higher Degree Research Candidate will master cutting edge cellular and molecular techniques to test hypotheses that changes in genomic and transcriptomic patterns among residual malignant cells in the early phases of chemotherapy indicate subclonal selection for chemoresistance and relapse in patients, some techniques will include:

1. Single cell RNA sequencing and development of drug combinations.
2. Forward genetics using gene overexpression, knockdown and knockout.
3. Cellular and molecular techniques including flow cytometry, RT-PCR and immunoblotting.
4. Experience in working with patient-derived xenograft models of sarcoma.
5. Bioinformatics



CHILDREN'S CANCER INSTITUTE
STUDENT PROJECTS

Project Title: **Therapeutic and preventative strategies for children with high-risk neuroblastoma: targeting high fat diet-related metabolism**

Supervisor: A/Prof Belamy Cheung BCheung@ccia.org.au, Dr Ritu Mittra RMittra@ccia.org.au

Suitable for: Honours, Masters or PhD Students

Project outline:

Amongst the most aggressive and treatment-refractory childhood malignancies is high-risk neuroblastoma (NB). Whilst the survival of high-risk NB patients has improved over time, relapse rates in high-risk NB remain high at 50-60% with 5-year survival rates being less than 50% for these patients. Considerable evidence suggests that NB begins in embryonal neuroblasts indicating an aetiological relationship between NB tumorigenesis and embryonal environmental factors. Some studies have suggested that maternal obesity and high birth weight are risk factors for childhood cancer. We found that neuroblastoma driven by the MYCN proto-oncogene, originates from embryonal precancer cells persisting postnatally due to the loss of the normal death response. We discovered a drug which specifically restored the death response to these persistent embryo cells without affecting normal cells, and reduced tumour initiation in mouse models of child cancer. This drug appears to work by blocking cholesterol metabolism in the embryonal precancer cells. This research project will investigate a mechanistic understanding of how high fat diet, maternal obesity and high birth weight contribute to the aetiology of childhood cancer initiation and development and will enable development of effective agents for intervention during pregnancy or in early life that may reduce the incidence of childhood cancer.

Techniques and key outcomes /learnings:

The Higher Degree Research Candidate will master cutting edge cellular and molecular techniques to test hypotheses that high fat diet-induced maternal obesity and high birthweight accelerates NB initiation by activation of fatty acid metabolism, leading to suppression of anti-tumour immunity, some techniques will include:

1. Therapeutic targets and drug identifications.
2. Molecular techniques using gene overexpression, knockdown and knockout.
3. Developing cancer prevention strategies.
4. Experience in working with transgenic and xenograft animal models.

Lab Olympics at the student and postdoc retreat cross over session

CHILDREN'S CANCER INSTITUTE
STUDENT PROJECTS

TUMOUR BIOLOGY AND TARGETING GROUP STUDENT PROJECTS

Project Title: **Engineering childhood cancer models for precision medicine**
Supervisor: Prof Maria Kavallaris ✉ MKavallaris@ccia.org.au and Dr Valentina Poltavets ✉ VPoltavets@ccia.org.au
Suitable for: Honours, Masters or PhD Students
Project outline:

Neuroblastoma and sarcoma patients with recurrent and drug resistant disease have less than a 30% chance of survival and limited therapeutic options. Preclinical models hold a great promise in improving personalised medicine approaches and as a result - patient outcomes. Our laboratory is using 3D bioprinting technology to create culturing conditions for patient-derived cancer cells that mimic native tumour microenvironments.

The extracellular matrix (ECM) is an important component of the tumour microenvironment. However, its roles in childhood solid tumours are not well characterised. Initial gene expression analysis indicates that specific ECM genes are abundantly expressed in these tumours. This project aims to investigate the ECM proteins in patient tissue samples as well as to understand connection between protein expression and patient survival. The impact of these ECM proteins on the tumour growth will be evaluated by establishing and investigating mini-tumours in a dish using advanced 3D bioprinting technology. This exciting project will contribute to developing predictive preclinical models of childhood cancers and improve therapy for high-risk paediatric cancer patients.

Project Title: **Investigating immune cell reprogramming mRNA nanotherapeutics in immunocompetent models of paediatric brain and neuronal cancers**
Supervisor: Dr Ernest Moles ✉ EMoles@ccia.org.au, Prof Maria Kavallaris ✉ MKavallaris@ccia.org.au, and Dr Maria Tsoli ✉ MTsoli@ccia.org.au
Suitable for: Honours, Masters or PhD Students
Project outline:

Cancers originating in the brain and peripheral nerves, such as diffuse midline gliomas and high-risk neuroblastoma, are among the most aggressive cancers during childhood. Chemotherapy and radiotherapy have been vastly unsuccessful, and there is an urgent need to develop safer and more potent treatment strategies for these cancers.

Herein, the student will participate in an innovative and multidisciplinary project whereby we aim to redirect the immune response in the patient, using injectable messenger RNA nanoparticles, to identify and eliminate the cancer cells. Moreover, this treatment approach will be investigated in advanced murine models of brain cancer and high-risk neuroblastoma that harbour an intact functional immune system and closely resemble the behaviour and pathophysiology of the human disease.

The student will learn innovative tools and acquire knowledge in cancer biology, cellular therapy, and mRNA nanomedicine to advance the next generation of therapeutics to fight the deadliest of all paediatric cancers.

CHILDREN'S CANCER INSTITUTE
STUDENT PROJECTS

MOLECULAR DIAGNOSTICS STUDENT PROJECTS

Project Title: **Nanomedicine for the targeted treatment of childhood leukaemia**
Supervisor: Dr Michelle Henderson MHenderson@ccia.org.au, Dr Toby Trahair TTrahair@ccia.org.au and Dr Benjamin Schreiber BSchreiber@ccia.org.au
Suitable for: Honours, ILP or Masters Students
Project outline:

In acute lymphoblastic leukaemia (ALL), the amount of malignant cells that remain in the bone marrow after chemotherapy, referred to as minimal or measurable residual disease (MRD), is highly prognostic of clinical outcome. Molecular monitoring of MRD during treatment is widely used to help predict relapse and to tailor therapy for individual patients. These analyses typically involve quantitative PCR based on leukaemia-specific IG/TCR gene rearrangements for each patient, but these are time-consuming to develop and not achievable for all patients.

Recent technological developments provide opportunities to improve the coverage and quality of molecular PCR-based MRD testing. Several projects are available:

1) A newly developed in-house software for identification of IG/TCR rearrangements from next-generation whole genome sequencing (WGS) data will be compared to traditional approaches.

2) WGS data will be used to identify alternative genomic breakpoints (other than IG/TCR genes) that can be used to design robust leukaemia-specific qPCR-based tests.

For 1) and 2), performance of each assay designed will be evaluated against the current MRD monitoring procedures using material available through the CCI tumour bank.

3) To most efficiently apply WGS for MRD monitoring, it would be ideal to be able to predict up-front which patients are more likely to fail conventional MRD marker development. Based on a hypothesis that this property might be influenced by the biology of the disease, clinicopathological and genetic data will be used to develop machine learning algorithms to help identify such cases.

4) Very low level MRD is of increasing clinical interest, especially for patients receiving bone marrow transplant or immunotherapies. We are investigating approaches to improve assay sensitivity and to discriminate true positive results.

Paint your thesis at the 2023 annual student retreat

CHILDREN'S CANCER INSTITUTE
STUDENT PROJECTS

TRANSLATIONAL TUMOUR BIOLOGY STUDENT PROJECTS

Project Title: **Integrative data analysis: from novel biomarker-drug response associations to predicting effective drug combinations**

Supervisor: Dr Emmy Dolman ✉ EDolman@ccia.org.au and A/Prof Paul Ekert ✉ PEkert@ccia.org.au

Suitable for: Honours, or PhD Students

Project outline:

More than 140 children with cancer die in Australia each year due to the occurrence of resistance to traditional chemotherapy. To improve overall survival rates for high-risk paediatric cancer patients, Children's Cancer Institute initiated the Zero Childhood Cancer national personalised medicine trial (PRISM). Within this trial, tumour biopsies from children with high-risk cancer are collected for full molecular profiling to identify cancer driver events and for the generation of patient-derived model systems to link these events to targeted therapies.

WGS, RNA-Seq and DNA methylation profiling of >350 tumour samples showed actionable events in only 70% of the patients. High-throughput drug testing on >150 patient-derived samples yielded unexpected efficacy patterns for single agent targeted drugs without an associated predictive biomarker, but clinical trials for paediatric cancer have proven that treatment with single agents is insufficient in most cases. The current study aims to integrate PRISM molecular profiling and in vitro drug efficacy datasets to identify novel biomarker-drug response associations and predict effective drug combinations for paediatric cancer by developing novel bioinformatic algorithms. Publicly available databases such as DepMap, CancerrXGene and NCI-ALMANAC that contain in vitro efficacy data for single drugs and drug combinations alongside molecular characterisation of the used model systems will be exploited for algorithm optimisation and deeper integrative analysis. Novel discovered biomarker-drug response associations and drug combinations will be validated in vitro and in vivo in patient-derived model systems to guide future clinical trials for paediatric cancer treatment.

Project Title: **Novel drug combination bullets for improved targeting of oncogenic signaling pathways driving high-risk paediatric cancer**

Supervisor: Dr Emmy Dolman ✉ EDolman@ccia.org.au and A/Prof Paul Ekert ✉ PEkert@ccia.org.au

Suitable for: Honours, or PhD Students

Project outline:

More than 140 children with cancer die in Australia each year due to the occurrence of resistance to traditional chemotherapy. The global effort to understand the molecular basis of high-risk paediatric cancers has unravelled several important signaling pathways frequently genetically altered, including Ras-MAPK, PI3K-Akt-mTOR, cell cycle, and DNA damage response. This has led to the clinical use of drugs targeting selective key players in these pathways such as trametinib inhibiting the Ras-MAPK key player MEK. However, clinical responses to many targeted drugs have been disappointing because of 1) the challenge to accurately predict which patients might benefit from targeted therapies
and 2) the occurrence of resistance to single targeted drugs. The current study aims to identify improved predictive biomarkers and combination strategies to overcome resistance for clinically available drugs targeting key oncogenic signaling pathways driving high-risk paediatric cancers. We will make use of the unique resources available through the national Zero Childhood Cancer personalised medicine program, including WGS and RNA sequencing data for >600 tumour samples, in vitro drug response data for >150 tumour samples, and >150 patient-derived models. Biomarker identification and validation will be performed using technologies such as integrative data analysis, phosphoproteomics, and CRISPR gene editing. Novel drug combinations will be identified by in vitro high-throughput combination testing and genome-wide CRISPR screening. Novel discovered biomarker-drug response associations and drug combinations will be validated in vitro and in vivo in patient-derived model systems to guide future clinical trials for paediatric cancer treatment.

CHILDREN'S CANCER INSTITUTE
STUDENT PROJECTS

Project Title: **Unlocking the full potential of personalised treatments – investigating novel mechanisms of kinase activation in paediatric cancer**

Supervisor: Dr Lauren Brown ✉ LBrown@ccia.org.au and A/Prof Paul Ekert ✉ PEkert@ccia.org.au

Suitable for: PhD Students

Project outline:

Personalised medicine programs like the Zero Childhood Cancer Program (ZERO) analyse individual patient tumours to identify molecular targets for therapy. Receptor tyrosine kinases (RTKs) can be effectively targeted with RTK inhibitors when activated in cancer, most notably by gene fusions and missense mutations. The challenge arises when genomic alterations are identified in RTK genes but the functional consequences (whether the alteration results in RTK activation and RTK inhibitor sensitivity) of the alteration are unknown. Through functional analysis of individual genomic alterations in RTK genes we have characterised novel mechanisms of kinase activation, identifying more patients that will benefit from RTK inhibitor therapy.

In this project, we will investigate a range of novel and suspected kinase-activating genomic events identified in ZERO. Examples of these events include:

1. Novel structural variants involving RTK genes
2. Alternative splicing of RTK genes
3. Mutation of RTK regulating genes

We will use well-established ectopic overexpression systems and CRISPR/Cas9 for gene knockout, as well as emerging genomic and RNA editing techniques, including CRISPR activation (CRISPRa) and CRISPR/Cas13, to generate accurate cell models of individual variants. We will then use molecular and cell biology techniques to characterise the capacity to drive cellular transformation, the molecular mechanisms by which the variant drives transformation, and sensitivity to targeted inhibitors.

By functionally characterising individual genomic variants, this project will enhance our understanding of RTK biology in cancer and importantly, identify a new class of patients that may benefit from RTK inhibitors.

Children's Cancer Institute

UNSW Australia

CRICOS Provider Code 0009