

CONNECT

Newsletter of the Lowy Cancer Research Centre

LOWY CANCER RESEARCH CENTRE



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UNSW
AUSTRALIA



CHILDREN'S CANCER
INSTITUTE AUSTRALIA

Message from the Director



Welcome to the spring 2012 issue of the Lowy Cancer Research Centre internal newsletter - CONNECT. This issue highlights the kids and adults neuro-oncology research at the Centre. Our brain cancer research is an emerging strength and an area where we are making an impact nationally and are beginning to be recognised internationally. We have been very successful in attracting support and funding for our brain cancer research from NH&MRC, Cure for Life Foundation, Cancer Council NSW and Cancer Institute NSW. Brain tumours are a heterogeneous group of malignancies and in terms of years of life lost are the highest of all the malignant cancers. They are very difficult to treat and we are in desperate need of new therapies. My hope is that our researchers will ultimately make a difference for kids and adults with brain tumours. We are now in our third year in the Lowy Cancer Research Centre. Thank you all for your efforts. Onwards and upwards.

Professor Phil Hogg, Director, Lowy Cancer Research Centre

Message from the CCIA Executive Director



It gives me enormous pleasure to welcome you to the 2012 spring edition of CONNECT. Our dedicated team at CCIA has achieved some great milestones, including our neuroblastoma research program being named as one of Australia's top 10 research projects. The annual NH&MRC publication, Ten of the Best Research Projects, features researchers who are leading the way in finding solutions to some of Australia's greatest health challenges. The researchers selected for publication were picked on the basis of the strength of science and significance of the outcomes, and it is a great honour to be included in the 2012 edition. In July we received the 2012 Premier's Award for Excellence in Translational Cancer Research – the highest accolade for translational research in NSW. The award specifically recognises the development of our PCR-based Minimal

Residual Disease (MRD) testing for childhood Acute Lymphoblastic Leukaemia (ALL). Using this same technology, a new clinical trial opened this year, aiming to increase survival rates of ALL even further, and to also look at using MRD testing to identify low-risk patients, which would then allow clinicians to reduce the intensity and toxicity of treatment.

I would also like to take this opportunity to congratulate Drs Jenny Wang and Tao Liu, recently awarded prestigious 2012 ARC Future Fellowships, on the back of their previous success in attracting Cancer Institute NSW Fellowships, which collectively represents over \$2.3M worth of funding.

2012 has been a year of significant growth for CCIA and I am extremely optimistic of what's to come in the next 12 months. I hope you enjoy reading about the remarkable work being undertaken across all levels of the Lowy Cancer Research Centre.

**Professor Michelle Haber AM
Executive Director, CCIA**

**Connect Editors:
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Operations Update

Scientific services in the Centre continue to evolve with the refurbishment of the lower ground (LG) area completed at the start of 2012, leading to the expansion of BioMedical Imaging Facility (BMIF), relocation of ACRF Drug Discovery Centre to LG and establishment of UNSW Flow Cytometry Facility. The installation of an intravital microscope and MRI in the Biological Resources Imaging Laboratory (BRIL). have strengthened our imaging capabilities. Commitment to providing expertise around these scientific services continues with the appointments of Dr Carl Power, UNSW BRIL manager, Chris Brownlee, UNSW Flow Cytometry Facility manager and Dr Andre Bongers UNSW MRI Fellow. UNSW BMIF, has appointed image analysis specialists, Drs Phillip Nicovich and Michael Carnell and microscopists Iveta Slapetova and Katka Bendova. Dr Greg Arndt (CCIA) continues as ACRF Drug Discovery Centre manager. We look forward to the world class research that will come from these activities. Finally, much thanks goes to the lab support and stores teams who provide excellent support for research staff in Centre and upper campus.

**Dr David Coomber
Operations Manager**

Visiting Academic program commences

This year, UNSW Medicine launched its Visiting Academic program where, over four years, four internationally-recognised brain cancer researchers will be invited to the Centre to work with Cure for Life Neuro-Oncology Lab. The program, sponsored by Cure for Life Foundation, will further enhance the Centre's brain cancer research by offering internationally-based academics the opportunity to be seconded to UNSW for six months. The first distinguished academic to accept this appointment is Swiss-



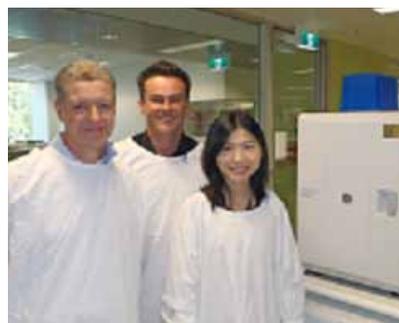
Paul Kleihues, Charlie Teo and Kerrie McDonald

based Professor Paul Kleihues M.D., He is a leader among brain tumour pathologists, having published more than 300 peer-reviewed papers, with a focus on the pathology and genetics of tumours of the nervous system. "We are delighted to announce the first of our visiting academic appointments under the UNSW Medicine Cure for Life Neuro-Oncology program, Professor Kleihues," said Professor Peter Smith, Dean of UNSW Medicine. "International collaboration is an invaluable way to accelerate answers to what causes brain cancer and how best to treat, manage and prevent the disease. Through funding esteemed visiting academics, Cure For Life Foundation is an enabler to insight sharing and knowledge exchange. We will be able to credibly benchmark our lab amongst the world's finest, and match our researchers with other great minds in ways that are without boundaries," said Dr Charlie Teo, neurosurgeon and founder of Cure for Life Foundation.

"As Australia's first research facility dedicated to tackling the rising incidence of brain tumours, the team welcomes Paul and we look forward to working closely with him to further our expertise and knowledge in this highly complex space." Professor Paul Kleihues said: "I am honoured to accept this highly coveted position and look forward to working closely with UNSW Medicine on this increasingly important research program."

Riding for cancer

Money raised by Tour de Cure, a cycling community that raises funds for cancer, has enabled the purchase of desperately needed laboratory equipment for the Cure for Life Neuro-oncology Laboratory. At a morning tea and lab tour held by the lab to say thank you to a riders and staff from Tour de Cure, Dr Kerrie McDonald, Head of the Cure for Life Neuro-Oncology laboratory said "Watching footage of your tour, meeting the riders and understanding what you have all sacrificed to raise money for cancer has been an inspiration to my research team" The three pieces of much needed equipment will provided benefits not only to the lab but to all cancer researchers across UNSW. The \$170,000 donation purchased equipment to help researchers understand cancer cells, mechanisms of invasion and assist with the development of personalised treatments.



Tour de Cure inspects the new equipment

Australian-first for DIPG



Dr David Ziegler has embarked on a project looking into the most aggressive form of paediatric brain cancer, Diffuse Intrinsic Pontine Glioma (DIPG), which is currently uniformly fatal.

David, a paediatric oncologist at Sydney Children's Hospital, aims to develop new treatments that will effectively attack these tumours. His research team has the first ever DIPG cell lines growing successfully in the lab, using samples from USA and recently received the first donated tumour sample from an Australian family whose child passed away from the disease. The next step is to screen a library of small chemical molecules using the robotic technology in the ACRF Drug Discovery Centre, to identify existing and potential new drugs that may be effective against the cancer. "We are starting with drugs we already know a lot about. If we do find something there, it may be a relatively fast process translating it into a clinical treatment, because of all the knowledge we already have about that drug – we know how to administer it to kids, so we can go and use it to treat children straight away. If, on the other hand, it's a molecule that no one has ever investigated before, we don't know what its side-effects are or how little bodies will handle the drug, so there is obviously a much longer and more involved testing process" says David.

- Brain Cancer Special -

Cure for Life Neuro-Oncology Laboratory - In the spotlight...

The Cure for Life Neuro-Oncology Laboratory was established in 2010, following a \$2.3m donation by the Cure For Life Foundation – it is Australia's first research group solely dedicated to tackling the rising incidence of brain tumours. The research facility is led Dr Kerrie McDonald.

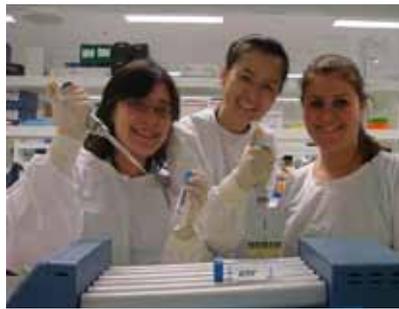
The past 6 months have been extremely busy with one of the essential elements of our translational research program being the collection of tumour specimens at the time of surgery. Prior to surgery, the surgeon or fellow will explain the purpose of the research and obtain consent to collect excess tumour tissue from their operation. The tumour is then “cryofrozen” in liquid nitrogen and transferred to our tumour bank for long-term storage. This tissue is vital for our research and we continue to seek funding to ensure this tumour bank continues as a core facility for cancer research.

Biological shift in sphingolipid patterns in brain cancer

PhD student, Dr Hazem Abuhusain, working with Dr Anthony Don, Team Leader, Bioactive Lipid Signalling, demonstrated there is a shift in the normal pattern of lipids in the brain. This important finding provides a novel target for treatment (95% of current clinical targets are proteins).

A rare variation in MGMT

Kerrie and epigenetics specialist, Dr Megan Hitchins, have discovered a rare variation in the DNA, specifically in the area where MGMT promoter methylation is measured. MGMT promoter methylation is used as a predictive biomarker for response to temozolomide. Detection of the variation (which constitutes a very simple DNA-based test) is highly predictive of response to temozolomide and longer survival. This



research is currently under peer review for publication with the finding presented at the European Association of Neuro-oncology meeting (Marseilles, France) in September.

New target, MIF, discovered

Dr Hatice Sevim, with colleagues from the Karolinska Institute, Sweden and postdoc fellow, Dr Jack Zhao, discovered a new protein, which when inhibited, sensitised cells without MGMT methylation to temozolomide treatment. The manuscript has been submitted for publication and Hatice presented the findings at the European Association of Neuro-oncology meeting.

Identifying molecular changes associated with tumour progression

This project is lead by Professor Paul Kleihues, oncologist Dr Helen Wheeler and Neurosurgical Registrar, Dr Grace Aw. Tumours were collected from individual patients when first diagnosed (usually with a low grade tumour) and at the time of progression. The analyses of these tumours has allowed us to identify critical changes occurring which may provide interesting clues as to how to slow down this progression.

Understanding acquired resistance

Using the samples in our tumour bank, we have been able to look at the molecular biology of the changes acquired directly as a result of treatment with either radiochemotherapy or avastin. Results of this study will be available at the end of the year.

Testing a novel anti-glycolytic compound.

Professor Phil Hogg and Dr Pierre Dilda have developed a drug (PENAO) which directly targets cancer metabolism. Cancer cells obtain their energy differently to normal cells and this difference is the target of PENAO. PhD students, Sylvia Chung and Han Shen have been running preclinical models for the past 18 months. A Phase 1 trial has commenced in Melbourne and we hope to start testing brain tumour patients by the end of the year for efficacy.

Awards and conferences

Dr Hazem Abuhusain presented his sphingolipid work at the American Association of Surgery. PhD student and Radiation Oncologist, Dr Eric Hae was awarded the prestigious MSD Hubert Stuerzl Award and the Hospira Withers and Peters Grant. Dr Kerrie McDonald was very fortunate to present at the International Conference on Brain Tumour Research, an exclusive invite only event, held at Niagara Falls, Canada. This opportunity facilitated high-level discussions regarding the treatment and biology of brain tumours and forged new international partnerships.

Personal update

With the completion of several projects, we farewell Sarita Tiwari, Siska Sumual, Jack Zhao and Hatice Sevim, wishing them every success in their future endeavours. We welcome researchers Dr Amanda Tivnan and Jennifer Campbell from Ireland and research assistant, Wenda Ha from Victoria.



Dr Kerrie McDonald at work

- Brain Cancer Special -

Profile:

Hazem Abuhusain



Lipid metabolism isn't the first thing that comes to mind when thinking about Glioblastoma (GBM), even less so for Sphingolipids. As I reach the end of my 3rd year as a PhD student, I'm excited by our discoveries to date. We illustrated a dramatic shift in the Sphingolipid pathway for GBM compared to normal tissue and lower grade gliomas. This is characterised by a reduction in apoptotic metabolites, mainly ceramides, and an increase in Sphingosine-1-Phosphate (S1P), a stimulatory bioactive signalling metabolite known to promote cell survival and aid in tumorigenic processes. We also identified in tandem the transcriptomic changes for enzymes catalysing the metabolites, and restored the metabolomic shift by inhibiting over-expressed enzymes. We are also exploring potential functional consequences of restoring the imbalance in the Sphingolipid pathway and aim to move into an animal model. For me, research within the Cure for Life Neuro-Oncology lab and Adult Cancer Program has been a positive learning process and a wonderful experience. My colleagues and friends make the Centre an exciting and enjoyable place to be. The research reflects fruitful collaborations and a drive to find new avenues in understanding and targeting this relentless disease. After my PhD, I plan to go back into clinical work and hope our results contributing towards patient care in the future.

Profile:

Sylvia Chung



Sylvia is 2nd year Research Associate in Cure for Life Neuro-Oncology lab. My love for science has flourished under the guidance of my mentors and I have benefited extensively from the collaborative nature of the Centre. My primary interest is GBM, the most aggressive of brain tumours which has an equally as aggressive treatment regime: surgical resection, chemotherapy and radiotherapy. Even with this treatment, overall median survival is only 15 months. Our efforts have focused on testing new therapeutically efficacious drugs. Recent work has highlighted, PENAO, an organo-arsenical based anti-tumour metabolism inhibitor as the latest novel candidate for GBM. Invented by Phil Hogg and Pierre Dilda, PENAO, has shown great potential efficacy *in vitro* as well as *in vivo* GBM animal models. This included PENAO's ability to achieve up to 440-fold higher in anti-proliferative activity *in vitro* compared to the standard chemotherapy agent, temozolomide in glioma cells. PENAO induces cellular death under both oxygenated and low oxygen (1%) conditions and inhibits cellular migration and invasion *in vitro*. *In vivo*, PENAO treatment in mice resulted in 8 partial and 2 complete therapeutic responses with no signs or symptoms of treatment toxicity. PENAO readily crosses the blood barrier and can accumulate to a higher extent in brain tumour tissue. These highly promising results have lead to human Phase I clinical trials beginning in 2012.

Profile:

Josh McCarroll



Dr Joshua McCarroll's research focuses on using nanotechnology to develop novel treatment therapies for advanced brain cancer; an area where there is currently very few treatment options. Nanotechnology involves using novel molecules, which allow the brain cancer cells to be marked out more clearly, to deliver therapeutic drugs specifically to a tumour site. He is investigating the use of nanotechnology to deliver genetic material as well as chemotherapy drugs directly to brain cancer cells. This will make the cancer more sensitive to the chemotherapy as well as reduce the toxic side effects on normal cells.

"Current chemotherapy drugs are unable to differentiate between cancer cells and normal tissues, which results in the toxic side effects. The drugs also need to be administered in larger quantities, due to the widespread distribution of the agents into non-targeted organs, which increases the toxicity further," says Josh.

His project also looks to identify and target the genes that are involved in brain cancer's drug-resistance to standard chemotherapy, and in promoting tumour growth. "Once we identify these genes, we can use nanoparticles filled with siRNA and deliver these systemically to cancer cells to 'silence' the genes that are promoting the resistance to chemotherapy, thereby increasing the cancer's sensitivity to chemotherapy, which in turn will increase the efficacy of treatment," says Josh.

Ten of the Best

Research uncovering the biology of neuroblastoma, conducted by Professors Glenn Marshall, Michelle Haber AM and Murray Norris, was announced in August as one of the best research projects in the country in the National Health and Medical Research Council's (NH&MRC) publication, Ten of the Best Research Projects 2012.

The team was awarded an NH&MRC Program Grant in 2006, resulting in over \$4.5M worth of funding over four years towards their research into neuroblastoma, a particularly aggressive form of embryonal cancer.

"We currently know that if embryonal cells survive postnatally, they can promote tumour formation and there is a high chance that a child will develop neuroblastoma, so we have posed the question: if we can find out what drives these cells and eliminate that driving force, could we prevent neuroblastoma from forming?" says Glenn.

The team has identified the proteins causing embryonal cells to persist beyond birth, and from here, plan to look at two things: developing a blood test at birth that can detect if these embryonal cells are present in the baby, and, finding existing and new drugs that can 'switch on' these proteins, which would enable the body's natural 'cancer barrier'.

The team also has several national and international clinical trials now either underway or about to commence as a direct result of their

research.

"Our work has identified several molecular targets in childhood neuroblastoma cells, for which we have successfully developed new treatment strategies that are now either in clinical trial, or about to commence clinical trial," says Michelle. One such discovery led to the development of a combination therapy that is now in a national clinical trial for relapsed neuroblastoma.

"We conducted a search for genes that cause resistance to a particular family of anti-cancer drugs and discovered that by incorporating an anti-angiogenic drug, which inhibits the growth of blood vessels in a tumour, it actually enhances the effectiveness of the anti-cancer drug," says Glenn.

The team has also discovered that combining an old drug (DFMO) with modern chemotherapy can be highly effective in treating the most aggressive cases of neuroblastoma. Our approach, combining DFMO with other chemotherapeutic drugs, has recently been approved by the USA-based organisation, "New Approaches to Neuroblastoma Therapy" (NANT) for a clinical trial, that will run in both the US and Australia. We anticipate an early phase clinical trial will open before year end," says Murray.

"These results were made possible through the funding of the NH&MRC, and I speak on behalf of our entire team when I say that we are extremely grateful for their recognition and ongoing support of our work," Murray concludes.



Michelle Haber, Glenn Marshall and Murray Norris

Student Profile: Tony Huynh



Tony is a third year PhD student at CCIA focusing on screening for novel compounds for the treatment of neuroblastoma. His project's aim is to investigate a potential new approach for the treatment of neuroblastoma through the inhibition of MRP4 using small molecule inhibitors.

"We know that overexpression of MRP4 in neuroblastoma is prognostic of poor outcome and is also able to cause drug resistance in various cancer cell lines. A diverse library screen of chemical small molecules has resulted in the identification of several chemical structures that can specifically block MRP4. My project has shown that these compounds reverse drug resistance in cells expressing high levels of MRP4 and slow neuroblastoma cell growth (whenever you can slow the growth of cancer cells, it's a good thing). The compounds identified cause the inhibition of cell growth and morphological differentiation, which means the cancer cells actually change shape to become more like non-cancerous cells. It's a bonus that these compounds can also reverse drug resistance caused by MRP4," said Tony.

"We have shown that these inhibitors have the potential to work in other MRP4 expressing cancers beyond neuroblastoma - such as ovarian and prostate cancers. These inhibitors may one day be used for more effective treatment of neuroblastoma and other cancers which rely on MRP4."

Highest accolade in the state for translational research



Adam Spencer, Glenn Marshall, Michelle Haber, Murray Norris and the Hon Jillian Skinner

Michelle Haber AM, Murray Norris and Glenn Marshall received the 2012 Premier's award for Excellence in Translational Cancer Research for their achievements in bringing scientific innovations into clinical practice and improving survival rates for children with cancer.

The team developed ground breaking minimal residual disease testing (MRD) acute lymphoblastic leukaemia (ALL), the most common childhood cancer. The test can predict which children suffering from ALL are at the highest risk of relapse on standard therapy, so that individualised treatment can be introduced in newly diagnosed children.

In an international clinical trial, which ran for almost a decade and involved more than 650 Australian children, the use of MRD testing has markedly improved survival rates for high-risk patients and contributed to the improved overall ALL survival rate to over 80 percent.

"It is immensely gratifying to see how our research can make a real difference to survival rates of children with cancer," says Michelle.

"The ability of the MRD test to identify children at high risk of relapse has dramatically changed our approach to treatment. We can now tailor a specific therapy regimen for these children shortly after diagnosis, based on the results of our test. As our studies have shown, this provides children at high risk of relapse with a much better chance of survival. MRD testing is now considered part of the Standard of Care, and our test results are routinely used to guide treatment decisions in clinics across the country," says Glenn. "We could not undertake our research without the close partnership that we have established between researchers and clinicians at CCIA and Sydney Children's Hospital Randwick," says Murray. "These close links are absolutely essential in helping drive improvements in the treatment, survival and quality of life for children with cancer."

Other successful recipients included Emma Ramsay of ACP's Cancer Drug Development Group, receiving The Pfizer Studentship award.

Promotions 2012

Associate Professor

(effective 01/01/13)

Dr John Pimanda
Adult Cancer Program

Senior Lecturer

(effective 01/06/12)

Dr Josh McCarroll
CCIA

New industry partnership

One of CCIA's most exciting developments this year is a new drug entering the final stages of development for clinical trial in partnership with US Biotech company, Cleveland Biolabs, and its subsidiary, Panacela Laboratories. The drug, Reversan, was identified through chemical small molecule screening technology used in the ACRF Drug Discovery Centre for Childhood Cancer. Reversan is designed to make the most aggressive and drug-resistant tumours respond better to chemotherapy.

"This is a key initiative for CCIA and one I am extremely proud of," says Professor Michelle Haber AM. "This is the way of the future, finding new ways to increase survival rates for children with cancer. "Our goal is to have Reversan approved for clinical trial in at least one country within two years," says Michelle.

This discovery was also a recognised part of the neuroblastoma research program named in the NH&MRC publication, Ten of the Best Research Projects 2012.

2013 Lowy Cancer Symposium: Discovering Cancer Therapeutics

*Focusing on the three key phases of oncology
drug development*

Discovery, Pre-Clinical and Translational
For further information visit:

<http://www.lowycancersymposium.org>

**Congratulations
to
Prof Katharina Gaus
2012 Gottschalk Medal
for Outstanding Research
in the Medical Sciences**

- 2nd Birthday Celebration -

On 28 May, 2012, the Lowy Cancer Research Centre celebrated the second anniversary of its official opening. Over 200 staff and students gathered to celebrate the achievements of the Centre over the past two years.

Lowy Cancer Research Centre's Director, Professor Philip Hogg praised the staff for their ongoing commitment to cancer research in Australia's first research centre to bring together adult and childhood cancer research under one roof. The cake, especially commissioned for the anniversary, was a fully edible scale model of the building and was created by Phil's wife, Dr Kim Faulkner-Hogg.



Lowy Cancer Research Centre - High Street view



Lowy Cancer Research Centre staff and colleagues gather to celebrate 2 years



Director Phil Hogg cuts the cake

We have come a long way in two short years. The depth and breadth of our cancer research has expanded wonderfully. The Lowy Cancer Research Centre has become a highly collaborative environment, which bodes well for our efforts to combat this disease in kids and adults"

Professor Phil Hogg, Director

Would you like to contribute to 'Connect'?
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c.kennett@unsw.edu.au