



**CHILDREN'S CANCER INSTITUTE AUSTRALIA
FOR MEDICAL RESEARCH (CCIA)**

**2008 GRANT OPTIONS FOR
THE APEX FOUNDATION**



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OPTION I

CONTINUED SUPPORT OF DR LESLEY ASHTON & MOLECULAR EPIDEMIOLOGY

“We cannot assume that saving the life of a child is enough. Our vision, to save the lives of all children with cancer and eliminate their suffering, echoes this. The suffering of survivors is often forgotten, yet we have perhaps an even more powerful duty of care to those who live, to ensure that they are offered the best life possible, a normal, healthy life.”



DR LESLEY ASHTON, GROUP LEADER

Dr Lesley Ashton heads the Molecular Epidemiology Group at CCIA. Molecular epidemiological research exposes the genetic and environmental factors that determine the risk of developing cancer, as well as the impact of anti-cancer treatments on long-term health outcomes in children. The Group works with epidemiologists and molecular biologists at CCIA and other research centres, and has strong links with

paediatric oncologists at Sydney Children’s Hospital (SCH).

CARMEN WILSON, PHD STUDENT

Carmen Wilson’s molecular investigations are aimed at finding out whether specific gene variations influencing a child’s ability to metabolise anti-cancer drugs are linked to an increased risk of adverse health outcomes later in life. DNA tests on 400 samples collected from childhood cancer survivors will determine the genetic and lifestyle factors affecting the long-term adverse health outcomes of these survivors.

MOLECULAR EPIDEMIOLOGY GROUP

Common diseases, such as cancer, are a result of the complex interplay between genes and the environment. We all carry genetic variations that can increase or decrease our susceptibility to disease. Identifying and characterising how specific gene variants interact with potential carcinogens in our environment, provides more opportunities to develop intervention strategies aimed at preventing childhood cancer or improving treatment outcomes. Many of the genetic risk factors for childhood cancer remain to be determined and the complex interactions between the genes, and between the genes and the environment is yet to be understood.

The Molecular Epidemiology Group lead by Dr Lesley Aston includes four key areas of research:

- The interplay between genetic susceptibility and the environment
- Childhood central nervous system tumours, genetics and the environment
- Treatment related outcomes in survivors of childhood cancer
- Describing genetic diversity in Australian newborns

Below is more information on one of these programs, treatment related outcomes in survivors of childhood cancer.

THE LATE EFFECTS STUDY

For survivors of childhood cancer who have overcome the trauma of the disease and standard therapies, an uncertain future awaits during which they may develop an array of so-called 'late effects' as a result of the anti-cancer treatments which they received. Investigations into the late effects experienced by childhood cancer survivors, including the causes of these effects and how damage might be avoided, has become a research priority in CCIA's Molecular Epidemiology Group. It is our intention to make significant inroads into this area, with a goal of discovering valuable new health advice for the treatment of children with childhood cancer today and bringing about an improved quality of life for children treated in the future.

OUR RESEARCH

The first research challenge was to establish a baseline of people to work with. In the Late Effects Project we needed to locate and recruit a large number of long-term survivors of childhood cancer, a difficult and time-consuming exercise.

To date we have successfully recruited 400 survivors who are willing to become involved in our research. Each survivor we recruit provides us with a DNA sample so that we can examine their genes, and completes a questionnaire about the late effects they have experienced as well as any lifestyle factors that could prove relevant.

Through this study we have identified a number of genes of interest which play a role in therapeutic outcomes, specifically genes that affect how a cell breaks down chemicals (such as chemotherapeutic drugs) and genes that affect how a cell responds to DNA damage (for example from radiotherapy). Variations in these genes between individuals are believed to account for why different people respond to treatment in different ways, and why some people experience certain late effects while others do not.

Our research aims to find answers to the many unanswered questions such as, "do people with certain gene variants need to receive lower doses of treatment to avoid long-term health problems such as heart damage or infertility?" Essentially we are trying to fully understand the causes of late effects in childhood cancer sufferers. This in turn will help us understand how best to minimise risks of these debilitating effects.

SIGNIFICANCE OF THIS RESEARCH

Our research is the *only* research in Australia being conducted on childhood cancer survivors which pieces together information about a survivor's genetic make-up, past treatment for cancer, late effects and lifestyle factors, all in one study, making it truly unique.

The results of this study will assist doctors in providing important health advice to today's childhood cancer survivors, such as their risk of late effects based on their genetic make-up and lifestyle factors and how they can prevent certain late effects from occurring.

In addition, understanding the causes of late effects will help doctors to know which treatment regimens should be avoided in certain patients and how to modify treatments to suit individual patients, based on their genetic profile. This means that doctors can offer 'tailored therapy' to each individual child, rather than the current 'one size fits all' approach.

Our hope is for new treatments to be developed that cause fewer or no long-term effects. Most importantly, we will be in a position to improve the health and quality of life of all children treated for cancer *in the future*, offering them a normal, healthy life.

MOLECULAR EPIDEMIOLOGY FUNDING REQUIREMENTS

The Molecular Epidemiology Group has a funding shortfall each year of \$211,465. We would like to invite APEX to support two PhD Students in the program.

1. Anthea Ferguson, PhD Student + on-costs	\$25,210
2. Sarah Beckett, PhD Student + on-costs	\$25,210
3. Carmen Wilson, PhD Student + on-costs	\$25,210
4. Dianna Lau, PhD Student + on-costs	\$25,210

OPTION 2

PROF GLENN MARSHALL & MOLECULAR CARCINOGENESIS

“About one in every 500 children born in Australia develops childhood cancer sometime during their first 15 years of life. Compared to adult cancer, this is a low incidence. However, in terms of potential years of life lost, childhood cancer has a huge impact on the community.”



PROF GLENN MARSHALL, PROGRAM HEAD

Prof Glenn Marshall heads the Molecular Carcinogenesis Program at CCIA. His research is focused on investigating how cancer first develops i.e. the processes by which normal cells become cancerous. As well as leading this research team, Glenn heads the Centre for Children's Cancer and Blood Disorders at Sydney Children's Hospital, a major treatment centre for

children with cancer. CCIA benefits enormously from the clinical perspective that Glenn brings to his laboratory research.

JESSICA KOACH, RESEARCH OFFICER

Jessica Koach has recently come to CCIA to take on the role of Program Officer for the Molecular Carcinogenesis Program. In this role, Jessica is involved in the research operations of the program. She is also conducting research to elucidate the molecular basis of neuroblastoma, the most common form of solid tumour in young children, and is investigating the effects of retinoids (Vitamin A) in neuroblastoma and its possible role in drug therapy.

MOLECULAR CARCINOGENESIS PROGRAM

This program has a strong focus on neuroblastoma, the most common solid tumour in young children, and is using neuroblastoma tissue and tumour cells directly grown from tumours, as well as transgenic mice, to investigate the processes of normal and malignant cell growth and differentiation. Definition of the critical genes involved in this process will allow the identification of therapeutic targets that may be used to design novel treatments for patients.

The Molecular Carcinogenesis Program lead by Prof Glenn Marshall includes five key areas of research:

- The origin of childhood leukaemia
- Brain cancer
- Combination therapy for childhood cancer
- Neuroblastoma tumour formation
- Vitamin A therapy for cancer

Below is more information on one of these programs, Vitamin A therapy for cancer.

VITAMIN A THERAPY FOR CANCER

INTRODUCTION

Chemotherapy is standard treatment for many types of cancer. This is a combination of anticancer drugs given either by tablet or intravenously. While it can be very effective, a major problem with chemotherapy is the high level of associated side effects, such as mouth ulcers, hair loss and severe constipation. New therapies are needed that harm only cancer cells (not normal cells), thus avoiding the problem of side effects.

OUR RESEARCH

One treatment that has proven effective for a number of types of cancer is retinoic acid (retinoid), a natural derivative of Vitamin A. Retinoid treatment has the advantage of having a low toxicity to normal cells, causing minimal side effects. However, some patients relapse following treatment because their cancer develops resistance to retinoic acid over time.

Our scientists are investigating what causes cancer cells to become resistant to retinoic acid. We are also working on developing new therapies that can be used in conjunction with retinoic acid, to enhance the response of cancer cells to retinoid treatment.

So far, we have found that a deficiency in an important protein (known as RAR β) can contribute to retinoid resistance in cancer cells. We have shown that cancer cells can be made more sensitive to retinoid treatment if the cells are genetically manipulated to increase their level of RAR β protein.

We have also found that another protein (EBBP) is very important in enabling retinoic acid to exert an anticancer effect. Our studies show that high levels of EBBP can help restore retinoid sensitivity in previously resistant cancer cells.

Recently, our team was the first in the world to discover that retinoid treatment of neuroblastoma cells (neuroblastoma is the most common solid cancer in children under five) causes a decrease in the amount of copper in the cells. More importantly, we have been able to show that deliberately altering the copper concentrations inside cancer cells can affect how those cells respond to retinoid treatment. This suggests that drugs that modify the copper concentrations of cancer cells may be useful in enhancing retinoid treatment.

SIGNIFICANCE OF THIS RESEARCH

These studies are providing important knowledge that can be used to improve the effectiveness of treatment as well as reduce the problem of unwanted side effects in children treated for cancer.

Because retinoids can be used to treat several types of cancer, our research has the potential to improve the treatment of a number of childhood cancers as well as some adult cancers.

MOLECULAR CARCINOGENESIS FUNDING REQUIREMENTS

The Molecular Carcinogenesis Program has a funding shortfall each year of \$136,660. We would like to invite APEX to support a portion of the Program Officer's salary or PhD students in the program.

1. Jessica Koach, Program Officer salary + on-costs	\$71,050
2. Andrew Tee, PhD Student salary + on-costs	\$25,210
3. Jessica Bell, PhD Student salary + on-costs	\$5,200^
4. Scott Brown, PhD Student salary + on costs	\$5,200^

^ unfunded portion of salary

OPTION 3

PROF MURRAY NORRIS & MOLECULAR DIAGNOSTICS

“Almost all children with leukaemia (the most common childhood cancer) initially respond well to treatment and go into remission. Unfortunately, up to a quarter of these children later relapse with the disease. The majority of children who relapse do not survive.”



PROF MURRAY NORRIS, PROGRAM HEAD

Prof Murray Norris, Deputy Director of CCIA, was one of the first three scientists to staff the Institute when its research laboratories opened in 1984. He heads the Molecular Diagnostics research program, which works on improving the diagnosis, risk classification and treatment of childhood cancer. Murray has an international research reputation for his research into

two of the most common childhood cancers: neuroblastoma and leukaemia.

JAYNE MURRAY, PROGRAM OFFICER

Jayne Murray has several years experience as a cancer researcher at CCIA and is a key member of Molecular Diagnostics research team. The focus of Jayne’s work is to test the effectiveness of potential inhibitors of the c-myc and N-Myc oncoproteins associated with a number of cancers. Promising inhibitors of these cancer-causing proteins have been identified by screening a large chemical library containing many small molecules. This laboratory-based research is identifying lead compounds for future drug development.

MOLECULAR DIAGNOSTICS PROGRAM

This program is utilising molecular genetic techniques to characterise alterations in the structure and expression of critical genes in paediatric malignancy. The analysis of these genes is being used to improve both the diagnosis and risk classification of childhood cancer. Major areas of focus within this program are molecular detection of residual disease following chemotherapy, the use of functional genomics and high-throughput screening strategies to detect novel molecular targets and relevant inhibitors, leading to new drug development, as well as molecular epidemiological studies of causative agents and genetic susceptibility to childhood cancer.

The Molecular Diagnostics Program lead by Prof Murray Norris includes five key areas of research:

- Targeted therapy for leukaemia
- Early detection of relapse in ALL
- A clinical trial for relapsed leukaemia
- Understanding relapse in leukaemia
- Genetic influences on childhood cancer

Below is more information on one of these programs, genetic influences on childhood cancer.

GENETIC INFLUENCES ON CHILDHOOD CANCER

INTRODUCTION

A number of adult cancers are known to be related to 'environmental exposure' – the exposure of the patient to cancer-causing agents in the environment, such as cigarette smoke.

In the case of infants developing cancers such as leukaemia and neuroblastoma, these children are too young to have gained much exposure to environmental agents. Instead, it could be that certain environmental exposures of the child's parents are relevant. In addition, there are almost certainly genetic factors (characteristics of an individual's genes) that combine with environmental exposures to make a child susceptible to developing cancer.

OUR RESEARCH

One group of genes that may be particularly important in determining a child's risk of cancer is that containing the Drug Metabolizing Enzyme or DME genes. DME genes are critical in enabling a normal, healthy cell to process any chemicals it is exposed to, thereby ridding itself of toxins. However, not all versions of DME genes are the same – some allow more efficient drug metabolism than others.

Variations within genes, known as 'polymorphisms', occur naturally in the general population. These variations appear to be important not only in influencing a child's susceptibility to cancer, but also in determining how the cancer will respond to treatment.

We are studying the genes of children with the most common type of leukaemia, Acute Lymphoblastic Leukaemia (ALL), as well as the genes of their parents, to find out whether particular genetic patterns predispose a child to developing cancer. To carry out this research, we are collaborating with several medical research facilities and major children's hospitals across Australia. The study represents a unique opportunity to find out more about the causes of cancer in children.

SIGNIFICANCE OF THIS RESEARCH

This research is providing valuable information about the genetic patterns of children who develop cancer and their parents. As more of this type of information becomes available, we believe it will become possible for doctors to tailor treatment to individual children based on each child's 'genetic profile' (gene patterns), providing the greatest chance of cure.

Ultimately, we are aiming to discover the causes of cancer in some children, leading to the development of prevention strategies.

MOLECULAR DIAGNOSTICS FUNDING REQUIREMENTS

The Molecular Diagnostics Program has a funding shortfall each year of \$157,870. We would like to invite APEX to support a portion of the Program Officer's salary.

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| 1. Murray Norris, Program Head salary + on-costs | \$70,985 [^] |
| 2. Jayne Murray, Program Officer salary + on-costs | \$81,685 |
| 3. Leanna Chung, PhD Student salary + on-costs | \$5,200 [^] |

[^] unfunded portion of salary