Chemotherapy hope for hard-to-treat childhood cancers

Susi Hamilton

Children with a particularly lethal cancer could benefit from potentially life-saving treatment, following breakthrough work led by researchers at the University of New South Wales (UNSW).

A whole new class of drugs has been developed that, for the first time, targets the structure of the cancer cell.

UNSW researchers have provided proof that the therapy is effective in two types of cancers in the animal model. They are neuroblastoma, a cancer that affects children, and melanoma. The resulting paper has been published in Cancer Research.

“It is much like what happens when you see a building collapse on the TV news,” says the lead author, Professor Peter Gunning, from UNSW Medicine. “Our drug causes the structure of the cancer cell to collapse – and it happens relatively quickly. “We’ve been surprised and excited by the potential of this treatment,” says Professor Gunning, the Head of the Oncology Research Unit, in the School of Medical Sciences.

The drug looks to be effective against every type of cancer cell.

The work could lead to an entirely new type of chemotherapy, which could have more positive outcomes for hard-to-treat cancers and have fewer long-term side-effects for survivors.

“Attacking the architecture of the cancer cell has long been an
obvious target, but until now, attempts have failed because the building blocks of the structure of the cancer cell are also used to build the heart and muscle, so the toxicity was unacceptable,” says the first author on the paper, Dr Justine Stehn, also from the Oncology Research Unit.

But the team recognised there was a second “building block”, the protein tropomyosin, in the cancer cell structure that was sufficiently different from those in the heart and muscle, which could be safely targeted.

This latest work is vindication for Professor Gunning’s team which was alone in its theory about the architecture of cells. The UNSW team is believed to be the only one working in this area internationally.

As toxicity had been a major stumbling block in earlier research, possible funders were scarce. Professor Gunning says the financial support of The Kids’ Cancer Project is the only way this research has been possible.

“This research opens up a door on something the pharmaceutical industry and science gave up on 25 years ago,” says the CEO of the Kids’ Cancer Project, Peter Neilson.

“It shows that our founder’s faith in this work was right,” he says. “We will continue to invest in this and we are determined to see it going into clinical trials in children with hard-to-treat neuroblastoma.

“Normally it would go into adults and it would take 7 to 8 years to be trialled in kids,” says Mr Neilson. The first clinical trials are expected in 2015. “Cancer in children is not the result of lifestyle issues, so you’re relying on medical research to see any improvement in survival rates,” says the Dean of UNSW Medicine, Professor Peter Smith, who is also the Chair of the Research Advisory Committee of The Kids’ Cancer Project.

Childhood cancer is the single greatest cause of death from disease in Australian children, with three children a week dying from the condition.

“In the 1960s, less than 10 per cent of children survived cancer and now it’s 80 per cent,” says Professor Smith, who campaigned to have chemotherapy used in children in the 1970s, dramatically improving survival rates. “That improvement is all down to research. So it shows how important these partnerships are.”

This work is also supported by the National Health and Medical Research Council, the Cancer Council NSW, the Cancer Institute NSW and the Office for Health and Medical Research, NSW Ministry of Health.
On October 23rd the Federal Government announced more than $559 million in funding through the NHMRC to assist Australian health and medical researchers generate new health discoveries.

This investment is aimed at finding better treatments for many common diseases such as cancer, diabetes, asthma, arthritis and cardiovascular disease as well as finding new ways of tackling mental illness, dementia and indigenous health.

The Federal Government is committed to ensuring Australia remains a world leader in medical research. We are among the top five countries in the world in producing scientific articles per capita and in the past decade alone, Australian’s health and medical sector has produced three Nobel Prize winners. It is only through sustained investment that scientific talent generate health discoveries.

This round of funding included 652 project grants, 6 partnerships and 293 fellowships.

Some fast facts:
- Overall funding rate is 19% across all schemes
- $423.5 million for 652 project grants
- $4.5 million for 6 partnership project grants
- $38.6 million for 128 early career fellowship grants
- $23.9 million for 60 career development fellowship grants
- $1.9 million for 11 TRIP fellowships
- $54.6 million for 78 research fellowship grants

Successful NHMRC grants being administered through the UNSW GMO. Congratulations:

- **Shane Thomas** - How is an important immune regulatory protein controlled?
- **Fabio Luciani** - Novel bioinformatic methods to study genomic complexity in liver disease
- **Nigel Turner** - Does GPR84 mediate the beneficial effects of medium chain fatty acids?
- **Annemiek Beverdam** - New methods of detecting diabetic neuropathy
- **Andrew Moorhouse** - Switching on brain transporters to switch off brain seizures
- **Nigel Turner** - Health and lifespan regulation by NAD+ and SIRT2
- **Magdalene Montgomery** - The beneficial effects of medium-chain fatty acids in obesity and insulin resistance
2013 has been a ‘cracking’ year for Nigel Turner. As if being awarded over a million for research by the National Health and Medical Research Council (“NHMRC”) wasn’t enough he also became a father for the third time welcoming a brand new son Benjamin on October 13.

Nigel is at a point in life where he is feeling contented but he is the first to admit that the road to this point is not an easy one. “Compared to many other professions, academics work incredibly hard, to do this kind of work you have to absolutely love what you are doing,” says Nigel. “

Growing up in the NSW rural township of Cessnock Nigel knocked about with his 3 brothers. Sport was a huge dominator in the Turner household and Nigel and his siblings had the usual partnerships and rivalries on the cricket pitch, the tennis court, the soccer ground and the golf fairways. Science’s loss could well have been soccer’s gain had Nigel decided to pursue sporting endeavours instead of academic ones.

One could then be excused for thinking he was intending to become an eco-warrior. During his PhD studies at the University of Wollongong Nigel was wrestling emus, chasing (but rarely catching) lizards in the outback, fishing deep seas and wrangling octopi in local rockpools. He was, in fact, studying why there were such large divergences in metabolism between different species. “I can’t say it wasn’t fun,” he says. “But I wanted to have more of an impact on human health. I decided to change my research focus from comparative physiology to investigative. I wanted to look into what goes wrong with energy metabolism in some of the major disease in Australia and worldwide My research is now focussed on understanding how cellular metabolism is altered in obesity, diabetes and cancer, as well as trying to identify metabolic pathways that may be targeted to help treat these conditions.”

Paying homage to his PhD supervisors - Paul Else and Tony Hulbert (University of Wollongong) and his postdoctoral mentor Greg Cooney (Garvan Institute) – he credits them with shaping the scientist he is today. “They provided guidance when it was needed and demonstrated research integrity. Each, in their own way, has become the academic standard that I strive for with my own students.”

The awarding of a PhD is a milestone in the life of any scientist and Nigel is no exception. The hard yards are what often comes next. “The transition from early career postdoc to mid career postdoc/group leader has been recognised as especially difficult. I was fortunate to be supported through this period, but it is a time that many good scientists move to other professions,” Nigel acknowledges. “It was definitely a career highlight when I first obtained independent funding from the NHMRC and was able to establish my own group. The system of Government Grants is formidable. I had been close on many occasions, but when I finally received the email with “Outcome: Successful” it was amazing.”

“I’m mindful with my own students of what I have been through in my career and try to steer them through these pitfalls. I really
enjoy mentoring students and younger scientists to help them achieve their goals. One of the things I make sure they understand is you have to work your backside off. The second thing is publish. There is no doubt that when it comes time to apply for fellowships and jobs, the quality and number of publications you have are viewed as a good indicator of your research capacity and productivity,” he says. “On the technical side, make the effort to learn new techniques and to understand what is being measured. A lot of researchers think if they buy in a kit and follow the instructions then everything is OK. I cannot stress enough the importance of knowing how the assay works and what it is really telling you. If you can do this then you can trust your own results. There are many high profile finds in Nature/Science/Cell that cannot be reproduced in other labs, so I think if you are careful in the design of your study and perform the experiments well, then you have to trust that the answer you have it the right one.”

Perhaps the hardest thing for all researchers is managing to have a home life. “There is always a long list of things to do at work,” says the proud new (again) father. “Since I became a Dad I have learnt to prioritise a bit better and simply accept that it will take longer to get some work-related things done. This change in mindset has allowed me to focus all of my energy on my family when I am home and also not to feel guilty when I take some time out from work. I was fortunate enough to meet my wife, Joanne, at University so she understands the pressures involved in juggling the demands of work and home lives.”

In a year of change; moving to UNSW, moving house and welcoming a new family member – Nigel has been glad of the fact that he likes variety. He sees this as one of the big draw cards to being an academic. “There are few jobs where you get to do something different on each day of the week. I’m a naturally curious person. I like to know how things work and why. I also like the idea that someday my research may have the potential to contribute to a treatment for human disease.”

When asked to ‘crystal ball’ his research future Nigel hopes that grant success continues. Funding would mean he could recruit more students and postdocs to his group and thereby establish a productive and dynamic research team.

What might also be nice is a little more time for golf – the sport that has stayed with Nigel throughout his life. And more experiments – of the kitchen variety on a weekend evening surrounded by his happy, healthy family.

Fact Box

Nigel is a research academic within pharmacology. His research investigates mitochondria, the primary site of energy production within cells. Mitochondrial dysfunction has been linked with a number of inherited and acquired human diseases and has also been implicated in the aging process. A major focus of our studies examines how alterations in mitochondrial function in different tissues influences insulin action in obesity and type 2 diabetes. We are interested in how certain drugs and different types of dietary fats affect mitochondrial content and metabolism. We are also examining the role of post-translational modification in the function of mitochondrial proteins. Another area of research is the importance of alterations in mitochondrial bioenergetics in certain types of cancers.
Smoking

UNSW introduced a smoke-free campus (except in designated areas) on 1 July 2012. It’s been over a year since the introduction and policy is up for review, perhaps the campus can become completely smoke-free?

The Smoke Free Environment Policy applies to all university grounds including vehicles, boats and residential accommodation. Smoking of any substance is prohibited in all areas except within the designated smoking zones. The UNSW Campus maps have each got the logo at the strategically-located designated smoking zones.

The sale of tobacco is prohibited at all campuses from retail outlets and vending machines.

Enforcement relies on persuasion and encouragement. If you encounter someone smoking outside a designated smoking zone, please remind them of the policy politely and ask them to stop or move to a designated smoking zone. The procedure outlines disciplinary procedures for non-conformance by staff, students, contractors and visitors.

Smoking is also banned at all bus stops and bus queues in NSW (see the public transport bulletin).

Health and Safety Update

Evacuation

Why do you hear different alarm tones throughout the Wallace Wurth building during an evacuation? This is because the Wallace Wurth building has a two-stage cascading evacuation system. The two stages are the initial prepare-to-evacuate tone, then the full-evacuation tone. The cascade means that if there is a fire detected on one floor, then the affected floor will go into alarm and then 2 minutes later the floor above it and the floor below it will both go into alarm.

For example, if a fire is detected on the 3rd floor, it will go into prepare-to-evacuate followed by full evacuation. Two minutes later the 4th floor and 2nd floor will go into prepare-to-evacuate followed by full-evacuation. Two minutes later the 1st floor and 5th floor will go into prepare-to-evacuate etc. This cascade system will carry on until the whole building is evacuated. Therefore, there could be a 15 minute difference between the initial floor and final floor evacuation.

The cascade system allows a staged evacuation so the fire stairwells aren’t packed with people, it also allows time to investigate the cause of alarm. Once inside the stairwell you are protected from fire/smoke for up to 2 hours due to the fire resistant nature of the doors and walls, therefore the time delay does not affect your safety. However, if necessary the cascade system can be over-ridden at the alarm panel and the whole building be evacuated at the same time. The fire brigade or the chief warden will make this decision.

Due to the atrium the sound travels easily throughout the building. So if you hear an evacuation tone while in the atrium it is best to check the sound from the office or lab area to determine what stage of the cascade your floor is at.
This instrument has a patented technology known as Taqman Array technology. The Taqman Array allows analysis of up to 384 separate genes in a single PCR run using Taqman Technology. The benefit of the technology is that it allows more data from a single sample or patient and the primers are highly specific.

The QuantStudio 12K Flex is the latest technology qPCR instrument, it takes an all in one approach by accommodating any one of 4 interchangeable blocks:

- **OpenArray Block**: for up to 12000 data points per run
- **TaqMan Array Cards Block**: microfluidic 384 format
- **384 well blocks**: for 384 well plates
- **96 Fast block**: for tubes and 96 fast plates

The QuantStudio 12K Flex can perform all the following applications:

- **Digital PCR**
- **Gene expression profiling of disease pathways (HTP)**
- **Biomarker validation in drug discovery**
- **Cancer biomarker discovery with miRNAs**
- **Pathogen detection, strain typing, and viral load**
- **Mutation scanning (High Resolution Melting)**
  - Methylation and other epigenetic application
  - Protein analysis with proximity ligation assays
  - Protein Thermal Shift

The flexibility of the QuantStudio, in terms of format and applications, makes it a platform of choice for translational research work.

For more details contact the custodians: Dr Phoebe Phillips p.phillips@unsw.edu.au, Dr Kenneth Hsu k.hsu@unsw.edu.au, Dr George Sharbeen g.sharbeen@unsw.edu.au

Location: 438 Wallace Wurth
Fact Box

Dr John Hunt is the Deputy Head of School. He is also a Senior Lecturer in Pathology and is a member of the Inflammation and Infection Research Group. John’s research interests focus on mast cell biology and the discovery and molecular characterisation of novel mast cell proteases. The team has recently discovered a number of novel human mast cell tryptases and are currently determining their substrate specificity. Another aspect of the research involves the characterisation of factors that control the biology of mast cells.

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A Guild D55 dreadnought guitar made with spruce and rosewood, and grover machine heads (50th birthday present from my wife and kids).

My worst job was... Powder monkey (person who carries explosives) for an explosives expert (who had only three fingers left after a number of mishaps with detonator caps).

The book that changed my life... This Way Southward: The Account of a Journey Through Patagonia and Tierra Del Fuego by Aime F. Tschiffely. The author describes meeting my great-grandfather in the 1930s at his ranch in Argentina. When I read this as a young boy it sparked a lifelong interest in visiting interesting places.

Where did you grow up? Under the east-west runway in Banksia, a southern suburb of Sydney.

What is your favourite food? (Almost) anything cooked by other people.

Have you ever met a famous person? At a 1993 Lorne Conference I played a round of golf with Ed Fischer (1992 Nobel Prize winner for describing reversible phosphorylation) – but I didn’t recognise him. I just knew him as Eddie. He beat me. I got a large shock when he took to the stage later that day.

How many cities have you lived in? Two, Boston and Sydney.

Truth and Trickery – share 2 unique things about yourself and your life, 1 of them is true and 1 false – let the reader guess which is which.

I was attacked by a crocodile and still have the scars to prove it.

My great uncle was Sir John Hunt who was the team leader for Sir Edmund Hillary’s 1953 ascent of Everest.
10 Things You May Not Know About John Hunt

What's your most treasured possession?
A Guild D55 dreadnought guitar made with spruce and rosewood, and grover machine heads (50th birthday present from my wife and kids).

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What was the last book you read, movie you saw, TV show you watched (pick one or all)?
The Bat by Jo Nesbo, Silver Linings Playbook, and The Newsroom by Aaron Sorkin

My last meal would be....
"White Adriatic" figs from South Australia with 1937 Chateau d'Yquem.
**ATP-gated ion channels mediate adaptation to elevated sound levels**. P NATL ACAD SCI USA (PNAS)110(18): 7494–99.

The mammalian auditory system can process sounds ranging from a whisper to a wailing siren. Researchers have long studied the mechanisms that allow the cochlea to transduce loud sounds without damage, given that sustained noise from sources like industrial workplaces and personal music players can exacerbate age-related hearing loss. Gary Housley et al. demonstrate that increases in sound intensity trigger a release of ATP into the cochlear partition, activating proteins called P2X2 receptors and reducing sound transduction and synaptic transmission from cochlear cells. The authors report that mice deficient in the P2RX2 gene, which encodes P2X2 receptors, lack a hearing-protective response known as “temporary threshold shift” when exposed to a sustained sound level of 85 dB (similar sound level as busy traffic). Furthermore, the authors report that P2RX2-null mice are more vulnerable to permanent hearing loss than wild-type mice at sound levels above 95 dB (music concert, sport events). The authors attribute this vulnerability to a lack of ATP-activated conductance across the cochlear partition and suggest that ATP-gated ion channels assembled from P2X2 receptor subunits might underlie hearing adaptation that sustains cochlear function at high sound levels.

**α1-Adrenoceptor and serotonin 5-HT(1A) receptor affinity of homobivalent 4-aminoquinoline compounds: An investigation of the effect of linker length**. Biochemical Pharmacology 15; 85(10): 1534-41.

This paper is Junli Chen’s first paper from her PhD studies and describes the α1 adrenoceptor (α1-AR) subtype selectivity of a series of homobivalent 4-aminoquinoline compounds. One of the most effective treatments for urogenital conditions, such as benign prostatic hyperplasia (BPH) is therapy with α1-AR antagonists, however, the α1-AR antagonists that are used currently have side effects due to a lack of α1-AR subtype selectivity, and off-target affinity for the serotonin 5-HT1A receptor. The compounds described in this study show selectivity for the α1A and α1B -AR but poor affinity for the 5-HT1A-R making them an ideal starting point for the development of improved treatments for conditions such as BPH.

**The orbitofrontal cortex is involved in emotional enhancement of memory: evidence from the dementias**. Brain, doi:10.1093/brain/awt185.

This paper is the first to investigate emotional memories in frontotemporal dementia. It arose directly from Fiona’s PhD research, which investigated the interaction between emotion and memory, in younger onset dementia syndromes. The study combined clinical and neuroimaging approaches to demonstrate a profound impairment of emotional enhancement of memory in frontotemporal dementia. The severity of this impairment was associated exclusively with atrophy of the orbitofrontal cortex and revealed a previously unrecognised aspect of emotional functioning impairment in frontotemporal dementia. These findings have important clinical and theoretical implications for the management of dementia patients and for our understanding of the neural organisation of memory and emotion.
In this study, mast cell-specific tryptase was shown to have prominent roles in articular cartilage catabolism by significantly increasing the levels of enzymatically active matrix metalloproteinases (MMP) in cartilage. The accumulated data suggest that human and mouse tetramer-forming tryptases are MMP convertases that mediate cartilage damage and the proteolytic loss of aggrecan proteoglycans in arthritis, in part, by activating the zymogen forms of MMP-3 and MMP-13. Therefore, targeting this mechanism of cartilage destruction via mast cell tetrameric tryptases may have therapeutic benefit in arthritic diseases.

In this study using our virtual screening and profiling methodology to search a database of ~240000 compounds, we have identified unique chemical compounds (hits) with the potential to bind to our target receptor selectively over an off-target receptor. Three of the tested hits demonstrate statistically significant selectivity for the target receptor. All seven tested hits bind to the target receptor, with two compounds displaying Ki values below micromolar, and a further two Ki values of around 10 micromolar.

The Cancer Research paper is a proof of concept study around a novel class of actin targeting compounds. These compounds are able to selectively disable the cytoskeleton of cancer cells without any adverse toxicity. Developing a class of compounds which target such a fundamental biological system essential for cancer cell growth and survival has enormous implication for the treatment of a wide variety of cancers.
It was a proud moment for Patsie Polly (pictured with her family) when she received her VC's Award for Teaching Excellence, along with colleague Gwyn Jones. Aside from the honour of having her teaching endeavours recognised the day was significant as this was her first formal ceremony. "At the time of my PhD I was in Germany post doc-ing," she said. "It was too costly to come back. So this is a big deal for me. What a moment, being up there with my Honours cohort of students!"

New Library Resource

Kate Dunn

**BioMed Tracker** is a recourse that analyses the market and provides insight into whether a drug is likely to be successful; its likelihood of approval, commercial potential, 10 year forecast.

It also assesses the relative strength of companies’ clinical drug pipelines and highlights potential future catalysts that could impact those pipelines.

For further information please contact your Outreach Librarian Kate Dunn, kate.dunn@unsw.edu.au; 51012

This year’s Open Day at UNSW was one of the most successful yet. It would not have been possible to achieve these results without the dedicated work of staff within the School.

Thanks goes to: Patrick de Permentier, Karen Gibson, Nicole Jones, Margaret Morris, Priti Pandey and Richard Vickery.

Special thanks also goes to Angela Finch and Patsie Polly for their presentations that attracted over capacity audiences, and to the SMSSOC students who gave their time to provide the student experience of studying at UNSW, Medical Sciences.

### Academic Success

Congratulations to Cindy Lin who was successful in the recent round of academic promotions. Cindy takes up the new title of Associate Professor on the 1st January 2014. The promotion recognises Cindy’s hard work and dedication to scientific endeavours.

"I would like to sincerely thank the university for offering me the position of Associate Professor at UNSW. This is an opportunity for advancement so I am very pleased and honoured to accept this offer," said Cindy.
Academic Success

I am very pleased to advise the School that the Vice Chancellor has approved the promotion of A/Prof Lars Ittner to the level of Professor, effective from 1 January 2014.

"I am honoured to become a Professor at the University of New South Wales and look forward to, hopefully many, exciting years of research in the School of Medical Sciences," said Lars.

I am sure you will join me in warmly congratulating Lars on this singular achievement. It reflects his very significant achievements to date in advancing the understanding of dementia and related neurological diseases, and his international standing in this field.

Masterclasses in Italy

Brian Freeman has recently been in Italy giving courses in Biomechanical Embryology. The first course was delivered as part of a Masters programme for the University of L’Aquila: 15 lectures were presented over three days at San Benedetto del Tronto, a port city on the Adriatic. The course was attended by 106 physicians, dentists, and osteopaths from all over Italy. The course was delivered in English with simultaneous translation into Italian by translators sitting in a sound-proof cabin near the podium. The second course, held over two days in Milan, was delivered in English with sequential translation into Italian and was also attended by about 100 physicians, dentists, physiotherapists and osteopaths from Italy and America.

Brian was interested to learn about the new technique of using gentle osteopathic treatment to reduce the time that preterm infants had to stay in Italian hospitals, and was impressed by the number of questions he was asked on the development of facial and dental anomalies in children.

The courses coincided with the publication of the Italian edition of an embryology book, based on Brian’s edited translation in 2004 of the original text in German. "I had to sign so many copies of the Italian edition for participants that I felt like a ‘minor celebrity’", he said.

Ask Not What Your School Has Done For You

The School’s altruistic endeavours often go unnoticed. However over the course of a year funds are invested into research consumables and equipment maintenance as a way of keeping lab costs to a minimum for the individual researchers.

A noble enterprise in the current climate of research grant funding.

This year we have recalibrated and serviced 680 pipettes and serviced and repaired 32 balances. A saving of around $30,000 across the School.

There is considerable annual investment in the supply of gowns, gloves, paper towel, buffers and other general use items in labs. This research support funding is ongoing. The vision is that it helps sustain work by researchers that otherwise would not be able to cover the cost of these necessities.
Thanksgiving Ceremony

Ken Ashwell

"The biennial Thanksgiving Ceremony to honour those members of the public who donated their bodies to the Department of Anatomy was held on Thursday 3rd October in LG03. This year we had over 100 donor family members in attendance and the service was filmed by ABC Compass for a program they are producing on body donation. The service was led by Rev Andrew Johnson and several Department of Anatomy staff were involved (Professor Ken Ashwell, A/Prof Pascal Carrive, Drs Elizabeth Tancred, Nalini Pather, Irina Dedova and Ms Julie Ash). We also had a lot of involvement by the medical students, with several students contributing in special roles (Shohini Mukerji, Rachel Clifford, Fiona Li) and participating in the flower laying (Girja Townshend, Francis Young, Sai Meng Ng, Zi Ying Su, Lucy Bracken, Gloria Giang, Michelle Chew). Marie Kwok did an excellent job of organisation and everyone was very happy with the result. ABC Compass also interviewed staff and students about the importance of body donation and our appreciation of the donors. Thank you to everyone who helped make the event a great success."

On the Lighter Side

Advances in Science, 37. Iconoclastic researcher Dr Alvin Henderson demonstrates that it IS in fact possible to become too familiar with the safety rules.

For more information or to send comments, suggestions, events notifications and items for future editions please contact: The School of Medical Sciences, Head of School Office. Tel: 02 9385 2531 or email s.dacre@unsw.edu.au