STUDENT PROJECTS 2019

Children's Cancer Institute

Children's Cancer Institute

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

STUDENT PROJECTS
2020 INDEX

CHILDREN'S CANCER INSTITUTE

A MESSAGE FROM EXECUTIVE DIRECTOR PROFESSOR MICHELLE HABER, AM

Children's Cancer Institute Executive Director: Professor Michelle Haber, AM

Today, as a result of medical research, eight out of 10 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 sole 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 in Sydneyat the Lowy Cancer Research Centre, UNSW Australia, 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 or our Researcher Development and Strategy Manager, Dr Amanda Philp ✉ education@ccia.org.au

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 teams directly to discuss a project to best suit both you and the rrea of reseach focus.

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 and the support of your peers through the Children's Cancer Institute Student Council that runs activities throughout the year, including an annual student retreat.

POSTGRADUATE SUPPLEMENTARY AWARD

We offer a Supplementary Award of $7000 per annum for up to 3.5 years to students who have been awarded a competitive scholarship. This will be awarded to students where the scholarship is equivalent to an Australian Postgraduate Award or University Postgraduate Award.

JOSEE HILTON POSTGRADUATE 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 $7000 top-up supplementary award.

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.

SUMMER STUDENTSHIPS

These scholarships are provided to outstanding undergraduate science students during the summer university break. Summer scholarships are a great way for students to get involved in real-life cancer research.

For further information and application forms for our Honours Scholarships and the Summer Student Program please visit the student pages on our website at www.ccia.org.au or contact
Dr Amanda Philp, Researcher Development and Strategy Manager
education@ccia.unsw.edu.au

Students prepare to go zip-lining on their annual student retreat

CHILDREN'S CANCER INSTITUTE

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, 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 three Honours Programs at UNSW that students may be enrolled in, please visit the following websites:

Bachelor of Science (Medicine) Honours Program (UNSW Medicine)

http://medprogram.med.unsw.edu.au/honours-program

School of Medical Sciences Honours Program (UNSW Medicine)

http://medicalsciences.med.unsw.edu.au/students/soms-honours/overview

School of Biotechnology and Biomolecular Sciences (BABS) Honours Program (Faculty of Science)

http://www.babs.unsw.edu.au/future_students/future-honours-students

POSTGRADUATE STUDIES

The majority of PhD students at the Institute are enroled throught the Faculty of Medicine, School of Women's and Children's Health, Paediatrics, Course Code 1825. Professor Richard Lock is the School's Postgraduate Coordinator and is responsible for advisiing 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.

http://research.unsw.edu.au/units/graduate-research-school

Professor Richard Lock

USEFUL LINKS FOR INTERNATIONAL STUDENTS

http://www.immi.gov.au/index.htm

http://www.international.unsw.edu.au

CANCER AND STEM CELL BIOLOGY

Group leader: Dr Jenny Wang

The main focus of research in the Cancer and Stem Cell Biology Group is to develop novel therapeutic strategies specifically targeting and destroying cancer stem cells that are often resistant to commonly used cancer therapies such as radiation therapy and chemotherapy, and that are now believed to be the engine driving the growth of a tumour and the root cause of treatment resistance and relapse in cancer.

Stem cells have become the centre of much attention because they are capable of dividing to produce copies of themselves (self-renewal) indefinitely and also generating multiple cell types. Genetic and epigenetic abnormalities enable cancer stem cells to hijack normal stem cell self-renewal mechanisms that multiply out of control, causing cancer. Cancer stem cells are able to evade treatment and regenerate cancer through their self-renewal capacity. Targeted disruption of abnormal stem cell self-renewal represents a novel therapeutic strategy that could significantly reduce the capacity of a tumour to regenerate itself after treatment and is becoming a central focus in new drug development.

Objectives:

- T0 understand the mechanisms by which genetic and epigenetic events are required for transforming normal stem cells into abnormal stem cells
- To identify key oncogenic self-renewal genes and pathways as novel therapeutic targets
- To investigate the interaction between the bone marrow microenvironment and normal/abnormal blood stem cells
- To identify inhibitors selectively targeting blood cancer (leukaemia) stem cells without harming normal stem cells

CANCER AND STEM CELL BIOLOGY STUDENT PROJECTS

Project Title: **Targeted elimination of leukaemia stem cells through disruption of key oncogenic self-renewal pathways**

Supervisor: Dr Jenny Wang ✉ jwang@ccia.unsw.edu.au

Suitable for: Honours and PhD Studies

Project outline: Cancer therapies have historically depended on the use of cytotoxic drugs that non-specifically kill cells Acute myeloid leukaemia (AML) is an aggressive blood cancer with a five-year survival rate of only 24% in Australia. Despite intensive chemotherapy, the majority of patients with AML relapse and ultimately die from their disease.

Clinical evidence has supported the important role of leukaemia stem cells in the high relapse rate of AML patients. Leukaemia stem cells reside in a mostly quiescent state and as such they are resistant to commonly used anti-proliferation cytotoxic agents. These cells possess several unique features, including increased self-renewal, blocked differentiation and escaping from cell death. These features are caused by aberrant expression of oncogenic genes, and can distinguish leukaemia from normal stem cells. Targeted elimination of leukaemia stem cells is now believed to be essential for patients with AML to achieve a complete remission.

Our studies have identified key oncogenic self-renewal pathways (e.g. beta-catenin and GPR84, Science 2010 and Blood 2014) for AML stem cell formation and our exciting new findings of pathway inhibitors provide promising therapeutic approaches and opportunities to specifically target leukaemia stem cells. This project is designed to understand the mechanism of action of these inhibitors in order to develop more efficient stem cell-targeted therapies. The outcome of this study will generate new insights into leukaemia stem cell biology and provide pre-clinical validation of therapeutic potential. This research therefore has the potential to lead directly to the development of novel therapeutic strategies that selectively kill drug-resistant leukaemia stem cells.

CANCER AND STEM CELL BIOLOGY

Project Title: **Epigenetic regulation of leukaemia stem cells - developing new epigenetic therapies**
Supervisor: Dr Jenny Wang ✉ jwang@ccia.unsw.edu.au
Suitable for: Honours and PhD Studies
Project outline: Epigenetic regulation of gene expression plays crucial roles in stem cell functions. Inappropriate maintenance of epigenetic 'marks' - that sit on the nuclear DNA of cancer cells and control the activity of genes - results in activation of oncogenic self-renewal pathways leading to the formation of leukaemia stem cells and the subsequent development of leukaemia. Unlike genetic alterations, epigenetic marks can be reversed by treatment with chromatin-modifying drugs, making them suitable targets for epigenetic-based therapy.

Our preliminary studies have identified several new chromatin modifiers that contribute to leukaemia formation and progression. This project aims at exploring epigenetic mechanisms that govern leukaemia stem cell functions and at discovering chromatin-modifying drugs that are capable of reversing cancer-associated epigenetic marks. The outcome of this study will identify epigenetic targets crucial for leukaemia stem cell survival with the potential to develop novel epigenetic cancer therapies.

Project Title: **Investigating tumour microenvironment in leukaemia stem cells**
Supervisor: Dr Jenny Wang ✉ jwang@ccia.org.au
Suitable for: Honours and PhD Studies
Project outline: The bone marrow niche is a local microenvironment that supports blood-cell formation (haematopoiesis) and allows a stem cell to maintain its stemness property. Perturbation in haematopoietic microenvironment could cause stem cell dysfunctions and as a result, lead to haematopoietic malignancies.

reasing evidence suggests that leukaemia stem cells also require support from the bone marrow niche to maintain their self-renewal capacities. Our previous studies (Blood 2011) have shown that pre-leukaemia stem cells can home to and engraft the bone marrow niche, suggesting that stem cell – niche interactions are required for leukaemia initiation. The objective of this project is to identify critical events that are capable of converting a normal stem cell niche into a leukaemia stem cell niche and to investigate genetic and epigenetic regulation of the niche and its associated stem cells. The understanding of this oncogenic process would permit the development of novel therapeutic strategies targeting the leukaemia stem cell microenvironment.

Project Title: **Developing RNA-based therapeutics targeting leukaemia stem cells**
Supervisor: Dr Jenny Wang ✉ jwang@ccia.org.au
Suitable for: Honours and PhD Studies
Project outline: The recent discovery of non-coding RNAs (ncRNAs) has dramatically altered our view of gene regulation in cancer. NcRNAs can serve as regulatory molecules, playing a pivotal role in cancer progression and metastasis. Long ncRNAs (lncRNAs) are defined as non-protein coding transcripts longer than 200 nucleotides and have demonstrated oncogenic or tumour suppressive capabilities.

Our preliminary studies have identified a novel lncRNA and defined its essential role in inhibiting β-catenin signalling, which is a critical driver of cancer stem cells in AML and several other such as lung, prostate and colon cancer. This study will characterise the role of the novel controlling the aberrant function of leukaemia stem cells and develop RNA-based therapeutics leukaemia treatment.

cancers,
lncRNA in
for

Techniques: Cell culture, cell-based assays, drug response assays, molecular biology, gene next-generation sequencing, protein expression, immunofluorescence, immunohistochemistry cancer mouse models

editing,
and

EXPERIMENTAL THERAPEUTICS

Group Leader: Professor Michelle Haber AM

Research in the Experimental Therapeutics Group is directed at identifying critical genes or proteins that contribute to the unregulated growth and malignant behaviour of cancer cells. By identifying these 'molecular targets', we can work towards developing new cancer therapies based on blocking or modifying the action of these molecules, either using existing anti-cancer drugs or by developing novel anti-cancer agents.

Objectives:

- To understand the role of the MYCN oncogene and the related c-myc gene in regulating the behaviour of multidrug transporter genes in childhood and adult cancers
- To understand how the MRP1 and MRP4 multidrug transporter genes are involved in mediating neuroblastoma development and progression
- To develop and optimise clinically relevant small-molecule inhibitors of the MYCN and c-myc oncogenes, and MRP 1 and MRP 4 genes
- To develop a safer more effective treatment for neuroblastoma, involving inhibition of the ODC1 gene by DFMO combined with modern combination chemotherapy
- To establish a new laboratory model of metastatic neuroblastoma to study genes that promote tumour spread and to identify new treatment approaches to block that spread.

EXPERIMENTAL THERAPEUTICS STUDENT PROJECTS

Project Title: **Targeting protein production in MYC-driven cancers**

Supervisor: Dr Michelle Henderson ✉ MHenderson@ccia.org.au&
Dr Jixuan Gao ✉ JGao@ccia.org.au

Suitable for: Honours and PhD Studies

Project outline: Less than half of the children with high-risk neuroblastoma survive their cancer. More selective and effective treatments are therefore needed. Some of the worst cases of neuroblastoma are driven by amplification of the MYCN oncogene, but direct targeting of MYCN has so far not been possible. We have identified the translation factor ABCE1 as a direct target of MYCN that is expressed at particularly high levels in the worst cases of neuroblastoma. Moreover, ABCE1 is essential for the growth and spread of high-risk neuroblastoma cells but not for survival of normal cells. We plan to exploit this discovery by developing a therapeutic against ABCE1 and thereby provide a safe and effective therapy for high-risk neuroblastoma and potentially other cancers that depend on this factor.

Projects working towards this goal are available in the following areas:

1) Identify small molecule inhibitors of ABCE1 using high-throughput screening of a library of compounds pre-selected by in silico screening

2) Examine the role of ABCE1 in other MYC-dependent cancers

3) Determine the precise mechanism of action of ABCE1 in MYC-driven protein synthesis

4) Examine the role of the related MYCN-driven translation factor ABCF1 in the malignant characteristics of neuroblastoma

EXPERIMENTAL THERAPEUTICS

Project Title: **Polyamine depletion as a therapy for childhood neuroblastoma**

Supervisor: Professor Michelle Haber ✉ MHaber@ccia.org.au &
Professor Murray Norris ✉ MNorris@ccia.unsw.edu.au &

Suitable for: PhD Studies

Project outline: Despite intensive treatments the majority of children with high risk neuroblastoma still die from disease, and surviving patients suffer from lifelong morbidities. Therefore new and safer therapies are urgently needed.

Amplification of the MYCN oncogene occurs in approximately 20% of neuroblastomas and is a powerfulmarker of aggressive disease and poor outcome. Since MYCN itself is pharmacologically difficult to target, an alternative approach is to target downstream pathways necessary for tumour maintenance and progression. One such pathway is the polyamine pathway. Polyamines are highly-regulated essential cations that are elevated in rapidly-proliferating tissues. Ornithine decarboxylase (ODC1) is the first and rate-limiting enzyme in polyamine biosynthesis, and high expression is highly predictive of poor outcome in neuroblastoma. In addition, ODC1 is a well-characterised transcriptional target of MYCN. We have recently shown that MYCN directly and positively regulates all of the other genes of the pathway involved in maintaining high polyamine levels, but negatively regulates those responsible for polyamine catabolism.

Targeting polyamine metabolism through ODC1 inhibition has long been an attractive approach for cancer therapy, and the first clinically approved ODC1 inhibitor to reach the market was difluoromethylornithine (DFMO). However, despite promising preclinical testing, early phase clinical trials in adult cancers were disappointing. DFMO treatment resulted in the activation of compensatory mechanisms, such as increased polyamine uptake from the bloodstream and tumour microenvironment, which counteracted the effect of inhibiting ODC1. Therefore to successfully deplete intracellular polyamines, multiple steps in the polyamine pathway need to be targeted.

We have demonstrated that neuroblastoma is particularly sensitive to polyamine depletion. In neuroblastoma mouse models, DFMO was found to significantly extend survival and to synergise with chemotherapeutics. Based on our findings, a clinical trial combining DFMO with conventional chemotherapy and celecoxib (an inducer of the catabolic arm of the polyamine pathway), is currently underway. Additional experiments in our transgenic mouse model suggest that combining DFMO with compounds that target other steps of the polyamine pathway will further improve the anti-tumour response. Approaches include inhibiting polyamine uptake, using polyamine analogues, and combining DFMO with compounds targeting metabolites upstream of the polyamine pathway.

The aim of this PhD is to identify compounds that can deplete polyamines, and to determine which combinations are optimal. We believe this is an exciting and powerful therapeutic strategy for the treatment of neuroblastoma.

Dr Michelle Henderson

Dr Jixuan Gao

EXPERIMENTAL THERAPEUTICS

Project Title: **Modelling personalised medicine for high risk neuroblastoma**

Supervisor: Dr Jamie Fletcher JFetcher@ccia.org.au &
Dr Alvin Kamili AKamili@ccia.org.au &
Dr Caroline Atkinson CAtkinson@ccia.org.au

Suitable for: Honours and PhD studies

Project outline: Cure rates for children with high-risk neuroblastoma remain less than 50%, with dose-limiting toxicities and the adverse effects of conventional chemotherapy presenting major challenges. These challenges may be partially resolved by the implementation of personalised medicine strategies. These approaches seek to match an individual's tumour to specific targeted agents and provide an alternative to the "one-size-fits-all" approach of conventional chemotherapy. Patient-derived xenograft (PDX) models can facilitate proof-of-principle studies for personalised medicine and in the longer term these models have the potential to be integrated into the decision making process for cancer therapy. The aims of this project re to increase the success rate and to decrease the establishment time for PDX models of neuroblastoma. These studies comprise part of a broader personalised medicine initiative within CCI and the Sydney Children's Hospital Network

Aims:

1. To increase the success rate and to decrease the establishment time for PDX models of neuroblastoma.

2. To validate models generated under optimised conditions

3. To generate matched patient-derived cell lines (PDCLs) from these models for use in drug screening and follow-up studies

Techniques: **Techniques:**

Mouse cancer models, histological and molecular analyses, cell culture techniques, drug response assays.

Dr Alvin Kamili

Dr Caroline Atkinson

EXPERIMENTAL THERAPEUTICS

Project Title: **Improving relapse prediction for high-risk neuroblastoma**

Supervisor: Dr Toby Trahair ✉ Toby.Trahair@health.nsw.gov.au &
Dr Jamie Fletcher ✉ JFetcher@ccia.org.au

Suitable for: PhD studies

Project outline: Neuroblastoma is a solid tumour of infancy and early childhood. Most children diagnosed with high-risk neuroblastoma (HR-NB) have disseminated disease at diagnosis, with survival rates ~50% despite combination chemotherapy, radiation therapy, and immunotherapy. Once a child with HR-NB relapses, there are no curative therapies available. While there is a robust pipeline of potential new therapies for HR-NB, there are substantial challenges with translating these new approaches into clinical reality.

Dr Jamie Fletcher

A key challenge is the need for reliable prediction or early identification of patients at very high risk of relapse. In this research project, we will take advantage of two clinical trials for HR-NB patients to address this challenge; the HR-NBL2/SIOPEN trial, which enrols HR-NB patients at diagnosis, and the PRISM trial, which enrols HR-NB patients at relapse. We will conduct genomic analysis of neuroblastoma patient samples to determine the origin of relapse and determine whether DNA-based minimal residual disease detection can reliably monitor disease course and predict impending relapse. The project builds on the expertise of the research team in high-risk neuroblastoma, clinical trials, patient-derived xenograft (PDX) development, genomics and minimal residual disease testing. The specific aims of this study are:

Aims:

1. To determine whether relapse of high-risk neuroblastoma is driven by disseminated tumour cells present at diagnosis

2. To determine whether DNA-based minimal residual disease detection can more reliably predict impending relapse than the current RNA-based approach for high-risk neuroblastoma patients

3. To determine whether the ability of a patient's tumour to xenograft is a predictor of relapse and whether engrafted tumours are representative of the donor tumour

FUNCTIONAL GENOMICS OF LEUKAEMIA

Group Leader: Dr Charles de Bock

Survival rates now approach 90% for children diagnosed with acute lymphoblastic leukaemia (ALL). However, current treatment often results in severe chronic health conditions, and outcomes for relapsed ALL cases remain poor. Considerable effort has been made to understand the molecular aberrations that underpin disease manifestation and progression, with the ultimate aim of developing novel therapeutic approaches tailored to an individual's mutational signature.

Although critical oncogenic mutations have now been identified through large-scale Next Generation Sequencing efforts, many of these mutations have only been studied in isolation, and targeting such mutations using a single therapeutic agent often fails to yield true clinical benefit. Hence, there is a critical need to move away from the current paradigm of 'one variant and one therapy'. To maximise clinical impact, we need to better understand the functional relationship between multiple co-occurring mutations, to enable the design of intelligent combination approaches for the treatment of ALL.

Our group aims to expand the understanding of how ectopic signalling and somatic mutations drive the development of ALL. For example, in T-cell ALL (T-ALL), these include activating mutations within JAK1, JAK3 and IL7R that lead to ligand independent activation of STAT5; inactivating mutations of PTEN that lead to PI3K/AKT signalling pathway activation; and a high frequency of NOTCH1 mutations. In addition, T-ALL is also characterised by the mutually exclusive expression of transcription factors including TAL1, TLX1, TLX3, HOXA9/10, LMO2 and NKX2-1, often the consequence of chromosomal rearrangements.

As part of our ongoing efforts, we use both cell line and in vivo mouse models together with CRISPR-Cas9, ChIP-seq, ATAC-seq, nanopore-sequencing and RNA-seq base technologies to model how these different mutations cooperate with one another and drive disease. It is hoped that this in turn will help us design more targeted therapies for patients.

FUNCTIONAL GENOMICS OF LEUKAEMIA

Project Title: **IOncogenic cooperation in T-cell acute lymphoblastic leukemia**

Supervisor: Dr Charles de Bock CdeBock@ccia.org.au &
Prof Richard Lock RLock@ccia.org.au

Suitable for: PhD studies

Project outline:

Clinically, T-cell acute lymphoblastic leukemia (T-ALL) T-ALL patients have 10-20 damaging genomic lesions targeting critical cellular pathways including lymphoid development, cell cycle regulation, tumor suppression, and lymphoid signaling. Sequencing data from large cohorts of T-ALL patients now provides us a unique opportunity to analyze the associations between these different genetic lesions in an effort to seek new therapeutic strategies.

This project will have three broad aims:

Aim1: Determine the higher order transcriptional complexes recruited to genomic loci co-bound by both HOXA9 and STAT5

This will use rapid immunoprecipitation mass spectrometry of endogenous proteins (RIME) to isolate and characterize the transcriptional complexes where both STAT5 and HOXA9 are present and performed primarily within in transformed primary mouse hematopoietic progenitor cells. This will then be followed by a CRISPR/Cas gene screen to determine the reliance on identified factors in driving the oncogenic cooperation between STAT5 and HOXA9.

Aim 2: Analyse Cooperation between TLX3 and inactivation of BCL11B, CTCF or KDM6A.

In vivo bone marrow transplant experiments with CRISPR-Cas9 mediated knockdown of BCL11B, CTCF or KDM6A in conjunction with inducible TLX3 expression within early T-cell development to define whether these associations are also cooperating lesions.

Aim 3: Investigate the cooperation between FLT3 mutation and HOXA9 or TLX3.

In vivo bone marrow transplant experiments will be used to over express HOXA9 or TLX3 with FLT3 mutations. The mechanism of cooperation will be investigated using ChIP-, ATAC- and RNA-seq.

HISTONE MODIFICATION

Group Leader: Associate Professor Tao Liu

Research in the Histone Modification Group focuses on the interplay among Myc oncoproteins, histone deacetylases (HDACs) and histone demethylases during tumour initiation and progression, the mechanism through which histone deacetylases and histone demethylases result in transcriptional repression of tumour suppressor genes, and the anticancer efficacy of histone deacetylase inhibitors and histone demethylase inhibitors.

Objectives:

- To investigate the role of the interplay among Myc oncoproteins, HDACs and histone demethylases in modulating gene transcription, the initiation and progression of neuroblastoma in children and pancreatic cancer in adults
- To determine the anticancer efficacy of novel inhibitors of the class III histone deacetylase SIRT1 against neuroblastoma
- To determine the role of histone demethylases in Myc-induced transcriptional modulation and tumourigenesis and the role of histone demethylase inhibitors in cancer therapy

HISTONE MODIFICATION STUDENT PROJECTS

Project Title: **Histone demethylases and histone methyltransferases in modulating gene transcription, tumour initiation, progression and metastasis**

Supervisor: A/Prof Tao Liu ✉ TLiu@ccia.org.au

Suitable for: Honours, Masters or PhD Studies

Project outline: One of the most important advances in cancer research in the last 5 years is the identification of histone demethylases and histone methyltransferases as critical players in gene transcription, tumour initiation, progression and metastasis. In collaboration with researchers at University of North Carolina (USA), Baylor College of Medicine (USA) and Nagoya City University (Japan), we are currently investigating histone demethylases and histone methyltransferases in modulating gene transcription, tumour initiation, progression and metastasis, as well as examining the use of histone demethylase inhibitors and histone methyltransferase inhibitors as novel anti-cancer agents in human cancer cell lines and in animal models of human cancers.

Techniques to be employed: cell culture, siRNA and plasmid transfection, cell proliferation, apoptosis, migration, invasion and metastasis assays, RNA, DNA and protein extraction, RT-PCR, immunoblot, immunoprecipitation, chromatin immunoprecipitation, molecular cloning, immunohistochemistry, immunocytochemistry, animal work, Affymetrix microarray and protein expression.

Project Title: **Identification of novel proteins critical for Myc oncoprotein stabilisation / degradation**

Supervisor: A/Prof Tao Liu ✉ TLiu@ccia.org.au

Suitable for: Honours, Masters or PhD Studies

Project outline: Myc oncoproteins including N-Myc and c-Myc are over-expressed in approximately 50% of tumour tissues from the general population of cancer patients. One of the most important aspects of Myc oncogenesis is the stabilization/degradation of Myc oncoproteins. In the last 2 years, we have identified two novel pathways through which Myc oncoproteins are stabilized/degraded. The novel pathways for Myc oncoprotein stabilization/degradation provide novel targets for cancer therapy, and we are currently investigating proteins critical for the pathways and their roles as novel anti-cancer targets.

Techniques to be employed: cell culture, siRNA and plasmid transfection, cell proliferation and apoptosis assays, RNA, DNA and protein extraction, RT-PCR, immunoblot, immunoprecipitation, chromatin immunoprecipitation, luciferase assay, ubiquitination assay and protein expression.

HISTONE MODIFICATION

Project Title: **The role of histone deacetylases in Myc oncogenesis and histone deacetylase inhibitors in cancer therapy**

Supervisor: A/Prof Tao Liu ✉ TLiu@ccia.org.au

Suitable for: ILP, Honours, Masters or PhD Studies

Project outline: Histone deacetylases (HDACs) repress the transcription of tumour suppressor genes and are involved in the initiation and progression of a variety of human cancers. Myc oncoproteins are over-expressed in approximately 50% of tumour tissues from the general population of cancer patients. We have found that Myc oncoproteins directly recruit HDACs to target gene promoters, leading to transcriptional repression of tumour suppressor genes and malignant transformation, and that therapeutic treatment with HDAC inhibitors reverses the effect of Myc oncoproteins in tumour-bearing transgenic mice.

In this project, we will further explore the interaction between HDAC and Myc oncoproteins, identify other components of the HDAC-Myc protein complex, and establish the role of HDAC inhibitors as effective agents for the prevention and treatment of Myc oncoprotein-induced cancers.z

Techniques to be employed: cell culture, siRNA and plasmid transfection, cell proliferation and apoptosis assays, RNA, DNA and protein extraction, RT-PCR, immunoblot, immunoprecipitation, chromatin immunoprecipitation, molecular cloning, immunohistochemistry, immunocytochemistry, animal work, Affymetrix microarray and protein expression.

Project Title: **The critical roles of long noncoding RNAs in tumourigenesis and as targets for cancer therapy**

Supervisor: A/Prof Tao Liu ✉ TLiu@ccia.org.au

Suitable for: ILP, Honours, Masters or PhD Studies

Project outline: Long intergenic noncoding RNAs (lincRNAs), which range in size from two hundred to tens of thousands of bases, comprise a distinct class of newly discovered noncoding RNAs. Although >3,000 human lincRNAs have been annotated and predicted by bioinformatics analysis, <1% of these have been experimentally characterized. Recent studies suggest that lincRNAs regulate gene transcription, tumour initiation, progression and metastasis. We have made the novel finding that gene amplification of a lincRNA is essential for the transcription of a critical oncogene, and is essential for neuroblastoma cell proliferation. We are currently investigating how the lincRNA modulates gene transcription of oncogenes and how to target the lincRNA for cancer therapy.

Techniques to be employed: RNA extraction, bioinformatics analysis of RNA sequencing data, cell culture, siRNA and plasmid transfection, cell proliferation and apoptosis assays, RT-PCR, immunoblot, immunoprecipitation, chromatin immunoprecipitation, molecular cloning, animal work, Affymetrix microarray and protein expression.

Project Title: **Enhancing the anticancer efficacy of BET bromodomain protein inhibitors**

Supervisor: A/Prof Tao Liu ✉ TLiu@ccia.org.au

Suitable for: Honours, Masters or PhD Studies

Project outline: BET bromodomain (BRD) proteins are emerging as critical oncogenic factors. The BRD inhibitor JQ1 and I-BET151 are among the most promising novel anticancer agents. Since discovered in 2010, JQ1 and I-BET151 have been shown considerable anticancer effects against leukemia, lymphoma, myeloma and lung cancer in vitro and *in vivo*, through blocking the transcription of oncogenes. Consequently, pharmaceutical companies are racing to test JQ1 and I-BET151 in cancer patients. However, the *in vivo* studies also show that JQ1 and I-BET151 do not cause cancer remission on their own. As such, combination treatment with the BRD inhibitors and other anticancer agents are expected to form the platform for novel efficient anticancer therapy in cancer patients. In this project, we would like to screen small molecule compound libraries, in order to identify the “hit” anticancer agent which exerts the best synergistic anticancer efficacy when combined with JQ1 or I-BET151. We expect that combination therapy with the “hit” anticancer agent and JQ1 or I-BET151 exerts dramatic and synergistic anticancer effects against cancer cell lines in vitro and causes cancer remission *in vivo* with no toxicity to normal tissues.

LEUKAEMIA BIOLOGY

Group Leader: Professor Richard Lock

The Leukaemia Biology Group maintains a focus on investigating how childhood leukaemia develops resistance to conventional chemotherapeutic drugs, how new drugs can be rapidly tested and prioritised for clinical trials and how novel targets can be identified to develop a new generation of more effective and specific drugs to treat leukaemia.

Objectives:

- To gain a greater understanding of drug resistance mechanisms in relapsed paediatric acute lymphoblastic leukaemia (ALL), and design and test strategies to reverse resistance in preclinical experimental models
- To use preclinical models to prioritise new drugs for clinical trials in children with aggressive and chemoresistant leukaemia
- To identify new molecular targets that can be exploited for the development of a new generation of drugs that will specifically target leukaemia cells and spare the normal cells of the body

LEUKAEMIA BIOLOGY STUDENT PROJECTS

Project Title: **Biosensors for the detection of minimal residual disease in leukaemia**

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

Suitable for: Honours Studies

Project outline: Despite dramatic improvements in the survival of children with acute lymphoblastic leukaemia (ALL) over the past 50 years, relapsed ALL remains one of the most common causes of death from disease in children. There is a significant association between poor response to induction chemotherapy and an elevated level of minimal residual disease (MRD) leading to poor survival. MRD is one of the strongest prognostic factors and powerful predictors of outcome in newly diagnosed paediatric ALL. Thus, there is a great need for developing feasible and highly accurate tests for the diagnosis and prognostic assessment of cancer.

Dr Narges Bayat

Circulating tumour DNA (ctDNA) is derived from cancer cells and can act as a surrogate for the whole cancer cell genome. Therefore, the use of ctDNA as a cancer biomarker in liquid biopsy could provide highly sensitive and specific cancer diagnostic and prognostic information.

In this regard, nanotechnology-based biosensors are sensitive, easy to use, have short assay time, are non-toxic, and are thus ideal for detecting ctDNA. In this project our aim is to analyse and quantify the ctDNA in high risk leukaemia samples with known genetic aberrations in order to develop a biosensor diagnostic system. We will utilise a variety of cell and molecular biology techniques and a clinically relevant xenograft model of childhood ALL.

LEUKAEMIA BIOLOGY

Project Title: **Nanomedicine For The Targeted Treatments Of Childhood Leukaemia**

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

Suitable for: Honours Studies

Project outline: Acute lymphoblastic leukaemia (ALL) is the most common form of paediatric malignancy, and accounts for the greatest proportion of deaths from childhood cancer. Progress in chemotherapy treatment has drastically improved the survival rates in 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 will investigate the efficiency of different targeting moieties for leukaemia cells; these include antibody fragments (i.e. extracted antigen binding domains of antibodies) as well as aptamers (i.e. oligonucleotides). Due to their small size, these moieties can penetrate tissues inaccessible to full-size antibodies and are less likely to instigate immune response. The advantages and specificity of each targeting species against different cell surface receptors expressed on high risk ALL cells will be assessed. The ideal targeting moiety chosen will be conjugated with a nanoparticles-drug conjugate system in order to ensure that the chemotherapeutic drugs specifically affect cancer cells.

Our aim is 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.

Project Title: **Molecular determinants of responses of paediatric acute lymphoblastic leukaemia to novel and established drugs**

Supervisor: Prof Richard Lock ✉ rlock@ccia.org.au &

Suitable for: Honours & PhD Studies

Project outline: Acute lymphoblastic leukaemia (ALL), the most common childhood cancer, causes an unacceptably high number of relapse related deaths in children. Therefore, new treatments for relapsed patients are urgently required. In the Leukaemia Biology Program at CCI we use cutting-edge technology to analyse molecular processes in relapsed ALL, gaining insight into dysregulated pathways and consequently identifying novel potential treatment targets. We have recently conducted whole genome sequencing (WGS) and transcriptome sequencing (RNAseq) to determine drivers of relapse in ALL patients. Potential drug targets, identified with these tools, can then be validated in proof-of-principle experiments and pharmaceutical treatment strategies can be tested in vitro using leukaemia cell lines. Additionally, we work with a well-established, pre-clinical experimental model of paediatric ALL whereby patient biopsies are engrafted directly into immune-deficient mice and can then be used to test novel treatment strategies in vivo, prior to translating these treatments into the clinic. We aim to:

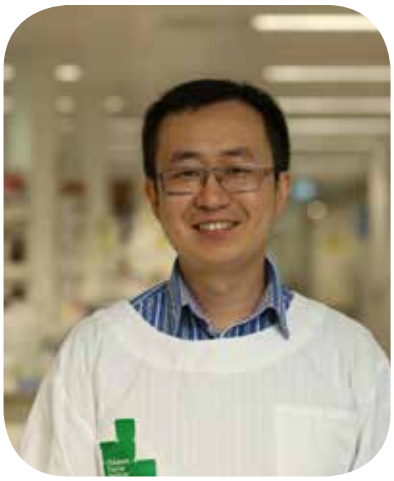
1. Analyse primary patient samples using WGS and RNAseq to define a molecular disease profile in relapsed intermediate risk paediatric ALL
2. Carry out in vitro proof-of-principle forced genetics experiments to test hypotheses arising from the next generation sequencing approach
3. Test and validate novel pharmaceutical strategies arising from molecular profiling in our in vitro and in vivo model systems

LEUKAEMIA BIOLOGY

Project Title: **Mechanisms of glucocorticoid resistance in acute lymphoblastic leukaemia**

Supervisor: Dr Duohi Jing DJing@ccia.org.au
Prof Richard Lock rlock@ccia.org.au &

Suitable for: Honours & PhD Studies



Dr Duohui Jing

Project outline:

Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer and it remains one of the most common causes of death from disease in childhood. Glucocorticoids are critical components of multi-agent chemotherapy regimens used to treat childhood ALL. A subset of childhood ALL patients responds poorly to initial glucocorticoid monotherapy, and resistance to glucocorticoids is common at relapse. Moreover, glucocorticoid resistance is an overall indicator of poor patient outcome, despite resistant patients frequently being treated with higher dose chemotherapy regimens. However, clinically relevant mechanisms of glucocorticoid resistance remain poorly understood.

Several Honours/PhD projects are available on the central theme of glucocorticoid resistance, all of which will utilise a variety of cell and molecular biology techniques and a clinically relevant xenograft model of childhood ALL. The projects are as follows:

1. Carry out genome-wide analyses for the identification of critical genomic regions with abnormal chromatin accessibility associated with glucocorticoid resistance, using cutting edge techniques, such as ChIP-seq, ATAC-seq, RNA-seq etc. And verify the function of the candidate regions using luciferase reporter assays and CRISPR/Cas knockout studies.

2. Define the cell type-specific mechanism of glucocorticoid-induced apoptosis, since glucocorticoids potently induce apoptosis in ALL but not in other types of leukaemia.

3. Study glucocorticoid-induced modulation on metabolomics of ALL cells, since defects in metabolomics may be associated with poor response to glucocorticoids.

4. Carry out a genome-wide CRISPR screen to identify genes involved in glucocorticoid-resistant ALL.

LEUKAEMIA BIOLOGY

Project Title: **New treatments for high risk Ph-like ALL in children**

Supervisor: Prof Richard Lock ✉ rlock@ccia.org.au

Suitable for: PhD Studies

Project outline: Despite dramatic improvements in the survival of children with acute lymphoblastic leukaemia (ALL) over the past 40 years, relapsed ALL remains one of the most common causes of death from disease in children. The Leukaemia Biology Program at CCIA is involved in national and international preclinical drug testing programs to prioritise new drugs for clinical trials in children with relapsed or drug resistant leukaemia.

Ph-like ALL is a high-risk subgroup with poor outcome often characterised by resistance to conventional chemotherapy, therefore new treatments for this subtype are urgently required. Ph-like ALL is generally characterised by a gene-expression profile similar to BCR–ABL1–positive ALL, except for the absence of the BCR–ABL1 fusion gene. Ph-like ALL exhibits deregulated phosphotyrosine-kinase signalling pathways, often involving mutations in the JAK-STAT pathway and frequent gene-fusions and overexpression of the CRLF2 gene. Apart from those common mutations, Ph-like ALL presents as a subtype with a high heterogeneity and patients could benefit from tailored treatments with drug combinations specific for their individual genetic lesions. A novel drug, the JAK-kinase inhibitor ruxolitinib, is currently being tested in a clinical trial against paediatric Ph-like ALL patients.

A diverse panel of Ph-like ALL patient-derived xenografts (PDXs) is available within the Leukaemia Biology Program and is currently being characterised by whole genome sequencing, exome-sequencing, DNA copy number analysis and RNA-sequencing. This distinct PDX panel will be used to identify and test novel treatment strategies for Ph-like ALL. In particular, the efficacy of the JAK-kinase inhibitor ruxolitinib will be tested in combination with other specific drugs against different genetic subtypes of Ph-like ALL.

Honours/PhD projects are available within the program to further study the activity of novel drugs such as ruxolitinib in different combinations against paediatric Ph-like ALL experimental models (cell lines and PDX cells) in order to guide future clinical trials.

Potential projects involve the following:

1.Carrying out cell-based screens to identify drugs that exert synergistic killing of Ph-like ALL cells when combined with ruxolitinib or other approved drugs and subsequent analysis of underlying molecular mechanisms of drug effects using cell and molecular biology techniques.

2. Analysis of drug effects on phosphotyrosine signalling pathways in Ph-like ALL cells using state-of-the-art mass spectrometry technology and molecular biology techniques.

MOLECULAR CARCINOGENESIS

Group Leader: Professor Glenn Marshall AM
Group Manager: Dr Belamy Cheung

The research focus of the Molecular Carcinogenesis Group:

The overall strategy of the Molecular Carcinogenesis Program is to dissect the mechanisms of cancer initiation and progression and use this information to develop more powerful treatments and prevention strategies for childhood cancer.

Objectives:

- To better understand the molecular basis of embryonal cancer initiation
- To evaluate p53 signal activators as postnatal rest deletion therapy
- To identify mechanisms of histone modification that contribute to carcinogenesis
- To better understand factors that promote the action of Myc oncoproteins in cancer cells
- To define molecular factors which increase retinoid sensitivity in cancer cells

MOLECULAR CARCINOGENESIS STUDENT PROJECTS

Project Title: **Elucidating molecular mechanism by which novel MYCN regulator stabilises MYCN and drives tumorigenesis**

Supervisor: Dr Belamy Cheung bcheung@ccia.org.au&
Dr Iris Wong IWong@ccia.org.au

Suitable for: ILP, Honours, Masters and PhD Studies

Project outline: MYCN amplification is an established indicator of poor-prognosis in neuroblastoma and is observed in several different types of cancer. In a big ENU mutagenesis study, our group has identified a list of genes, when mutated, inhibit neuroblastoma tumourigenesis. Of note, mutation in one of the genes resulted in complete loss of tumour development and the protein was shown to be a novel regulator of MYCN stability. This project will investigate mechanisms by which the novel MYCN regulator stabilises MYCN and drives tumorigenesis. This will involve one or more of the following areas:

Dr Belamy Cheung

1. In vivo studies: genetically modified mouse and xenograft models

2. In vitro studies: genetic manipulation in cell culture using siRNA and plasmid transfection and lentiviral transduction; RNA and protein analyses using qPCR, immunoprecipitation and western blot; functional assays such as proliferation, apoptosis and ubiquitination assays; cellular analyses involving flow cytometry, immunocytochemistry and microscopy

3. Drug screening: to identify compounds with activity against the novel MYCN regulator and minimal side effects

MOLECULAR CARCINOGENESIS

Project Title: **Targeting ALYREF for the treatment of neuroblastoma**

Supervisor: Dr Zsuzsanna Nagy ZNagy@ccia.org.au &
Dr Belamy Cheung bcheung@ccia.org.au

Suitable for: Honours, Masters and PhD Studies

Project outline: Neuroblastoma, the most common cancer in infants, arises from the developing sympathetic ganglia. Amplification of the MYC oncogene family member, MYCN, is the most important prognostic factor. Using MYCN deletion mutants, we found that the conserved MBII region responsible was necessary for death resistance. Our findings align with recent studies of a calpain cleaved product of MYC, called MYC-nick, which lacks the C-terminus and is crucial to resist nutrient factor deprivation in colon cancer. This project will examine the roles of MYCN and MYCN-nick in neuroblastoma initiation and progression. We hypothesise that the MBII region, will be necessary to apoptotic resistance and that MYCN-nick induces tumour promoting phenotypic changes. To test this hypothesis, we will transfect deletion mutants of MYCN and a plasmid construct for MYCN-nick into neuroblastoma cell lines to determine which structural regions are necessary to overcome stress stimuli. Additionally, we will determine if MYCN-nick induces anchorage independent growth and increases cell motility, which is necessary for neuroblastoma tumour progression. Further characterisation of MYCN protein domain structures may prove critical to the development of more effective neuroblastoma treatments.

Techniques

Cell culture, RNA extraction, siRNA knockdown, plasmid DNA transfection, apoptosis assays, immunoblot for protein expression.

Project Title: **Perinatal factors associated with initiation and development of childhood cancer**

Supervisor: Dr Belamy Cheung bcheung@ccia.org.au&
Dr Mukesh Raipuria MRaipuria@ccia.unsw.edu.au

Suitable for: Honours, Masters & PhD Studies

Project outline: Neuroblastomas (NB) are pediatric malignancies with heterogenous phenotypes, ranging from spontaneously regressing to highly aggressive, incurable tumors. Although NB is considered a genetic disease, its etiology and heterogeneity cannot be explained solely by genetic aberrations. NB arises due to defects in sympathetic neuron (SN) differentiation occurring during fetal development. Our research lab has been working on mouse models of child cancer NB. NB arises due to defects in sympathetic neuron (SN) differentiation occurring during fetal development. The environmental factors and genetic epidemiology studies aims to improve knowledge in the prevention of diseases, particularly child cancer. With several children's cancer such as Neuroblastoma and ALL, genetic factors, though important, are not sufficient to explain the increase in these diseases.

Recent findings from our lab and collaborators suggesting that environmental factors such as high birth weight, maternal diet supplemented with folate and omega 3 and nitrous oxide exposure during neonatal age are associated with occurrence of childhood cancer. The molecular mechanism behind these association are unknown; thus, we are establishing in vitro and in vivo animal model to understanding these association in relation to initiation and development of child cancer.

Aim 1. To evaluate impacts of dietary supplements, hormone and vitamins during pregnancy on initiation and development of NB in mice offspring.

Aim 2. Carry out in vitro studies to understand initiation and development of NB in presence/absence of different environmental factors by using different cell lines and neurosphere.

MOLECULAR DIAGNOSTICS

Group Leader: Professor Murray Norris

The Molecular Diagnostics Program uses molecular genetic technology and small molecule drug screening approaches as a means of improving the diagnosis and treatment of children with malignant disease.

To isolate potential new pharmaceutical agents that target cancer-associated genes, we have been employing high-throughput screening of small molecule chemical libraries. Our research has identified a number of small molecule inhibitors of these targets in childhood neuroblastoma, as well as in infants with leukaemia. Both these groups of children have particularly poor survival rates compared with children with other tumour types.

The development of inhibitors of defined molecular targets – such as the MYCN and MLL oncoproteins and the MRP1 and MRP4 multidrug transporters – provides the opportunity to devise therapies that are more specific in their action and effective at low concentrations, and have an irreversible effect on cancer cells.

Objectives:

- To develop molecular targeted therapies for childhood neuroblastoma based on specific small-molecule inhibitors of key target genes
- To develop clinically relevant chemical small molecules that specifically inhibit leukaemia cells with an abnormal MLL gene
- To use large scale mutagenesis screens to identify novel genes and co-factors involved in MycN-driven neuroblastoma

MOLECULAR DIAGNOSTICS STUDENT PROJECTS

Project Title: **A novel molecular target capable of abrogating neuroblastoma development**

Supervisor: Prof Murray Norris ✉ MNorris@ccia.unsw.edu.au &
Prof Michelle Haber ✉ MHaber@ccia.org.au

Suitable for: PhD Studies

Project outline: Although modern combination chemotherapy has significantly improved survival rates for many childhood cancers, the outlook remains dismal for a majority of children with advanced staged childhood neuroblastoma. These patients frequently display alterations in the cancer-causing gene MYCN and in order to improve their survival, alternative treatments are urgently required. Although MYCN has a clearly established role in driving the development of this disease, as yet, the critical molecular interactions involving this master gene regulator have not been sufficiently well defined to allow a clear understanding of how neuroblastoma develops. Using pre-clinical models and genome-wide technology, we have discovered a loss of function mutation in a gene that can completely block neuroblastoma growth. The gene is known to encode a non-DNA binding transcriptional regulator and importantly has not previously been implicated in neuroblastoma development or MYCN ongogenesis, although it has an established role in specific adult cancers. We hypothesise that this gene regulator forms a complex with MYCN to drive the expression of other cancer-promoting proteins, and as a result has a critical role in the initiation and development of neuroblastoma. This project will utilize a range of molecular and cellular technologies in order to investigate and understand the mechanism(s) behind the function of this complex. Given the current paucity of understanding of the processes involved in neuroblastoma initiation and development, these studies have the potential of elucidating an entirely novel approach to the treatment, and ultimately, prevention of this refractory childhood malignancy.

MOLECULAR DIAGNOSTICS

Project Title: **Novel therapeutic approaches for high-risk leukaemia in children: targeting the immune system and leukaemic stem cells**

Supervisor: Dr Michelle Henderson ✉ MHenderson@ccia.org.au
Dr Klaartje Somers ✉ KSomers@ccia.org.au

Suitable for: Honours and PhD Studies

Project outline: Dramatic improvements in the long-term survival of children with ALL over the last 50 years have resulted in current cure rates exceeding 80% but there are certain subgroups classified as 'very high-risk' for whom the relapse rates are high and prognosis is dismal. Novel therapies that specifically target leukaemogenic pathways are urgently needed to improve the outcome for these patients. With this in mind we have been studying a new, targeted agent, named CBL0137, which blocks tumour growth by several mechanisms including by the inhibition of a histone chaperone called "FACT" and the activation of an interferon response. Moreover, work with other cancers indicates that CBL0137 can eradicate the cancer stem cells that are responsible for disease relapse. CBL0137 is about to enter paediatric cancer clinical trials and we have found this drug to be highly effective at killing leukaemia cells in animal models, without harming normal healthy cells.

The aim of this project is to further characterize the molecular effects of CBL0137 on leukaemias.

A number of approaches will be used to achieve this aim:

1.Generate novel immunocompetent patient-derived xenografts to evaluate the role of the immune response in the anti-tumour actions of CBL0137

2. Determine whether CBL0137 exerts part of its anti-tumour effect through inhibiting leukaemic stem cells

3. Develop novel patient-derived xenografts that can be used to model the emergence of relapsed ALL and to evaluate the effect of CBL0137 on factors driving disease relapse

4. Use molecular profiling of patient-derived samples to identify and validate determinants of response to CBL0137

Dr Michelle Henderson

Dr Klaartje Somers

TUMOUR BIOLOGY AND TARGETING

Group Leader: Professor Maria Kavallaris

Tumour Biology and Targeting Program, Children's Cancer Institute

Australian Centre for NanoMedicine, UNSW

Cancer remains the major cause of disease-related death in children in Australia. The Tumour Biology and Targeting Program research focuses on understanding cancer biology (how tumours grow and move), cancer therapeutics (drug resistance and drug discovery) and the development of effective and less toxic therapies using nanotechnology.

TUMOUR BIOLOGY AND TARGETING STUDENT PROJECTS

Project Title: **Precision nanomedicine for the treatment of neuroblastoma**

Supervisor: Prof Maria Kavallaris mkavallaris@ccia.unsw.edu.au &
A/Prof Joshua McCarroll jmccarroll@ccia.org.au &
Dr. Ernesto Moles emoles@ccia.org.au

Suitable for: PhD Studies

Project outline: Childhood cancer is responsible for the greatest number of deaths from disease in children and young adolescents in Australia. One of these childhood cancers is neuroblastoma. It is often diagnosed at advanced stage disease which means it has already spread to multiple sites in the body. High-risk neuroblastoma patients represent half of all new neuroblastoma cases each year and less than 50% of children are alive 5 years after diagnosis.

Children presenting with high-risk neuroblastoma tumours undergo invasive and toxic medical procedures during treatment, which can severely impact their quality of life. Even if treatment is successful, they often suffer from life-long consequences of the aggressive therapy. There is an urgent unmet need for new therapies, which are not only effective but also reduce the toxicity to normal healthy tissue.

This research project will focus on developing new classes of medicines using nanotechnology. Nanotechnology is the engineering of materials at the nanometer scale – or to put in perspective this is one thousandth the width of a human hair. We are developing nanoparticle delivery systems that can be packaged with drugs or gene silencing material, and can carry their cargo and target tumour cells where they can release the drug where it is needed. The aim of this approach is to spare the normal healthy cells.

The exciting aspect of this PhD project is that it will focus on the development of a new targeted nanomedicine therapy for neuroblastom

A/Prof Joshua McCarroll

D.r. Ernesto Moles

TUMOUR BIOLOGY AND TARGETING

Project Title: **Dissecting the role of endoplasmic reticulum stress in cancer cell progression and metastasis in the tumour microenvironment**

Supervisor: Dr. Angelica Merlot amerlot@ccia.org.au&
Prof Maria Kavallaris mkavallaris@ccia.org.au

Suitable for: Honours & PhD Studies

Project outline: Cancer metastasis is a major clinical problem that accounts for almost 90% of cancer-related deaths. Understanding the fundamental biological processes that lead to tumour metastasis is critical for the development of effective anti-cancer drugs. Moreover, there is an urgent need to better understand the molecular pathology of cancer to improve patient selection for current treatment options and develop novel therapeutic strategies.

Dr. Angelica Merlot

This project aims to dissect the mechanism by which the pro-survival pathways of the Endoplasmic Reticulum modulates cancer progression and metastasis. Moreover, studies have demonstrated that these signals can be transmitted between cancer cells and cancer-associated helper cells, known as stromal cells. Considering the importance of cancer-stromal cross-talk in cancer development, we aim to elucidate the functional significance of this transmission for the first time.

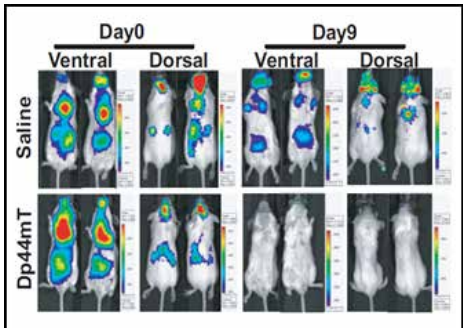
This study will use cell culture (a range of cells lines, including glioblastoma, pancreatic, etc.), molecular biology techniques, fluorescent/confocal microscopy, orthotopic mouse model, immunohistochemistry of patient samples, etc.

Project Title: **Developing albumin-based nanoparticles that overcome drug resistance and metastasis**

Supervisor: Dr. Angelica Merlot amerlot@ccia.org.au&
ProfMaria Kavallaris mkavallaris@ccia.org.au

Suitable for: Honours & PhD Studies

Project outline: This project will result in an exciting new class of albumin-based nanoparticles that markedly increase the efficacy of novel anti-tumour drugs, known as thiosemicarbazones, that are currently in clinical trials. These agents possess a unique combination of potent and selective properties against cancer cells that effectively inhibits the “triad of death” in cancer: namely primary tumour growth, metastasis and multi-drug resistance, representing an exciting new therapeutic avenue.



Dp44mT reduces the incidence and growth of metastatic cancer cells. Lui W, et al. (2012) EMBO Mol Med; 4:93-108.

The project will use a combination of techniques including: nanoparticle synthesis, the use of patient derived cell lines, orthotopic mouse models, molecular biology experiments, microscopy, invasion/migration assays, etc.

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