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National Health and Medical Research Council

TEN OF THE BEST RESEARCH PROJECTS 2012

75 YEARS OF WORKING TO BUILD A HEALTHY AUSTRALIA

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Leadership in making lives healthier

The Hon Tanya Plibersek MP
Minister for Health

JFK's biographer, Theodore Sorenson, used to say that Kennedy was a happy President, because happiness was, to paraphrase Aristotle, the full use of one's faculties along lines of excellence.

If that's true, then this book is full of happy people.

In *Ten of the Best Research Projects 2012*, the Australian Government and the National Health and Medical Research Council (NHMRC) recognise the results of work that some of our finest Australian scientists and researchers have been putting their minds to.

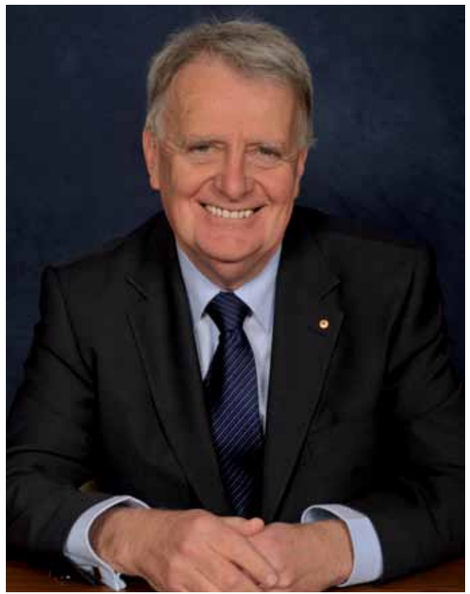
We can see research that takes new and innovative approaches to helping bridge the gap between the health of older Aboriginal and Torres Strait Islander people and their non-Indigenous counterparts; new ways of better caring for premature babies; better outcomes for people waiting on joint replacements.

From the smallest, sub-molecular systems, to our health system as a whole – this research covers a whole range of challenges.

By turning their minds to these challenges, our researchers don't just get the satisfaction of using their faculties along lines of excellence; they know they are benefiting all Australians. They also add to the sum of human knowledge and potentially benefit many millions of people around the globe.

Over the 75 year life of the NHMRC, we have seen life-changing, world-changing research supported, and evidence built for innovations in diagnosis, management and treatment of conditions.

I'm proud of our Australian researchers; and pleased to be able to bring you this small but important taste of their work.



The creation of knowledge is a collaborative effort

Professor Warwick Anderson AM
Chief Executive Officer, NHMRC

Australian health and medical researchers are world leaders. They have contributed to some of this century's most important medical discoveries.

With NHMRC support, Australian researchers are tackling all the health issues that Australians and people around the world face. Our researchers work, too, on ways of preventing ill health, and ways of more effectively delivering care to patients. Working across the board, they have created knowledge to improve the quality of life for all Australians, they have worked to use that knowledge in a range of practical settings, from innovative businesses to health policy.

The launch of this year's Ten of the Best coincides with the start of a new triennium in NHMRC's strategic planning cycle. We will continue our work to ensure that the evidence generated by research informs and influences clinical practice and health policy.

This year's Ten of the Best highlights how important research and research translation are to improved health outcomes.

A strong underlying theme of all research is collaboration. As you will see in this edition, health and medical research is rarely the result of one individual's effort. Within and across teams, we see what can be achieved when people combine their experience, ideas and efforts.

Collaboration is a core philosophy for NHMRC. We work with international organisations in global health and medical research efforts. We are moving to develop new ways for researchers, health educators and patients to work together to benefit from research evidence. We are building alliances in our region, including China and Singapore to improve health for all peoples.

On behalf of the NHMRC, I thank all researchers who have contributed to these efforts to assist in improving health through evidence in the 2009-12 Triennium. Selecting just ten of the many hundred reports is not an easy task considering the wealth of talented researchers supported by NHMRC. I congratulate the researchers profiled in Ten of the Best 2012 for their work, passion and achievements.

Breaking the life cycle: stopping the transmission of parasitic disease

Key facts

NEUROCYSTICERCOSIS

- **Around 50,000 people die each year from neurocysticercosis.**
- **50 million people are infected with the parasite which causes the disease.**

HYDATID DISEASE

- **The World Health Organisation estimates that between two and three million people worldwide suffer from hydatid disease.**
- **The parasite causing hydatid disease in Australia was introduced with the importation of sheep.**
- **In Australia, there are between 1,000 and 2,000 people currently being treated for the disease.**

'Parasitic organisms are complex genetically; they have developed very sophisticated methods to avoid being destroyed by their hosts.'

Professor Marshall Lightowlers has spent thirty years studying parasites. He and his team's most recent contributions are vaccines for neurocysticercosis and hydatid – the diseases that occur when humans are infected with the larval stages of two particular tapeworm parasites.

Neurocysticercosis develops through fecal-oral contact with eggs of what's colloquially termed the 'pork tapeworm'. People with neurocysticercosis suffer from small, fluid-filled cysts that form in the brain and the spinal cord. In hydatid disease, cysts typically form in the liver and lungs, with severe to fatal effects if the cysts leak or rupture.

The statistics are grim: around 50 million people worldwide have these infections. And each year, neurocysticercosis kills nearly 50,000 people.

'These are diseases which infect the poorest people in the poorest countries in the world,' Professor Lightowlers says.

In developing vaccines to combat these problems, Professor Lightowlers opted to target the livestock rather than the people who are affected.

'The parasite is transmitted by animals and by livestock animals, which gives us an indirect option to prevent human infection,' he explains. 'Doing this is a much less expensive option than developing a human treatment.'

Professor Lightowlers' ability to develop a vaccine was given a major boost in the 1980s when DNA technology became available.

'We extracted a gene from the parasite that encodes a specific protein, and from there produced that protein for use in making our vaccine,' Professor Lightowlers says.

Having achieved this breakthrough, the team went on to conduct field trials in many countries including northern Cameroon.

'The results were quite spectacular,' Professor Lightowlers says. 'When we examined our vaccinated pigs at the age when they are normally slaughtered and eaten, they didn't have a single parasite in them. We had achieved complete elimination of the transmission of the disease.'

Left to right: Professor Marshall Lightowlers, Dr Charles Gauci, Ms Julia Lackenby, Dr Cristian Alvarez, Dr Abdul Jabbar

Other trials, including a recent trial in northern Peru, were similarly successful, with every trial resulting in more than 99 per cent protection.

Meanwhile, a vaccine based on the technology developed by Professor Lightowlers and his team to protect livestock from hydatid disease, is close to commercial production.

Professor Lightowlers believes that his vaccines may curb the devastation caused by these two diseases.

'Neurocysticercosis is identified as one of around six human diseases that have the potential to be eradicated because it is only transmitted by pigs and humans,' he says.

'Now that is never likely to happen for hydatid disease in many parts of the world because it has a foothold in wild animals, but I'm hopeful that we can help decrease infection rates in humans by more than 90 per cent.'

Next steps

Professor Lightowlers and his team are now looking at how the vaccine against neurocysticercosis could be administered in one dose instead of two and still provide lifelong protection.

'Going to the affected regions, which are often poor and remote, is a challenge for the people vaccinating the animals,' he says.

'As a result, only having to administer the dose once would be a huge advantage.'

Another challenge Professor Lightowlers foresees is the possibility that a vaccine-resistant parasite could evolve and pose a threat to the gains he and his team have made. To counter this, Professor Lightowlers is carefully monitoring the genetic variability in the parasitic population that may lead to resistance.

Chief Investigator background and motivations

After completing his PhD in immunology at the University of Western Australia, Professor Lightowlers looked for a way that he could apply his skills in a practical way.

His early work at Adelaide's Institute of Medical and Veterinary Science focused on immunity to parasites.

In 1980 he joined a research team at the University of Melbourne which later developed the first non-living vaccine against a parasitic disease – the 45W vaccine against *Taenia ovis* in sheep.

Throughout his career, Professor Lightowlers has held a firm determination to achieve practical outcomes from his research.

'I see myself as extraordinarily fortunate for two reasons,' he says.

'Not only do I perform scientific research for a living, which allows me to do something new and exciting more or less every day, but I can also see the products of my research going towards something that is genuinely going to improve human health.'

CHIEF INVESTIGATOR

Professor Marshall Lightowlers

AFFILIATION
The University of Melbourne

TEAM MEMBERS
See Project Honour Roll page 28

GRANT AMOUNT
$ 739,574 (2006–2010)

Conquering childhood cancer

Key facts

- **Cancer is the second most common cause of death in children.**
- **About one quarter of children diagnosed with cancer die of the disease.**
- **Even when treatment is successful, the short and long term side-effects are often serious.**

'Our work includes trying to understand how child cancer starts at the very beginning. This knowledge will be very helpful in identifying a method of preventing child cancer. If we're able to do this, I'll be out of a job which would be a good thing.'

The broad mission of Professors Glenn Marshall, Michelle Haber and Murray Norris is both a difficult and affecting one: improving the outcomes of children with cancer. The main challenge is that there is no magic bullet – you have to target cancer in numerous ways to defeat it. Moreover, current therapy is extremely toxic to normal cells in children. The team's research identifies cancer genes specific to child cancer cells, and not normal cells, and uses novel drug discovery techniques to identify new treatments.

In addressing each of these factors, Professor Marshall and his team decided to focus on neuroblastoma.

'Our first goal was to try and better understand why embryo cells persist beyond birth to later become embryonal cancer,' Professor Marshall says.

'More than half of all childhood cancer derives from these cells that should have died off. We focused on a particular embryonal cancer called neuroblastoma because it is a common cause of death among child cancer patients.'

The findings of Professors Marshall, Haber and Norris in studying neuroblastoma can be categorised into three groups.

Firstly, they identified the proteins causing embryonal cells to persist beyond birth. They next investigated drugs which inhibit these proteins, thus leading to a child cancer prevention strategy.

Secondly, multidrug resistance-associated protein 1 (MRP1) and ornithine decarboxylase 1 (ODC1) were two proteins that the team identified as being integral to the growth of established neuroblastoma and thus major therapeutic targets.

Professor Marshall says, 'ODC1 essentially provides the petrol that drives the cancer's engine through effects on polyamine biosynthesis, which is the production of chemical building blocks for multiple cellular metabolic processes.

Left to right: Professor Michelle Haber, Professor Glenn Marshall, Professor Murray Norris

'The team have shown that an inhibitor of ODC1, difluoro-methylornithine (DFMO), was highly effective when used in combination with chemotherapy in animal models of the disease. This finding has generated a new international clinical trial for children with neuroblastoma.'

The team further showed that MRP1 promotes neuroblastoma by interfering with the cancer cell's normal processes of terminal differentiation – a process which ultimately causes the cancer cell's death.

With this in mind, Professors Haber and Norris invented an inhibitor of MRP1 as a potential therapy.

The third finding was the identification of novel combinations of existing drugs that have anticancer effects. Valproate and Interferon are one such combination which are the focus of an ongoing trial in neuroblastoma, and they work by blocking the action of histone deacteylases (HDAC).

Professor Marshall is keen to emphasise that the gains made in the field of child cancer have been a collaborative effort.

'You really have to work as a team, particularly if you want to take your findings from the bench to the bedside.'

Next steps

Clinical trials are currently underway to test the effectiveness of several new cancer treatments. An international trial to test the combination of DFMO and chemotherapy as a therapeutic measure will soon commence in Australia and the United States.

The combined use of HDAC inhibitors, Valproate and Interferon is also being trialed on Australian patients with relapsed neuroblastoma. It is also hoped that a clinical trial to test an inhibitor of the protein MRP1 will be underway within the next two years.

Chief Investigator background and motivations

Professors Marshall, Haber, and Norris have worked together for 20 years and have developed an internationally recognised translational research team.

Professor Marshall trained as a pediatrician and oncologist at Sydney Children's Hospital. Returning from a research fellowship at Children's Hospital Los Angeles, he focussed on neuroblastoma and leukaemia as the major unsolved child cancer problems.

The promise of what a child could go on to do and achieve is what drives Professor Marshall's research.

Professor Marshall says, 'I spoke at a law firm a couple of years ago about my research, and I noticed that one of the audience members was a patient I had treated some 15 years earlier.'

As it turned out, she was working at the firm, and had become a bright young star within the firm.

'That's what makes our work so important: helping children who go on to contribute to society for decades to come.'

CHIEF INVESTIGATOR

Professor Glenn Marshall

AFFILIATION

Children's Cancer Institute Australia and Sydney Children's Hospital

TEAM MEMBERS

See Project Honour Roll page 28

FUNDING AMOUNT

$ 5,029,092 (2006–2010)

The eyes have it: improving the success of corneal grafts

Key facts

- The cornea is the transparent window at the front of the eye which, if damaged, can cause blindness.
- Corneal damage is the second most common cause of blindness worldwide.
- 1,200 Australians need a corneal transplant each year — all graft donations are derived from human eyes.
- While 90 per cent of corneal grafts survive for 1 year, less than 50 per cent of corneal grafts survive for 10 years.

'We've been able to show unequivocally that people, including quite elderly individuals, can be a corneal donor. What it means is that in Australia now there is virtually no waiting list for corneal transplantation.'

With corneal damage the second most common cause of blindness worldwide, the success of a corneal graft can be life changing for the 1,200 Australian patients who need a transplant each year.

Unfortunately, corneal grafts have a high long term failure rate, with many corneal transplant patients requiring more than one transplant over their lives.

The challenge of turning this around has been taken up with determination, ingenuity and persistence by Professor Keryn Williams and her team.

'Twenty-seven years ago, we established the Australian Corneal Graft Registry – a clinical database of over 24,000 Australians who have received a corneal transplant,' Professor Williams says.

'This registry has allowed us to study the conditions crucial to corneal graft survival over time, and our findings have shaped the way corneal transplants are carried out.'

One of their most important research breakthroughs debunked the widely held view that corneal donors must be young – a belief that had severely limited the pool of potential cornea donors and often meant long waiting times. The research of Professor Williams' and her team helped to prove that corneas harvested from older donors 'do just as well' as those from younger donors.

'This led to a dramatic cut in the waiting time for corneal grafts and today there is almost no waiting list for patients requiring a corneal graft in Australia, compared with other eye banks across the world that are struggling to meet demand.'

Thanks to Professor Williams and her team, the chances of the body rejecting a corneal graft have now also been reduced, after their discovery that immunological rejection was the most common cause of corneal graft failure.

As Professor Williams explains, 'In order to combat immunological rejection, drugs must be administered to the local area as well as targeting the systemic immune system, which controls the body's response to the graft.'

Next steps

One of the areas showing promise that Professor Williams and her team are focusing on is gene therapy. In particular, they are examining gene treatment to increase the longevity of corneal grafts.

The team are also busy using nanostructured porous silicon as a scaffold to support ocular cells that can be transplanted into the eye. 'We know that normal cells can be transplanted into a healthy human eye. We're now looking at ways that we might be able to create a model of ocular surface disease to test the success of cell transplantation in repairing disease.'

In addition, retinopathy of prematurity is a condition affecting a proportion of premature babies that can lead to blindness,' Professor Williams says. 'Early research is showing that a group of genes known as microRNAs might play a role in susceptibility to the disease in some very, very premature babies.'

Front row: Ms Melinda Tea, Professor Keryn Williams, A/Professor Sonja Klebe
Back row: Dr Michael Michael, Ms Madi Helm, A/Professor Celia Chen, A/Professor Richard Mills, Dr Miriam Keane, Dr Alex Colella, Dr Helen Brereton, Mrs Marie Lowe, Ms Lauren Mortimer

Chief Investigator background and motivations

After studying biochemistry and microbiology, Professor Williams spent her postdoctoral years at the University of Oxford's Department of Surgery.

'There, I was a part of cutting-edge research in transplantation biology and became hooked on the challenge of ensuring the survival of transplanted organs and tissues,' she says.

On returning to Australia, Professor Williams was offered a research fellowship in the newly-established Department of Ophthalmology at Flinders University in Adelaide. Having seen the benefits of a registry approach to organ transplant research during her time in the UK, she set her sights on establishing the Australian Corneal Graft Registry.

Professor Williams says, 'The longer I spent working on the eye, the more I realised that you can make a real difference to people's lives. The collaboration with my staff, students and colleagues has been essential to our successes – and they've made our work fun and rewarding.'

CHIEF INVESTIGATOR

Professor Keryn Williams

AFFILIATION
Flinders University

TEAM MEMBERS
See Project Honour Roll page 28

GRANT AMOUNT
$ 739,574 (2006–2010)

Equality for all: an evidence-based approach to patient care

Key Facts

- Professor Osborne and his team's earlier research indicated that approximately 20 per cent of people waiting for a joint replacement rated their quality of life as nearly or as bad as being dead.
- Professor Osborne and his team's Victorian orthopaedic waiting list reform program has been applied to all Victorian public hospitals and is helping to improve equity and access to timely health services.
- Around 37,000 hip replacement procedures were conducted in Australia in 2011.

'I cannot tolerate health inequalities that are needless. They exist because of poor process, poor consideration, vested interests and old approaches to health care management. It's just intolerable and doesn't need to be there.'

The health system is a vast and complex machine. For many people, understanding how it works and how it could be improved is too hard a task or simply not of interest to them. But for Professor Richard Osborne, this challenge has become a strong passion and his life's work.

Professor Osborne believes that innovative research is essential to enabling all people to receive equitable health care. With his team, Professor Osborne is reforming how people interact with the health system as well as how health professionals view and treat the people they care for.

One of their main areas of research is new approaches to providing support for self-management of illness or disease. They have developed an innovative web-based support system for people with muscoskeletal or mental health problems, which provides information on the many challenges of dealing with a chronic disease, as well as pathways for discovering solutions to achieving positive and active engagement in life.

Already this system is attracting interest from European health agencies, which are keen to adapt it for use in their own countries.

What makes this system special is the way information was gathered to inform its development; Professor Osborne and his team used an approach that in many ways was a radical departure from established methods.

'We recognised the importance of taking a ground-up approach rather than using research that was based on past and potentially flawed theories. We listened to patients, practitioners and policy makers to find out what their needs were from their own perspectives. From there, we were able to develop a system that can serve all those needs.'

Professor Osborne was similarly interested in improving treatments for patients requiring a joint replacement. Here he also sought to do things differently.

'We didn't want to base our research wholly on previous thinking because we were aware that a lot of research is tainted by, and were causing, health inequalities,' he says. 'Basically, if you use questionnaires that only the well-educated can read and understand – and then you base policies on the results of these questionnaires – you risk inadvertently developing both models and policies that don't accurately reflect the cross-section of the population. This in turn creates inequalities in the provision of care.'

His team also expanded the scope of factors that are examined in measuring whether a person has hip or knee joint disease that is so severe that they need a joint replacement.

'We didn't just look at individual joint replacements in isolation. We considered patients' overall health, their jobs, their caring roles, as well as their medical needs.'

This innovative approach enabled the development of a new model of care that properly prioritises and manages people with hip and knee osteoarthritis on waiting lists for joint replacement in public hospitals.

Professor Osborne says, 'In the past, people would be waiting at home for months or years until the system picked them up, and sometimes it would be too late – they had deteriorated so much that they lost their jobs and could not care for their loved ones. As it was, the system could not identify or support these people.'

The team's model has now been implemented across all Victorian public hospitals – and it is being taken up by most other Australian states and territories.

Next steps

Professor Osborne and his team are now squarely focused on implementing this research across Australia and internationally.

They're working to incorporate new research approaches into health policy and practice, working with patients, policy makers and innovators. Professor Osborne is adamant that collaboration is crucial to achieving better patient care, saying that the silo approach stifles creativity and finding much needed solutions.

One source of the team's creativity has been what they call 'concept mapping'. It's a relatively new method which facilitates engagement with all stakeholders to capture the community's understanding and experience of a health issue. With this tool, Professor Osborne and his team hope to design new approaches for assessing patients and healthcare reform.

Professor Richard Osborne

Chief Investigator background and motivations

Professor Osborne began his career as an epidemiologist at the University of Melbourne. His studies have always sought to engage with policymakers, health services, practitioners and patients to inform both the development of research ideas and the development of how the research findings should be implemented.

He was promoted to Professor at Deakin University where he currently heads the Public Health Innovation Unit and is Co-Director of the Population Health Strategic Research Centre which is home to over 50 researchers and their programs.

The 'needless inequalities in patient care' are what motivate Professor Osborne.

'These have driven me to identify evidence-based strategies to eradicate these inequalities through better systems and practices,' he says. 'I am committed to collaborative processes, including working with policymakers to create solutions, which I believe delivers the best health outcomes.'

CHIEF INVESTIGATOR

Professor Richard Osborne

AFFILIATION

Deakin University

TEAM MEMBERS

See Project Honour Roll page 28

GRANT AMOUNT

$ 462,290 (2006–2010)

Under pressure: improving treatment of Type 2 diabetes and Duchenne Muscular Dystrophy

Key facts

TYPE 2 DIABETES

- Type 2 diabetes is the sixth leading cause of death in Australia.
- Type 2 diabetes is the fastest growing chronic disease.
- Up to 60% of Type 2 diabetes can be prevented.

DUCHENNE MUSCULAR DYSTROPHY

- Duchenne Muscular Dystrophy is a severe and progressive muscle wasting disorder.
- DMD affects about one in 3,500 live male births.
- At present there is no cure for muscular dystrophy and existing therapies are ineffective.
- Most patients die in their 20s or 30s from respiratory or cardiac failure.

'Science is always about serendipity — sometimes the greatest discoveries you make aren't the ones you intended to make.'

Ten years ago, Professor Mark Febbraio was working as an exercise physiologist when he made an intriguing observation. He noticed that heat stress on the body during exercise was causing the expression of a heat stress protein (HSP72) in the muscle. His next question was, 'what does that mean?' And, 'what does that do?'

The answers to these represent major progress in developing treatments for Type 2 diabetes and Duchenne Muscular Dystrophy (DMD).

It all began with the discovery that increasing the expression of HSP72 blocked insulin resistance. Insulin resistance is a disorder associated with obesity that leads to the development of Type 2 diabetes.

In experimenting with a mouse that over-expressed HSP72, Professor Febbraio and his team found that even if they put the mouse on a high fat diet, it was protected from diet-induced diabetes and insulin resistance.

That wasn't really the major breakthrough though.

'We worked with researchers in Hungary who had developed a molecule (BGP-15) that activated HSP72,' Professor Febbraio says. 'We tested this molecule on mice that lacked leptin – that is, they don't have the chemical signal that tells them to stop eating, which then makes them become fat. In treating them with BGP15, we saw some fairly spectacular results.'

Since then, a similar trial was conducted with human participants that resulted in a marked reduction in their insulin resistance.

'On the basis of that finding, the molecule is now undergoing further clinical trials in Europe. If these results are positive, the drug could be on the market within five years.'

But that was just the beginning.

Professor Febbraio and his team's research produced solid evidence that by activating HSP72, it was possible to preserve the function of the mitochondria – the 'energy powerhouse' of the cell. This has extraordinary implications for not just insulin resistance, but all diseases where there is a decline in mitochondrial function.

'This next chapter is where it becomes very exciting and important,' Professor Febbraio says.

Together with a colleague at the University of Melbourne, Professor Febbraio and his team were able to show that increasing the expression of HSP72 preserved muscle strength and slowed the progress of muscular dystrophy in mice with this condition.

'The trials conducted by Professor Gordon Lynch and my group suggested that increasing the expression of HSP72 in muscle using BGP-15 could potentially become a treatment for DMD. This would not only improve the quality of people's lives, but it could also increase their life expectancy.'

Next steps

'Further research into Type 2 diabetes will include looking at the precise mechanism that causes HSP72 to block insulin resistance,' Professor Febbraio says. 'It was first thought that this occurs by blocking the protein c-Jun N-terminal kinases (JNK), but this is now under review. The focus is turning to whether the major mechanism is by increasing mitochondrial stability or through biogenesis.'

Research into Duchenne Muscular Dystrophy, conducted by Professor Lynch in collaboration with Professor Febbraio and his team, is also continuing:

'We are looking to see what happens if you delete HSP72, and whether HSP72 is necessary to prevent disease progression. We are also interested in not just muscle disease, but any situation where you have muscle weakness or muscle wasting.'

Left to right: Professor Mark Febbraio, Dr Clinton Bruce, Dr Darren Henstridge

Chief Investigator background and motivations

Professor Febbraio is the first to concede that he didn't take a traditional path into science.

After completing a PhD on the effect of heat stress on the body during exercise, he went into teaching at the University of Melbourne's Department of Physiology and conducted his research around undergraduate teaching commitments. But in 2001, he came to the realization that he 'didn't want to be an exercise physiologist anymore and really didn't like teaching.'

He subsequently applied for, and obtained, an NHMRC Senior Research Fellowship. Since then, he has been a full-time research fellow – nearly a decade now – and last year he was promoted to the position of NHMRC Senior Principal Research Fellow.

'Without being clichéd, the real motivation behind being a scientist is to one day say you had a hand in a drug that makes a sick person better,' Professor Febbraio says.

He describes this as the 'Holy Grail' of what he and his team do.

'I guess you get to a point in your career where that's the driving force behind it all. What it boils down to is making a difference in a sick person's life.'

CHIEF INVESTIGATOR

Professor Mark Febbraio

AFFILIATION

Baker IDI Heart and Diabetes Institute

TEAM MEMBERS

See Project Honour Roll page 29

GRANT AMOUNT

$ 467,720 (2008–2010)

Birds of a feather: tracking the path of avian flu

Key facts

- Between 10 and 20 per cent of Australians are infected with seasonal flu each year.
- An average of 2,500 to 3,500 Australians die from seasonal flu every year.
- Australia spends about $600 million every year on seasonal flu, including hospitalisation and loss of productivity in workplaces.
- About 60 per cent of people worldwide that contract H5N1 die of the virus.

'Infections of humans with the H5N1 influenza virus, although rare, are usually fatal. It's not yet pandemic, but if it acquired the ability to move from human to human, we'll be in very serious trouble.'

Professor Lorena Brown is not one to underestimate the health risk posed by the flu virus: 'The recent swine flu pandemic was relatively mild, but we shouldn't be lulled into thinking that a pandemic of Avian H5N1 virus would be the same.'

One of the first major breakthroughs of Professor Brown, Doctor Deborah Middleton and other colleagues was the establishment of the first highly contained, animal model of human Influenza A virus subtype H5N1 infection in Australia.

'This has enabled research into how this potentially deadly virus operates and how it might be stopped,' Professor Brown explains.

'With PhD student Kathryn Edenborough, we are now tracking the virus around the animal model's body from different entry sites. It appears that breathing in large amounts of the virus results in compromised respiratory function and is invariably fatal, whereas swallowing the virus results in a lower incidence of death.'

'Breathing in small amounts of virus, insufficient to reach the lungs, is also fatal, because the virus travels directly from the upper respiratory tract to the brain.'

The team discovered that the presence of virus in the blood in the first 24 hours of infection heralds severe disease and death.

'These findings tell us that it is crucial to rapidly treat infected patients, even those with no pneumonia, very early after infection to prevent neurological symptoms.'

Professor Brown and Postdoctoral Fellow Brad Gilbertson are also studying how natural inhibitors of the virus can reduce the spread of infection. In another research breakthrough, they located the binding site of a flu inhibitor in the saliva of mice.

'We had previously shown that if you give a mouse 30 times the normally lethal dose of the virus as an upper respiratory tract infection to the nose, that mouse will be perfectly happy and survive,' Professor Brown says. 'So there was clearly something in the mouth that stops the virus progressing down to the lungs and killing the mouse.'

'Brad has now pinpointed where the inhibitor binds onto the virus, thus identifying a weak spot where the virus could be attacked.'

Next steps

Now that Professor Brown and her team have identified a flu inhibitor in mouse saliva, the next step is to see whether humans carry a similar inhibitor.

'We are particularly interested in whether babies may have inhibitors of influenza in their saliva that might give them some protection prior to their first vaccination,' she says.

Meanwhile, Professor Brown and her team are researching possible implications that changes in the H5N1 virus, as it evolves in bird populations, may have for humans who become infected.

'We have already confirmed in our animal model that Australia's H5N1 vaccine is protective.' Professor Brown says. 'Although some of this vaccine is stockpiled, it may no longer be effective if the H5N1 virus changes significantly.'

It would also take several months before enough of the modified vaccine can be created to be available for everyone if an H5N1 pandemic occurs.'

Left to right: Dr Brad Gilbertson, Ms Kathryn Edenborough, Professor Lorena Brown

Chief Investigator background and motivations

Professor Brown started her career as a virologist and vaccinologist at the University of Melbourne's Department of Microbiology. She then spent her postdoctoral years at Saint Jude Children's Research Hospital in Memphis, Tennessee, studying the impact of different influenza viruses and how the body fights them.

On returning to the University of Melbourne, it was clear to Professor Brown that becoming a 'flu fighter' was her calling.

'I've now been working to better understand the flu virus, including how it might be prevented and possible treatments, for over three decades.'

More than ever, she sees the importance of that work: 'I think it's essential that we're ready to face any threat. I've been afforded the brilliant opportunity of helping boost Australia's capacity to deal with the H5N1 virus.'

Along the way, Professor Brown has taught and mentored Australia's new generation of virologists.

'Having the opportunity to train new young influenza virologists has been a real privilege. I think it's important for this country to be well prepared for fighting this lethal disease.'

CHIEF INVESTIGATOR

Professor Lorena Brown

AFFILIATION
The University of Melbourne

TEAM MEMBERS
See Project Honour Roll page 29

GRANT AMOUNT
$ 513,717 (2008–2010)

Addressing the unmet needs of remote Indigenous people with dementia

Key facts

- Life expectancy for Indigenous Australians is 17 years less than non-Indigenous Australians.
- Risk factors known to contribute to dementia — including obesity, mid-life hypertension and diabetes — occur at a higher rate and at an earlier age among Indigenous Australians.
- A study of 363 people over the age of 45 in the Kimberley found that 12.4 per cent of participants suffered from dementia — five times the rate among non-Indigenous Australians.

'Ours is a community-driven model of dementia care that has been trialled and shown to work. It has brought about better community understanding of dementia, and better education and training for caregivers. Dementia patients have also benefited from culturally appropriate respite, and have the comfort of being able to be cared for in their own communities.'

In the remote Kimberley community of Looma – population 350 — the approach to caring for family members with dementia is straightforward: 'Gotta be sit down and worked out together.'

For Melbourne geriatrician Dr Dina LoGiudice, this philosophy has guided her pioneering research into improving dementia care for Aboriginal Australians. But before care could be improved, Dr LoGiudice and her team of health professionals[1] had to go back to basics, working with local people and service providers to construct a culturally and linguistically appropriate tool to assess levels of dementia.

What emerged was the development of the Kimberley Indigenous Cognitive Assessment (KICA) – the first of its kind, given that no culturally appropriate dementia assessment tool previously existed.

'If you want to try to screen for dementia, you have to assess different domains of cognition such as memory, thinking and language. The tools that were available were culturally inappropriate, particularly for rural and remote older Aboriginal people; many of whom were illiterate or had only a few years of schooling. They also often spoke many languages, with English being their third or fourth language.'

This tool facilitated a study of 363 people over the age of 45 living in six Kimberley communities; a study which revealed that the rate of dementia amongst Indigenous Australians was five times higher than in non-Indigenous Australians – and it was appearing at a younger age.

Once Dr LoGuidice and her team determined that there was a high level of dementia, they visited different remote communities to identify what the main issues were for people with dementia and their caregivers.

Armed with this knowledge, they travelled to Looma in Nyikina country, 120 kilometres south east of Derby.

'We wanted to develop a collaborative model of care for people with dementia living in remote Indigenous communities, starting with a year-long pilot project in Looma,' explained Dr LoGuidice.

'This was a project developed within the community, by the community[2]: it employed local people and local people were given education and training to care for frail aged residents, and residents of all ages with disabilities and mental illness. This represented a shift from the old model of external service providers being the sole trained caregivers, to that of educators.'

Working from Looma community, the service *Lungurra Ngoora* – 'blue tongue lizard home' in the Walmajarri language – local people provided hands-on care, activities and respite in partnership with government and NGO service providers. Through this new approach, resources were better targeted, community members stopped falling through service gaps, and the number of services increased significantly.

Although the year-long pilot project in Looma has been completed, aspects of the community-driven approach to dementia care has continued.

'Our work has had an impact on Looma – it gave them a sense of ownership and empowerment,' Dr LoGuidice says. 'The local people felt happy being cared for by their own community, and they now have a working knowledge of how things could be done differently.'

Left to right: Dr Dina LoGiudice, Ms Emily Carroll

Chief Investigator background and motivations

'I'm from Melbourne, of Italian background, which is how I ended up seeing many older Italian people with dementia. These beginnings led me to an interest in cross-cultural assessment.

'Older people are a vulnerable group and with that comes many challenges for caregivers. Quite often, the usual systems don't cater very well for these people.'

A visit to the Kimberley and conversations with colleagues working in remote communities prompted her initial investigations into the early onset and prevalence of dementia.

'I knew that the remoteness of these communities brought its own difficulties. Service providers may only visit two or three times a year and it can take a day or two to get there. So we wanted to develop a pilot program that was very much decided and driven by the community.'

'I've always worked in aged care. My work is in clinical research, but I'm a clinician first.'

CHIEF INVESTIGATOR

Dr Dina LoGiudice

AFFILIATION

Royal Melbourne Hospital, Royal Park Campus and Western Australian Centre for Health and Ageing

TEAM MEMBERS

See Project Honour Roll page 29

FUNDING AMOUNT

$ 1,081,062 (2007–2010)

Next steps

A follow up study to determine the rate of progression and underlying causes of dementia in remote communities. The initial cohort of 363 people will be assessed after 5 years and their incidence of dementia and outcomes will be addressed. Building on our previous work with the KICA, other culturally appropriate screening tools will be developed for pain, depression, function, carer burden and falls.

Dr LoGiudice says, 'More research is needed to develop appropriate models of care for people with dementia and their families living in remote Indigenous communities. Prevention is another key area that needs more work, to delay the onset of dementia.'

'This means developing programs that are not only deemed important by community members, but ones which involve their participation. Their help is essential if we want the right research questions and outcomes, also if we want to facilitate acceptance of these programs.

'The path to all these things is empowerment and reciprocal education.'

Giving premature babies a better start in life

Key facts

- Preterm birth occurs when a baby is born before 37 weeks of gestation.
- 'Very preterm babies' are babies born between 24 and 28 weeks of gestation.
- In Australia, preterm birth occurs in approximately 1 in 10 babies.
- Very preterm birth is the most common cause of illness and death in newborn babies.
- The majority of very preterm babies do survive but there is a high instance of ongoing disability and developmental challenges.

'In the absence of a breakthrough in preventing premature birth, we felt it was important to deal with the ten per cent of babies that are born prematurely and solve the immediate problems they present with.'

The care of preterm babies, who are often born with lungs that are too immature to breathe independently, is the most serious and costly problem in neonatal medicine. And, as Professor Richard Harding points out, the incidence of preterm birth is not declining.

'Preterm birth will continue to pose a great medical risk to babies and cost to Australia's health system for years to come,' he says.

So while other researchers focus on preventing preterm birth, Professor Harding and his team have made it their mission to improve health outcomes for the one in ten Australian babies who are born preterm – some as early as 24 weeks gestation.

Using premature lambs as animal models, Professor Harding and his team have been able to uncover more about the multitude of changes that take place at birth, particularly how the lungs function independently.

'We now know that maintaining constant gas pressure in a baby's lungs can prevent the injury caused by the lung collapsing during expiration.'

They also found evidence that contrary to the common practice of administering high levels of oxygen – as much as an adult human would require – lower levels of oxygen can do the same job and minimise injury in preterm babies.

'Keeping carbon dioxide and pH levels within normal limits are the most vital factors in ensuring healthy development of the brain and other organs,' Professor Harding says. 'This means that neonatologists can administer lower levels of oxygen in order to protect the lungs, without the risk of adverse neurological effects.'

Overall, their studies have led to a new and deeper understanding of the complex changes that occur in the lungs and cardiovascular system following preterm birth.

'This knowledge has been translated into safer, more effective ways of supporting very premature infants, in the delivery room and during intensive care, both within Australia and overseas.'

Next steps

Professor Harding and his team are very interested in the role hormones called corticosteroids have on the health outcomes of preterm babies.

Corticosteroids are administered to a mother prior to a preterm delivery to stimulate the lung maturation of the foetus. While these drugs often ensure a successful birth and initial survival, there is concern about possible long-term side-effects. Professor Harding's group wants to test whether more specific corticosteroids can be used, that could replicate the benefits of currently used corticosteroids on the lungs without possible harmful effects on other organs.

Further steps include testing whether antioxidants can protect the lungs and brain from injury and determining the effectiveness of stem cells in treating any injury sustained.

At the same time, the team is broadening its research to gain a better understanding of how preterm birth affects other vital organs such as the heart, blood vessels and kidneys.

Left to right: Professor Richard Harding, Professor Stuart Hooper, Associate Professor Tim Cole, Professor Peter Davis

Chief Investigator background and motivations

Professor Harding completed his PhD in neuroscience, but afterwards, became interested in the control of breathing from a neurological perspective.

During his postdoctoral years at Oxford University, he began to examine how the foetus makes the transition to becoming independent after birth.

He did – and still does – want to know more about the maturation of the lungs: 'Like most scientists, I'm fascinated by how biological beings work because we're incredibly complex – more complex than I could have imagined at the outset.'

Professor Harding regards the NHMRC grant he received as the highlight of his career, saying that it has allowed for the formation of his team, comprising neonatologists and basic scientists including himself.

'The clinicians tell us what the problems are, and we use animal models to provide further understanding. At the same time, we basic scientists get to go to the intensive care nursery and see the babies, to develop a better appreciation of what their problems are, so we can solve those problems.'

CHIEF INVESTIGATOR

Professor Richard Harding

AFFILIATION
Monash University

TEAM MEMBERS
See Project Honour Roll page 29

FUNDING AMOUNT
$ 8,381,821 (2006–2010)

Food for thought: investigating the rise in food allergies

Key facts

- Access Economics predicts that by 2050, 47 per cent of people will have some form of allergy.
- Children with food allergies are more likely to suffer from asthma than those without allergies.
- The rise in food allergy appears related to the 'modern lifestyle'.

'I really found my home in epidemiological research, where I enjoyed looking at general population questions that have an impact on a large amount of people in a small way.'

It was a bold step to go from conducting skin prick tests to determine the prevalence of childhood allergies to actually administering the food suspected of causing the allergies. But with food allergies reaching what's being described as 'epidemic levels' in Australia, Professor Katrina Allen knew it was vital to find more accurate methods of assessing children for food allergies.

She and her team set about uncovering whether there had been an increase in the instance of food allergies as reported. Their research has given scientists the first true picture of the prevalence of allergies in Australia today.

They tested 5,300 children aged 12 months. Around 20 per cent of the children recorded a positive result to a skin prick test for one or more allergies to egg, peanuts, cows' milk and sesame seeds. But these results were complicated by the fact that a skin prick test is only accurate in around 50 per cent of cases.

With this in mind, the more than 1,000 children who had tested positive to a food through skin prick tests were given the food in a controlled hospital environment.

'As you can imagine, it was frightening for parents to agree to having their child exposed to certain foods, knowing there was a good chance that they would have an allergic reaction,' Professor Allen says.

'Reactions can be as serious as anaphylaxis. But most of the parents were relieved that their child was being exposed to the risk in a controlled medical environment with doctors present, not at a child's birthday party.'

Prior to skin prick testing in the community, parents of all 5,300 children were given questionnaires to try to identify associations that might explain why some children develop food allergy.

Having discovered that allergy prevalence is on the rise, Professor Allen and her team are now hot on the trail to find out why. They are examining combinations of genetic, epigenetic, immunological and environmental factors and have already published discoveries including an improved 2-step test for increasing peanut allergy diagnosis and a gene that increases the risk of food allergy.

Their work has already led to many practical outcomes, most notably, changes to the National Health and Medical Research Council's *Infant Feeding Guidelines for Health Workers*. The team's research contributed to the recommendation that parents introduce egg into their child's diet between four and six months, not after 10 months as initially directed. This step may increase a child's tolerance to egg and is proof of the benefits of Professor Allen's research to public health.

Next steps

What's extraordinary is we proved that one in ten infants had child food allergies,' Professor Allen says.

Having identified this, the next step for Professor Allen and her team is to conduct further trials to measure the impact of allergies and any correlation between allergies and other medical conditions such as asthma.

Professor Allen and her team have both learned a lot and made important contributions through national and international collaborations. With the establishment of the Centre of Research Excellence in Paediatric Food Allergy, they hope to generate enough data to 'move the field to the next level.'

There is also work to be done on food labelling.

I'm involved in both national and international committees that make decisions on food labelling. It's important that the need for allergy sufferers to be safe is balanced with the need for the general public to be able to access reasonably priced food.'

Left to right: Miss Tina Tan, Associate Professor Mimi Tang, Mr Thanh Dang, Professor Katrina Allen, Professor Melissa Wake, Associate Professor Shyamali Dharmage, Dr Jennifer Koplin, Ms Leone Thiele

Chief Investigator background and motivations

Professor Allen began her career as a paediatric gastroenterologist, and was the first to develop liver cell transplantation in Australia, although she subsequently proved it was not ready for further clinical application. She eventually found her niche in general population research and is now focused on the causes and prevalence of childhood food allergies – a burgeoning area of research.

Professor Allen describes herself as being 'nuts about child health' and is committed to making a difference to the health of the broad Australian population.

She attributes the success of her research program to collaboration: 'I'm lucky to be part of a team of very smart people who continually help me to challenge the science to ensure our results are robust.'

'We need to ensure that the community is getting the very best interrogation of the data so they can rely on our recommendations, which inform public health policy and clinical practice.'

'Having the courage to report findings that are contrary to what is expected is an important aspect of science,' she adds.

CHIEF INVESTIGATOR

Professor Katrina Allen

AFFILIATION

Murdoch Childrens Research Institute

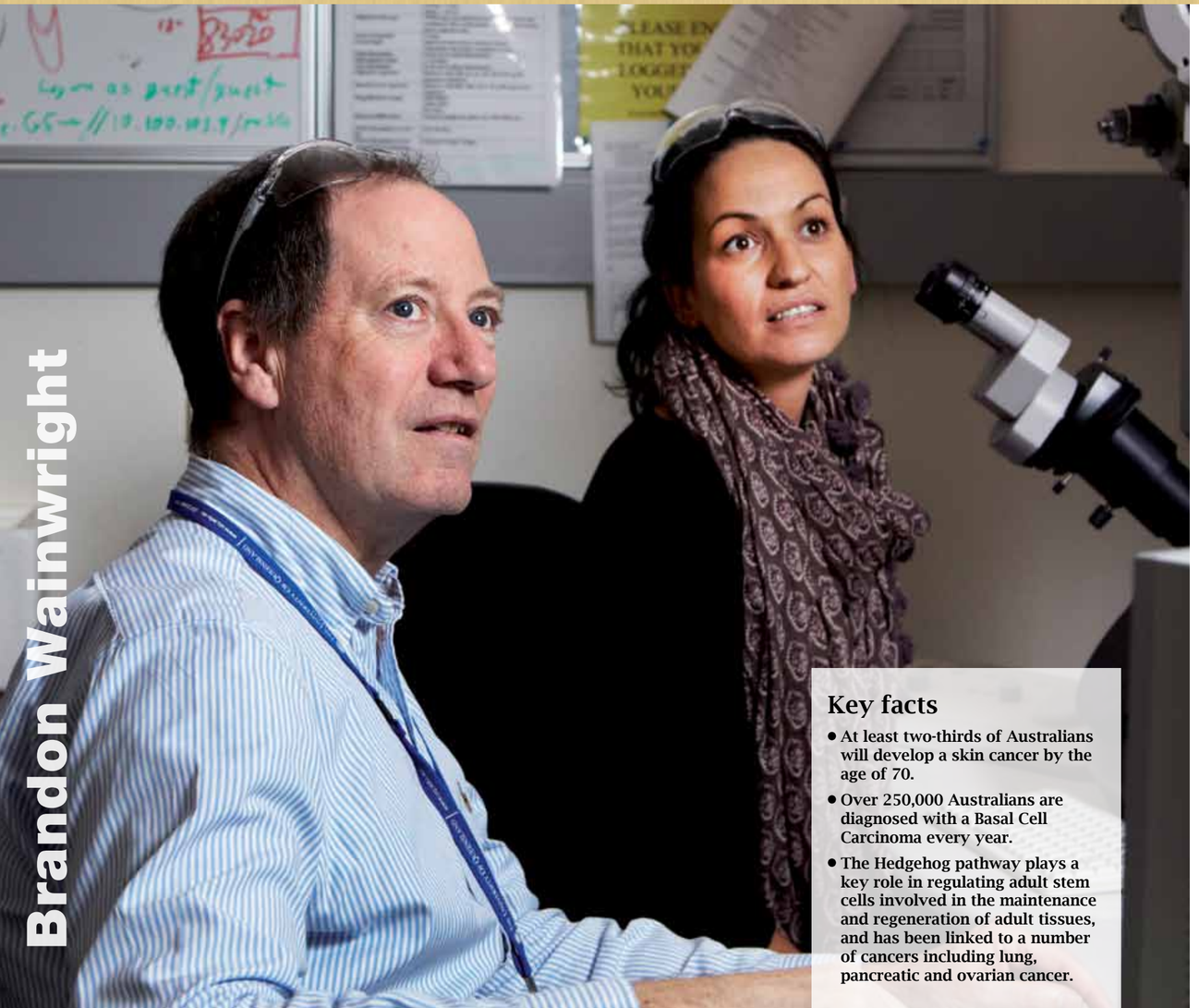
TEAM MEMBERS

See Project Honour Roll page 30

FUNDING AMOUNT

$ 274,961 (2006–2010)

More than skin deep: turning up the dial on skin cell research



Key facts

- At least two-thirds of Australians will develop a skin cancer by the age of 70.
- Over 250,000 Australians are diagnosed with a Basal Cell Carcinoma every year.
- The Hedgehog pathway plays a key role in regulating adult stem cells involved in the maintenance and regeneration of adult tissues, and has been linked to a number of cancers including lung, pancreatic and ovarian cancer.

'Skin stops us from dehydrating, makes us waterproof, holds us together and protects us from our environment. It's very important.'

Professor Brandon Wainwright thinks that the importance of skin as an organ cannot be overlooked. This is why he, Co-Chief Investigator Pritinder Kaur and their team have committed years to researching it – and Basal Cell Carcinoma (BCC) in particular.

BCC is a skin cancer and the most common cause of cancer in Australia. Professor Wainwright and his team's first major research breakthrough came with the discovery of the gene named 'Patched', which causes BCC.

In mapping the gene, they discovered that Patched is part of a larger genetic pathway which has another funny name of the 'Hedgehog' pathway.

Professor Wainwright says, 'Here was a very common human cancer gene that had a role in the normal development of the body, which was part of a very important pathway that virtually every organ in our body uses to develop appropriately.'

We now know that the Hedgehog pathway contributes to the development of a wide range of tumour types, including lung, pancreatic and ovarian cancer. What Professor Wainwright and his team found was that in 90 per cent of Basal Cell Carcinomas the Hedgehog pathway is switched on when it should be off.

There is more to it than that though, as Professor Wainwright explains: 'People tend to think of genetic pathways as either being on or off, like a TV signal. What we found is that genetic pathways are less on or off, and more about turning a volume dial.

'You can have the pathway on at low strength, but it can also be turned up.'

By manipulating the amount that the hedgehog pathway is 'turned up' or 'turned down', Professor Wainwright and his team believe that cells can either be replenished or become cancerous.

'We think that Basal Cell Carcinoma occurs when the Hedgehog pathway is at middle strength,' he says. 'Our view is that turning the strength up higher promotes an expansion of stem cells and the replenishment of skin.'

'This has further applications – for instance, it could be relevant in the treatment of burns or improve our ability to heal wounds.'

Next steps

Professor Wainwright and his team have made great headway in understanding the genetic pathway behind skin cancer and generating the replenishment of damaged skin. They are aware though that they 'may only have uncovered a fraction of the picture, and that there will be more to the story.'

The first step is to prove that the cells generated by manipulating the Hedgehog pathway are, in fact, true stem cells. And also, that they can use the Hedgehog pathway to affect, repair and regenerate skin.

Once this is established, the team will examine other genetic pathways that the Hedgehog pathway is 'talking to' in order to achieve this effect.

After that, the team plans to test whether the Hedgehog pathway is involved in the repair of tissue damage to other organs, including the lungs.

'There is evidence that the Hedgehog pathway may be involved in other forms of cancer including lung and pancreatic cancer. We're hoping that what we're learning about with the skin is applicable to many cancers.'

Left to right: Professor Brandon Wainwright, Dr Christelle Adolphe

Chief Investigator background and motivations

Professor Wainwright completed his PhD on the cloning of alpha and beta globin genes in marsupials – an area that might seem a long way from human skin cells. But it was the skills he acquired that were important: 'I learned about DNA cloning, DNA sequencing and gene mapping. All of these techniques were directly applicable to human genetics.'

Then followed some fortuitous timing. Professor Wainwright responded to an advertisement seeking geneticists to work at St Mary's Hospital, Imperial College London. He got the job and spent the following years working to identify the cystic fibrosis gene.

'What I didn't realise was that I was walking into one of two world centres of the genomics revolution at the time,' he says. 'The work was revolutionary and I was incredibly lucky to be there.'

Upon returning to the University of Queensland (UQ), Professor Wainwright focussed on the genetics of childhood brain tumours and skin cancers. He collaborated with numerous experts including Professor Georgia Chenevix-Trench working on skin cancers and they found the Basal Cell Carcinoma gene.

Professor Wainwright then became Director of the Institute for Molecular Bioscience at UQ.

CHIEF INVESTIGATOR

Professor Brandon Wainwright

AFFILIATION

Institute for Molecular Bioscience

TEAM MEMBERS

See Project Honour Roll page 30

FUNDING AMOUNT

$ 521,961 (2008–2010)

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Honour Roll Ten of the Best Research Projects 2012

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Dr Clinton Bruce
Professor Mark Hargreaves
Dr Sean McGee
Professor Gordon Lynch
Dr Stefan Gehrig

Professor Lorena Brown

Dr Deborah Middleton
Ms Kathryn Edenborough
Dr Brad Gilbertson
Professor David Jackson

Dr Dina LoGiudice

Dr Kate Smith
Ms Geraldine Shadforth
Professor Leon Flicker
Dr Melissa Lindeman
Ms Emily Carroll
Dr David Atkinson
Professor Osvaldo Almeida
Mr Frank Schaper
Professor Nicola Lautenschlager
Ms Rhonda Murphy

Footnotes:

1. Including Prof Leon Flicker and Dr Kate Smith (project coordinator) and others (including Geraldine Shadforth and Emily Carroll (Project officers)).
2. There were many community members who contributed greatly to this project including project workers Michelle Skinner, Mark Pindan, Cullimurra Woia, Johnny Juboy and Roy Juboy.

   Additional workers based in the community included Kim McGaffin, Chrystal Simpson and Patrick Hughes. Community council members were heavily involved with the project, particularly chairman Harry Skinner, Michelle Skinner, Miranda Killer, Joe Killer, Leanne Henry and Lynley Juboy.

Professor Richard Harding

Professor Colin Morley
Professor Peter Davis
A/Professor Stuart Hooper
A/Professor Tim Cole

Professor Katrina Allen

A/Professor Shyamali Dharmarge
A/Professor Lyle Gurrin
Professor Melissa Wake
Professor Anne-Louise Ponsonby
A/Professor Mimi Tang
Dr Jennifer Koplin
Dr Melanie Matheson
Dr Adrian Lowe
Dr David Hill

Professor Brandon Wainwright

Dr Pritinder Kaur
Dr Rehan Villani
Dr Christelle Adolphe

Notes

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