

MAURICE WILKINS CENTRE

New Zealand's Centre of Research Excellence
for the discovery of new medicines

Annual Report 2009

Maurice Wilkins Centre

The Maurice Wilkins Centre brings together leading biologists, chemists, and computer scientists to target serious disease. The Wilkins Centre includes New Zealand researchers with world-class reputations for inventing new drugs targeting cancer, diabetes, and infectious disease, several of which are in clinical trials.

The Wilkins Centre also develops new vaccines targeting infectious disease and cancer, and new tools to help basic research and clinical medicine, including sophisticated software for medical use. In bringing together scientists and doctors from a wide range of backgrounds, the centre sponsors cutting-edge research that would not otherwise have been carried out. This intense research environment provides an outstanding training ground for the next generation of leaders in New Zealand biomedical science.

As well as coordinating a national network of leading researchers across New Zealand, the Wilkins Centre provides world-class research infrastructure, including both cutting-edge equipment and highly specialised technical training. These two fundamental activities – enabling nationwide multi-disciplinary collaboration, and maintaining internationally competitive research infrastructure – support our mission to ensure that New Zealand capitalises on its outstanding reputation for biomedical research.

For more information see www.mauricewilkinscentre.org

For more information on New Zealand Centres of Research Excellence see www.acore.ac.nz

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Collaborating Institutions





MAURICE WILKINS CENTRE
FOR MOLECULAR BIODISCOVERY

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Director's Report

The Maurice Wilkins Centre brings together doctors and scientists with a range of skills to tackle major health issues that concern New Zealanders. In a nation rich in pioneering individuals, in science and medicine just as in many other parts of our culture, the Wilkins Centre aims to stimulate collaboration and sharing of expertise, to maximise the impact of our medical research.

Of the many highlights reported here for 2009, the Wilkins Centre's seventh year, there are three that are emblematic of our values.

The award of the country's top scientific honour, the Rutherford Medal, to Peter Hunter reminds us that the Wilkins Centre is founded on scientific excellence. Peter's outstanding work is now well known at home and abroad, and although it is delivering very practical outcomes for health, it is important to remember that his science is rooted in fundamental curiosity – a basic drive to discover how biological processes are connected. We celebrate Peter's inspirational thinking and the fact that despite his international success, he still bears the classic kiwi attributes of enthusiasm, humility, and warm good humour.



The event that most symbolised the national role of the Wilkins Centre was the New Zealand Drug Discovery Symposium we convened in Auckland. Over 450 delegates from throughout New Zealand joined us to celebrate the nation's burgeoning portfolio of new medicines entering clinical trials, and to plan how to capitalise on the country's remarkable record in discovering new drugs. The delegates included representatives from industry, the investment community, and government agencies, as well as doctors and scientists from many different disciplines. After updating the progress of 9 new drugs discovered here, we reviewed the country's substantial infrastructure in clinical trials, and drug manufacture and distribution. The concluding panel discussion addressed the question of how to connect these resources better with our drug discovery, to accelerate development of useful new medicines, and increase their value to our economy.

The third highlight of 2009 that epitomises the Wilkins Centre is our research seeding programme. Some of the research projects initiated under this programme are named later in this report, but this list tells only part of the story. Behind the scenes, this scheme in its first full year of operation has generated a storm of exciting new interactions between scientists affiliated with the Wilkins Centre. The rules of this programme are exacting: projects proposed must be highly novel, to the extent of being world-leading, and they must involve scientists from different scientific disciplines. Such a programme is only possible because the Wilkins Centre can draw on a depth of talent in biological sub-disciplines as well as chemistry and computational biology, in order to address major challenges in human health. Just as we had hoped, this programme has galvanised our best and brightest into harnessing each other's talents in new collaborations. Many of the

projects are highly ambitious – some may even falter as a result – but such projects represent exactly the type of high-end research likely to deliver the greatest gains for the country.

With this report we also welcome seventeen prominent scientists as Associate Investigators. Our lead investigators now comprise 76 scientists from six Universities, three Crown Research Institutes, and one private research institute, the Malaghan Institute for Medical Research. Our research network continues to grow as more scientists are identified who can make major contributions towards our core mission of attacking cancer, diabetes, and infectious disease. Already the benefits of a wider national network are flowing through the Wilkins Centre, with exciting new collaborations, greater interactions between institutions, and better transfer of knowledge and expertise. However we recognise that this network will not grow indefinitely, since it will only flourish so long as its members feel integrated into a community that enables and accelerates their work. As well as expanding the number of lead investigators, the Wilkins Centre has also redoubled its engagement of younger scientists. Major initiatives for early career scientists and graduate students are underway and will be highlighted in the 2010 Annual Report.

Finally, this is my first Annual Report as Director, and it has been both a pleasure and a privilege to begin this role. I am especially grateful to the seven other members of the Management Committee for their continued energetic commitment to the Wilkins Centre, and the wise counsel and encouragement they have freely provided. I also need to express my thanks to the Governing Board for their calm and steady guidance, and to Rochelle Ramsay and Peter Lai for their efficient execution of the Wilkins Centre's programmes.

I succeed Professor Ted Baker as Director. Ted is a scientific icon in New Zealand and internationally, amply demonstrated by the numerous prizes and accolades awarded to him, as well as his dazzling record of scholarship. He is also an outstanding leader. As Foundation Director of the Wilkins Centre he worked with the four other founding members (Bill Denny, Garth Cooper, John Fraser and Peter Hunter) not only to win funding for the concept of the Wilkins Centre, but also to set in place its administrative structure and guide its day-by-day activities and development. The strong ethos of collaborative, interdisciplinary science that permeates the Wilkins Centre emanates to a large degree from Ted's approach to his own science – open, inclusive, and broad-minded. However Ted also possesses a strong sense of what's needed to establish conditions conducive to great science, and he has been persuasive and decisive in guiding the Wilkins Centre towards such a state. Given the impossible challenge of following in Ted's footsteps, I am delighted that he retains his role as a Principal Investigator on the Management Committee, so the Wilkins Centre can continue to benefit from his wonderful attributes as a scientist, a colleague, and a mentor.

Rod Dunbar
Director



MAURICE WILKINS CENTRE
FOR MOLECULAR BIODISCOVERY

Contribution to National Goals

The Centres of Research Excellence are collectively charged with making a contribution to national goals, including innovation, and social and economic development. It was anticipated that the CoREs would each contribute to these goals in different ways and in different proportions, depending on their particular research focus. The Maurice Wilkins Centre has its own unique place in this spectrum. Our focus on the development of new approaches to human disease is based on a multidisciplinary platform that extends across chemistry, biology and medicine and also incorporates key ideas and technologies from physics, engineering and mathematics.

Innovation

The Wilkins Centre conducts highly innovative research and enables innovation in the wider research and business sector. Its goal is to become the engine for discovering new therapies and diagnostics in New Zealand. Innovation in research is often to be found at the interface between disciplines, through cross fertilisation of ideas and technology. The Wilkins Centre brings together researchers from a range of disciplines to tackle complex questions that no one field could address alone. It also encourages a more collegial approach within the biomedical research sector in New Zealand. The Centre's work leads to the establishment of new spin-out companies and contributes directly to innovation within established biotechnology companies through contract research, consultation, and sharing of facilities and expertise. These activities lead to fundamental scientific discoveries and the development of novel technologies that enable new lines of research, advance our understanding of human health and disease, accelerate the development of new approaches for human disease, and advance other research fields (including having demonstrable impact on our primary industries).

Social Development

One of the Wilkins Centre's contributions to social development in New Zealand is through improvements to human health. Our major focus is to improve the diagnosis and treatment of diseases such as cancer, diabetes, and infectious disease – all increasing challenges for New Zealand society. At the same time, science is an important aspect of our culture, and the Wilkins Centre plays a role in increasing the impact of science within New Zealand, as well as connecting us strongly to the international scientific community. The multi-disciplinary and collaborative ethos of the Wilkins Centre ensures an excellent training environment for graduate students and younger scientists, including exposure to the ethical, managerial and entrepreneurial aspects of translational science. It is particularly important for students at all levels of education to see that scientific research of the highest international quality can be done in New Zealand, and that it can make major contributions to the social and economic well-being of their country. The example set by Wilkins Centre leaders in choosing to return from research posts overseas, committed to carrying out world-class research in New Zealand, provides a powerful incentive for our top students to do likewise in future.

Economic Development

The Wilkins Centre's focus on new approaches to human disease has dual importance for the New Zealand economy, in both improving health and providing direct economic gains. Wilkins Centre investigators have to date been responsible for bringing a large portfolio of drugs to clinical trial, with a deep pipeline of new projects in pre-clinical development. This strong portfolio means that New Zealand maintains its exciting potential in the biopharmaceutical sector, one of the few economic sectors capable of driving explosive economic growth. The intimate links between the Wilkins Centre research programme and recent start-up companies demonstrates that research findings can and will be developed for the national good. Direct economic gains also come from international research contracts, and milestone and licensing revenue from overseas partnerships – effectively a “weightless” export industry already worth tens of millions per annum. Less direct economic gains come from Wilkins Centre investigators' significant impact on the international rankings of our educational institutions, which affect their ability to attract international students. The Wilkins Centre also plays an important role in promoting and validating our national scientific capabilities abroad, increasing the reputation of New Zealand as a source of high-value research.





Dr Garth Carnaby, Dr Di McCarthy, Hon Dr Wayne Mapp, Professor Peter Hunter and Ms Karin Nielsen.
Photo courtesy of the Royal Society of New Zealand.

Highlights

The following stories describe 2009 highlights for the Maurice Wilkins Centre in the areas of research, training and science education.

Professor Peter Hunter awarded nation's top science honour

Professor Peter Hunter was presented with the prestigious 2009 Rutherford Medal at the Royal Society of New Zealand annual Science Honours Dinner. Professor Hunter, founder and director of the Auckland Bioengineering Institute and a Principal Investigator with the Wilkins Centre, won the medal for his ground-breaking work on the Physiome Project, a major international project to build sophisticated computer models of human organs.

The Rutherford Medal recognises exceptional contributions to New Zealand science and technology by a person or group in any field of science, mathematics, social science, or technology. The president of the Royal Society of New Zealand, Dr Garth Carnaby, said Professor Hunter was a "true scientific pioneer" whose revolutionary approach to modelling the human body had led to new and exciting areas of research that would eventually help advance treatments for a number of life-threatening diseases.

Professor Hunter began working on the Physiome Project in 1996, after spending many years developing the world's first anatomically based computer model of the human heart at The University of Auckland. The project soon spread from the heart to the lungs, and eventually to all twelve organs in the human body. "The idea is to create mathematical models that link genes, proteins, cells, tissues, organs and the whole body into one cohesive framework that will in time become a web resource for diagnosing and treating patients, surgical planning, education and the design of medical devices," explains Professor Hunter.

Professor Hunter says he was very honoured to receive the award, which was recognition of the role that engineers and mathematical scientists can play in biology. "I owe an enormous debt of gratitude to many students, both past and present, and to my colleagues at the Auckland Bioengineering Institute, especially Associate Professor Bruce Smaill who I have worked with for nearly thirty years."

The Auckland Bioengineering Institute is working on all parts of the Physiome Project in close collaboration with the Maurice Wilkins Centre, the New Zealand Institute of Mathematics & its Applications, and many international partners, including the University of Oxford and Massachusetts Institute of Technology.





Jenny Morel speaking during the panel discussion at the Drug Discovery Symposium.
Photo courtesy of Godfrey Boehnke.

Creating connections between drug discovery and business

The Maurice Wilkins Centre hosted the New Zealand Drug Discovery Symposium in September 2009, bringing together more than 450 delegates from science, medicine, business, and venture capital.

The symposium showcased local drug discovery research and infrastructure, and how the next generation of New Zealand-designed medicines could benefit the economy and our health. Local investors and drug development companies provided their perspectives on key factors for success in the industry.

“Drug discovery, development and manufacturing in New Zealand is already an industry worth hundreds of millions of dollars per year” says Wilkins Centre Director Associate Professor Rod Dunbar. “and it has strong potential for growth. The goals of the symposium were to plan how to capitalise on the country’s remarkable record in drug discovery, and to build the relationships that will accelerate growth of the sector.”

Associate Professor Dunbar says that a highlight was a panel discussion on how to enhance connections between drug discovery research and the substantial local infrastructure that already exists in clinical trials, drug manufacture and distribution.

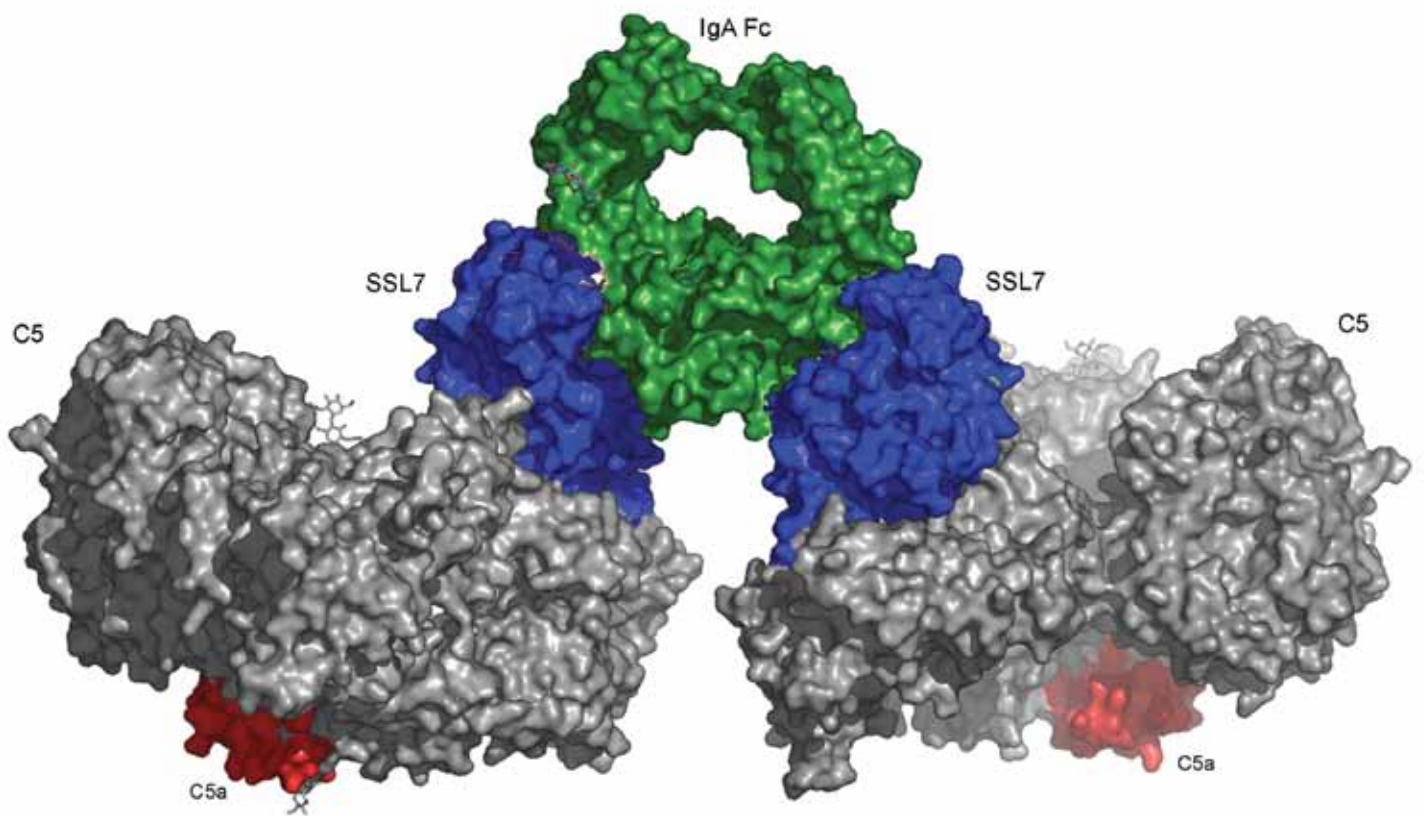
Nine New Zealand-designed drugs with potentially big futures were showcased at the symposium. “Several of these drugs are already earning tens of millions of dollars for New Zealand, either through payments from overseas companies developing the drugs, or from direct overseas investment in New Zealand drug development companies,” says Associate Professor Dunbar

Three drug development companies that have spun-out from The University of Auckland, including the newly-formed Saratan Therapeutics, were presented to delegates by Will Charles from the university’s research and development commercialisation company Auckland UniServices Limited.

Professor Peter Shepherd, Wilkins Centre Principal Investigator and co-founder of spin-out cancer drug company Pathway Therapeutics, spoke about what is needed to develop a successful drug company in New Zealand. He emphasized close collaboration between biologists and chemists, great people and excellent commercialisation processes.

Jenny Morel, whose company No 8 Ventures helps young technology companies realise their potential, spoke about how to attract investment in new medicines, saying that the reputation of researchers like Professors Bill Denny and Bill Wilson had proven crucial in mobilising local and international investment.





Representation of the 3D structure of the SSL7 protein (blue) in complex with IgA (green) and C5 (grey) proteins.
Image courtesy of John Fraser.

Study exposes superbug defences

An international study between scientists from New Zealand and Denmark has revealed exactly how the bacterium *Staphylococcus aureus* evades the human body's key immune defences.

Maurice Wilkins Centre scientists led by Professor John Fraser at The University of Auckland and a scientific team led by Professor Gregers Anderson at The University of Aarhus, Denmark, published a paper in the journal *Proceedings of the National Academy of Sciences (PNAS)* in January 2010 describing how a protein from *S. aureus* interferes with the human immune system.

In New Zealand, as with most other countries, *S. aureus* is the most common cause of hospital-acquired infection. It also causes serious outbreaks in the community where antibiotic resistant strains such as *Methicillin-resistant S. aureus* (MRSA) are proving very difficult to treat.

Professor Fraser, Deputy Director of the Wilkins Centre, says the study focuses on a small protein that the bacterium produces called SSL7 (Staphylococcal Superantigen-Like protein 7). The team has shown how this protein binds to Immunoglobulin A (IgA), a special defence antibody in our gut and lungs. The SSL7 protein also binds to complement C5, one of a series of proteins that "complement" the work of antibodies in destroying bacteria.

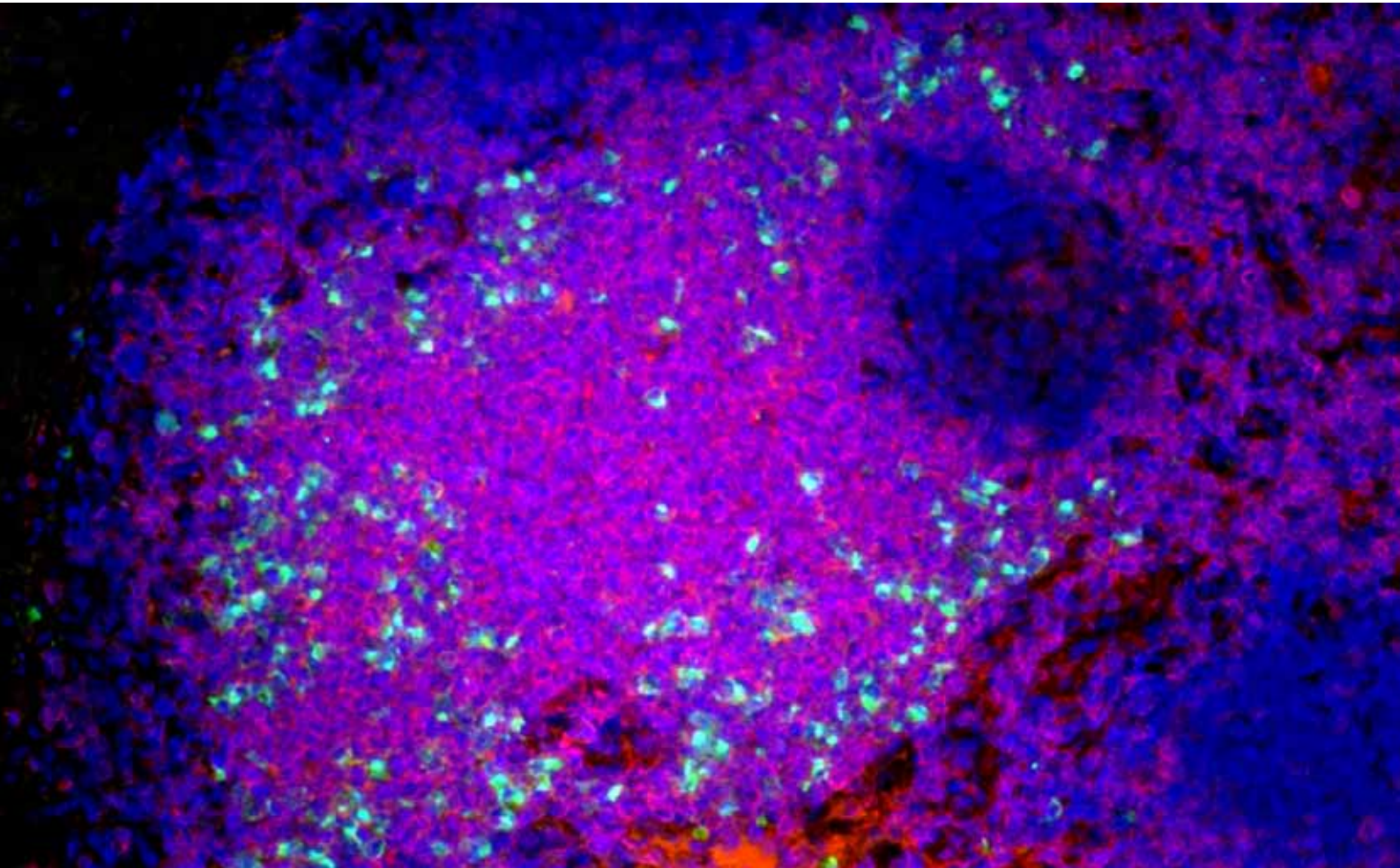
"We've created a structural model of the complex formed when SSL7 binds to IgA and C5," says Professor Fraser. "The model has enabled us to see how SSL7 cleverly uses IgA as a 'scaffold' to capture two molecules of C5. By doing this, the reaction that brings complement proteins together to destroy the bacteria's cell wall can't take place."

"By binding to IgA and C5 at the same time, the SSL7 protein simultaneously blocks several crucial parts of the body's immune defence against bacterial infection."

Professor Fraser says that by knowing how *S. aureus* works to block the immune system, scientists can begin to develop therapeutic drugs that directly target proteins like SSL7.

"Remarkably, SSL7 also highlights exactly where to pin-point drugs designed to prevent the unwanted over-activation of C5 that normally leads to a serious inflammatory disorder."





Magnified image of a human lymph node treated with coloured stains to show antigen presenting cells (green), T-cells (red) and the nuclei of all cells in the lymph node (blue).

Image courtesy of Catherine Angel, Jenni Chen and Rod Dunbar.

Lighting up lymph nodes

Lymph nodes are crucial parts of the human immune system. These small, bean-shaped “glands” are found throughout the body – including the neck, armpits and groin – and most of our immune responses to foreign substances (antigens) start there. Fluid from throughout the body flows into the lymph nodes via a network of fine tubes, carrying a wide variety of cells and molecules. White blood cells gather in lymph nodes, and more cells collect there during an infection, making lymph nodes swell – a classic medical sign of infection.

A research team led by Maurice Wilkins Centre Director Associate Professor Rod Dunbar has been investigating a group of white blood cells called antigen-presenting cells (APCs) with a view to designing better vaccines. Their work has led to exciting new insights into how human lymph nodes work.

“APCs are specialised white blood cells that take up foreign substances and ‘present’ fragments of them to other immune cells. White blood cells called T cells are particularly important in recognising these fragments, triggering the body’s most sophisticated immune responses,” says Dr Dunbar. “There have been plenty of studies of these APCs in mice, but surprisingly little is known about APCs in human lymph nodes.”

Dr Dunbar and his team at The University of Auckland’s School of Biological Sciences used sophisticated stains to study frozen samples of normal human lymph nodes, provided by the Ludwig Institute for Cancer Research in Heidelberg, Melbourne. Their findings were published early in 2009 in the high-profile journal *Blood*.

“We discovered that most APCs in human lymph nodes fall into two classes. APCs in the first group have migrated from the tissues, after taking up foreign material. In the lymph nodes, these APCs are found only in the areas where T cells gather, suggesting they move there as soon as they arrive from the tissues. In contrast, APCs in the second group sit mainly in positions where they can take up material from the fluid flowing into the lymph nodes. Importantly, these APCs are also found in the T cell areas, suggesting they can transport foreign material from lymphatic fluid to areas where it can be examined by T cells.”

Dr Dunbar says this work immediately suggests new strategies to improve the design and delivery of vaccines for treating cancer, by targeting the second group of APCs. A similar approach might improve vaccines for infectious diseases like tuberculosis.

The tissue staining techniques developed during this research have also led to many new studies, including collaboration with clinicians at the Auckland District Health Board to analyse the lymph nodes of patients with lymph node cancer (lymphoma).





Professor Martin Evans and Wilkins Centre students.
Photo courtesy of Godfrey Boehnke.

Stem cell pioneer delivers “knockout” lecture

Stem cells have the capacity to replenish any type of cell in the body. It's this quality that gives stem cells the potential to transform modern medicine and excites so much interest throughout the world. Scientists hope that some day stem cells can be used to replace cells in the human body that are damaged due to disease or injury. Although the use of stem cells from adult humans is widely supported, the potential use of embryonic stem cells has raised moral and ethical concerns both in terms of human therapy and manipulation of animals.

In the thick of the stem-cell debate is British Professor Sir Martin Evans. Sir Martin was the first to identify and isolate embryonic stem cells from mice and show that these cells could be grown in the lab. His pioneering work paved the way for gene targeting by so-called “knockout technology” – a technique that allows scientists to determine the role that individual genes play in health and disease. Sir Martin's work also earned him and two other scientists, Oliver Smithies and Mario Capecchi, the 2007 Nobel Prize in Medicine.

On 10 September 2009 Sir Martin delivered an inspiring talk about his stem cell research to students and members of the public at the Maurice Wilkins Lecture in Auckland. He described how he discovered that stem cells could be genetically altered in the laboratory then injected into a mouse embryo to create offspring with changes in their DNA. Sir Martin also took time out to talk to Maurice Wilkins Centre graduate students about what it takes to do world-leading research. He advised the students to spend as much time as possible doing their own experiments, even if this means challenging the advice of their supervisors, and to “expect the unexpected”.





Dr Michael Hay, Dr Jack Flanagan and Dr Muriel Bonnet.
Photo courtesy of Warren Jones.

Kidney cancer researcher scores a first for New Zealand

In December 2009, Maurice Wilkins Centre investigator Associate Professor Michael Hay became the first New Zealand scientist to receive a grant from a leading international charity for funding cancer research.

Dr Hay, a medicinal chemist at The University of Auckland, was awarded the £137,000 (\$NZ 290,000) grant by the UK-based Association for International Cancer Research (AICR). The grant will help Dr Hay and his colleagues Dr Muriel Bonnet and Dr Jack Flanagan at the University's Auckland Cancer Society Research Centre identify molecular targets in kidney cancer tumours that can be used to design more effective anticancer drugs. The research expands on Dr Hay and Dr Flanagan's work designing new drugs for kidney cancer using computational modelling, a project funded by the Wilkins Centre.

Renal cell carcinomas (RCC) often do not respond to standard chemotherapy or radiotherapy, and an advanced RCC has an extremely poor prognosis. "Cancer is caused by changes to either the structure or activity of key genes that control cell function," says Dr Hay. "In many RCCs, the von Hippel Lindau (VHL) gene is inactivated. Without this gene, a relatively benign tumour can turn into a more aggressive, invasive tumour."

Dr Hay, in conjunction with Professor Amato Giaccia and colleagues at Stanford University, recently discovered two new classes of molecules that can selectively kill RCC cells lacking VHL, either by causing the cells to "eat themselves" (by inducing autophagy) or by inhibiting glucose uptake and thereby cutting off their food supply. However, the exact interactions between these molecules and their protein targets are not yet known. "With this grant we're using 3D computer modelling techniques to help us identify these targets, and show how potential drugs for treating kidney cancers might interact with their target molecules," says Dr Hay.

AICR Scientific Advisor Dr Mark Matfield said the charity supports only the very best funding applications, which it hopes will ultimately lead to powerful new treatments for cancer. "This is the first time we have given a grant to a scientist in New Zealand, and we believe this innovative work could produce significant results."

The project is supported by the Auckland Cancer Society Research Centre and the Wilkins Centre. It involves collaboration with the Department of Radiation Biology at the Stanford University School of Medicine, USA.





Professor Ted Baker and Ms Emily Cole.
Photo courtesy of Amy Campbell.

Mixing with Asia's best and brightest

St Cuthbert's College student Emily Cole says that going to the 2009 Asian Science Camp in Tsukuba, Japan was an incredible experience. A highlight was attending challenging talks on topics ranging from nuclear energy to how to win a Nobel Prize. "The lectures were high level, in-depth and unlike anything I had ever heard before ... It was both humbling to be in the presence of the Nobel Laureates and uplifting to be able to share in their knowledge," she says.

Counterpart Andi Liu from Palmerston North Boys' High School agrees that the camp was a unique opportunity to interact with scientists at the top of their fields. Andi plans to study biomedical or chemical and material engineering and wants to become a respected scientist. In that role, he says he would encourage students to consider science careers and to apply for opportunities like the science camp.

The Maurice Wilkins Centre was proud to sponsor both students, and Manurewa High School physics teacher Fenella Colyer, to attend the camp. The MacDiarmid Institute sponsored two further New Zealand students, Hugh McHugh and Georgina Stewart.

The camp brings together more than 200 final year high school students and accompanying teachers from in and around the Asia region. It is an invaluable opportunity to learn directly from Nobel Laureates and other eminent scientists working in the fields of physics and chemistry. Delegates can further develop their interest in science and mix with some of the best and brightest from the region.

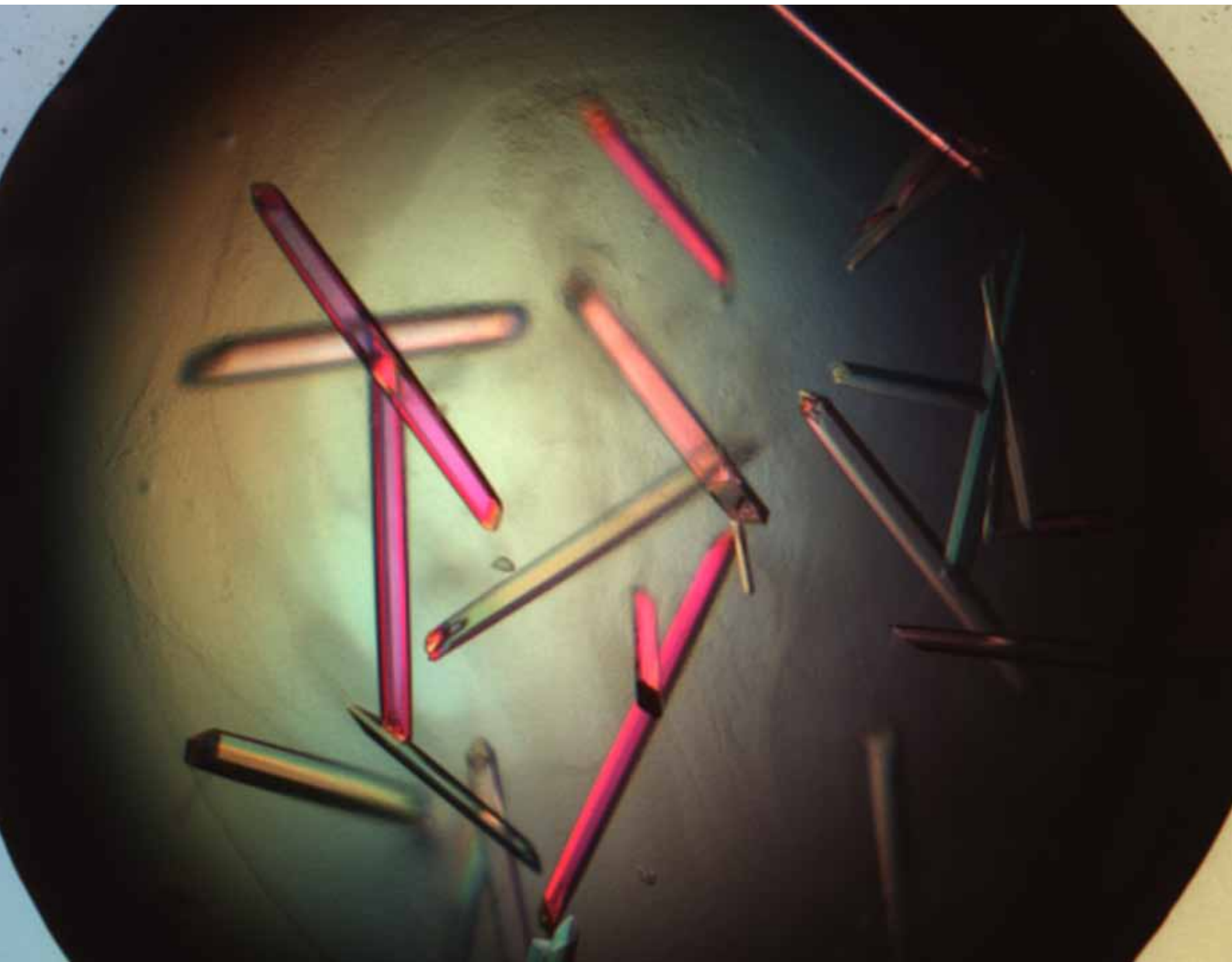
Fenella believes that the benefits of such events cannot be overstated. "I attended similar events as a school student and their impact remains with me to this day. You find when students go to events like this that it opens up their eyes to the different fields that they can study. It's often what finally helps them to make the decision to study science at a higher level," she says.

"These students will become the scientific leaders of the future. By attending this camp, they've already got a head start. They've learned about how the language of science can cross barriers and facilitate international co-operation and communication."

But the students who attended the camp weren't the only ones to benefit. The teachers also went to all of the lectures and group discussions, and took what they learned back to their own schools.

"Every single lecture I attended I gave back to my students," says Fenella, who transcribed her notes into a teaching booklet which she used for advanced tutorials with her senior physics students.





Crystals of the Rv1738 protein from *Mycobacterium tuberculosis*.
Image courtesy of Kalyaneswar Mandal.

Crystals of mirrored proteins

Crystals. Just the word itself conjures up something magical, and crystals really do hold a promise of magic for structural biologists – the chance to see proteins and DNA in atomic detail. The atomic structure of molecules in a good crystal can be worked out by X-ray crystallography, and used to design drugs or reveal the mechanisms of disease.

It's not easy to grow crystals though. Proteins are especially difficult to crystallise. One reason for this is that proteins have a natural "handedness" because they are built only from left-handed amino acids. Right-handed amino acids, their mirror image, are not used in nature. The result is that natural proteins can only fit into 65 of the possible 230 types of crystal. The remaining 165 crystal types would require equal numbers of left-handed and right-handed molecules.

Professor Steven Kent of the University of Chicago, an adjunct professor in the Maurice Wilkins Centre, has devised an innovative solution to this problem. He advocates making the right-handed form of a protein by chemical synthesis, mixing it with the natural left-handed form, and crystallising the mixture. This should make all 230 types of crystal possible.

Now Richard Bunker, a Wilkins Centre PhD student, has joined forces with Professor Kent to solve the structure of an important protein from *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis (TB). This protein, Rv1738, appears to be heavily involved in the development of persistent disease, in which the bacteria adopt a dormant state and become resistant to most drugs. Knowledge of the structure and function of Rv1738 may help in the development of new anti-TB therapies.

Despite exhaustive efforts by a former Wilkins Centre PhD student, Jessica Chaston, all previous attempts to crystallise Rv1738 had failed. The solution was to make the right-handed form of the protein in Professor Kent's lab and crystallise the mixture of right- and left-handed proteins. Mr Bunker then did the rest, solving the atomic structure of Rv1738 at high resolution. The structure reveals two molecules packed together, with an unusual distribution of charge that appears to be important for its function.

This method promises to be another powerful new weapon for structural biology, and one that the Wilkins Centre is well placed to exploit. Professor Margaret Brimble's peptide synthesis facility in the Centre provides state-of-the-art techniques that will make this method fully accessible to scientists studying medically-important proteins.





Dr Mia Jüllig, Professor Garth Cooper and Mr Martin Middleditch.
Photo courtesy of Iain MacDonald.

Maurice Wilkins Centre technology helps Auckland Hospital with difficult diagnosis

Maurice Wilkins Centre scientists have developed a new way of classifying patients with rare forms of amyloidosis – a potentially fatal disease where protein deposits called amyloids accumulate in various tissues.

Under the direction of Professor Garth Cooper, Dr Mia Jüllig and Mr Martin Middleditch have identified the proteins in some unusual amyloid samples using the Wilkins Centre's advanced mass spectrometer.

Professors Peter Browett and Kathy Crosier, both clinicians at Auckland Hospital, approached Professor Cooper about examining unusual amyloid samples after conventional laboratory studies failed to determine the type of amyloid protein in their patients. Professor Cooper took up this challenge with his team, armed with more than 30 years of clinical interest in amyloidoses and a strong track record in cutting-edge techniques to identify novel proteins.

"Amyloids are typically made up of a single main protein called an 'amyloid monomer', and a number of minor matrix proteins. The identity of the monomer yields key information that supports both diagnosis and specific therapeutic options," explains Professor Cooper.

"There can be dozens of other proteins in an amyloid," says Dr Jüllig, a Wilkins Centre research fellow. "Some of these proteins provide further clues as to how the amyloid developed."

Most pathologists identify which proteins are in amyloid samples by probing them with antibodies. However, this technique is not always accurate and is limited to known proteins, so it's hard to identify new types of amyloid proteins in unusual patients.

The Wilkins Centre team took a high-tech approach to three patient samples that couldn't be classified with existing techniques. "Amyloids are clumps of insoluble protein," says Mr Middleditch. "Our technique relies on performing the difficult task of converting these proteins into a soluble form so that they can be processed and identified in our mass spectrometer. We can then get a very good picture of what proteins are in the diseased tissue."

The three amyloid samples, from the heart, liver, and radial nerve (in the arm), have all produced clear, unambiguous results.

"We'd like to use this technology to help as many patients as possible, both nationally and internationally," says Mr Middleditch.





Dr Catherine Lloyd and Dr Matthew Chung.

Past graduates – where are they now?

In 2008, the first students to receive full scholarships from the Maurice Wilkins Centre graduated with their PhDs. The first to graduate was Dr Catherine Lloyd. Catherine did her PhD at The University of Auckland's School of Biological Sciences under the supervision of Maurice Wilkins Centre investigators Associate Professor Rod Dunbar and Professor Garth Cooper. Catherine looked at the interaction between metabolism and the immune system in non-alcoholic fatty liver disease – the most common type of liver disease in the world. She identified a protein – MCP-1 – as having a major role in the inflammation of the liver, something that occurs as the disease progresses. Because fatty liver disease can often go undetected for a long time, Catherine suggested that MCP-1 could be used as a marker to test for the disease, or as a target for future drugs.

With her PhD under her belt, Catherine gained a post-doctoral position at the Auckland Bioengineering Institute. Today she translates mathematical models of biological processes into a computer language developed at the institute called CellML. A large part of her work is focused on making improvements to the online repository of more than 400 CellML models, a role she likens to being a curator at a museum - "except that I'm a curator of a database." Catherine also helps PhD students who are using CellML to model different cells and metabolic pathways in the human body. "My PhD was such a personal challenge," says Catherine, "but it gave me a huge confidence boost. I can now help the engineers here learn more about the biology side of their work."

Dr Matthew Chung also graduated with a PhD in 2008 following his Wilkins Centre scholarship. Matthew investigated the structure and function of a protein (SSL11) produced by the bacterium *Staphylococcus aureus*. Under the guidance of Mrs Heather Baker and Wilkins Centre investigators Professors Ted Baker and John Fraser, Matthew solved the structure of SSL11 and identified an entirely new mechanism by which these bacteria can evade and disrupt human immune defences. He determined that SSL11 interfered with a key process in the recruitment of white blood cells to the site of infection.

Like Catherine, Matthew has been extremely busy since graduating. He is now working as a postdoctoral fellow in the Biota Structural Biology Laboratory of St. Vincent's Institute of Medical Research in Melbourne, Australia. Matthew's main focus is on designing new drugs that target cancer cells. Once he knows what a protein looks like and how and where it binds to its target, he then begins to design drugs to block this interaction. "My PhD gave me valuable experience in producing and handling the proteins I'm interested in, which is particularly useful for difficult proteins that don't like to do what I want them to do!"





Outreach Sponsorship

Maurice Wilkins Centre Prize for Excellence in Chemical Research

The annual Maurice Wilkins Centre Prize for Excellence in Chemical Research is sponsored by the Wilkins Centre in partnership with the New Zealand Institute of Chemistry (NZIC). It is awarded to an NZIC member who has made a significant contribution to chemical science in the past five years.

The 2009 prize was awarded to Professor Sally Brooker from the Department of Chemistry at the University of Otago. Professor Brooker's research interests are in transition metal and macrocyclic chemistry and members of her research group are involved in developing metal compounds for use in nano-devices. She was elected a Fellow of the Royal Society of New Zealand in 2007.

Conferences and Meetings

Scientific conferences, meetings and networks are important fora to share knowledge and form collaborative relationships. The Wilkins Centre supports international scientific meetings held in New Zealand as well as smaller local scientific meetings and networks.

In 2009 the Wilkins Centre sponsored:

- The 2009 Queenstown Molecular Biology Meeting. This meeting attracted over 400 national and international delegates and speakers, including many from the Wilkins Centre.
- Stratus. This network at The University of Auckland supports emerging researchers and raises their profile in both academic and public communities.
- Protein Engineering and Evolution Symposium. This meeting, held at the University of Canterbury Cass Field Station, was a forum for discussing leading-edge research into protein structure and function, with particular emphases on engineering and directed evolution.
- The third CellML workshop. Organised by Wilkins Centre research fellow Catherine Lloyd, this workshop on Waiheke Island attracted over 50 delegates from New Zealand, Japan, Australia, the United States, the United Kingdom, Singapore and Germany.
- Australasian Society of Immunology 2009 New Zealand branch meeting. This meeting in Wellington involved many Wilkins Centre investigators and students from around the country

Industry engagement

The Maurice Wilkins Centre supports innovation in the biotechnology and drug development sector by providing companies with the expertise and facilities that their research and development programmes require. Headquartered alongside the Institute for Innovation in Biotechnology at The University of Auckland and Auckland UniServices Limited, the Centre is part of a significant industry research hub. In 2009 the Wilkins Centre provided expertise and / or facilities to:

- AFT Pharmaceuticals Ltd. This full service pharmaceutical company, which also undertakes drug development, has operations in Australia and New Zealand. In 2009, the company contracted Wilkins Centre investigator Professor Margaret Brimble to synthesise an established anti-rheumatic drug in sufficient quantities for testing.
- Androgenix Ltd. This Auckland biotechnology company applies genomic technology to the development of products for the world-wide livestock industry. The company needed access to state-of-the-art cell sorting technology to progress its business plan. The establishment of the Wilkins Centre' cell sorting facility in 2007 has enabled this and Androgenix is the major external user of the facility.
- Bomac Laboratories Ltd. This Auckland-based company develops and manufactures animal health products for sale in New Zealand and around the world. Wilkins Centre investigator Professor Margaret Brimble is designing and synthesising new molecules based on a lead compound identified by the company.
- ParaCo Technologies Ltd. This subsidiary of AgResearch Limited screens libraries of novel molecules for potential animal health activity. Access to established libraries is required for this work, and in 2009 an agreement was reached giving the company exclusive animal health screening (and subsequent commercialisation) rights to the libraries of Wilkins Centre investigators Professor Margaret Brimble and Professor Bill Denny. Professor Denny has also been contracted to synthesise promising molecules in sufficient quantities for further evaluation.



- Pathway Therapeutics Ltd. This New Zealand-based company was established to discover and develop the next generation of PI3-kinase inhibitors for the treatment of cancer. Wilkins Centre investigators Professors Bill Denny and Peter Shepherd are the company's scientific founders. Pathway Therapeutics requires screening facilities to search for potential PI3-kinase inhibitors, and the purchase of a computer-controlled robot by the Wilkins Centre has enabled this work to proceed.
- Proacta Inc. This clinical-phase biopharmaceutical company, headquartered in San Diego, is developing hypoxia-activated prodrugs for the treatment of cancer. Wilkins Centre investigators Professor Bill Denny and Professor Bill Wilson are two of the company's scientific founders. Proacta uses mass spectrometry capabilities purchased by the Wilkins Centre as part of its ongoing research into new compounds.

In addition to these examples Wilkins Centre investigators have established a variety of other relationships with companies and non-profit organisations that drive the translation of their research and expertise into new approaches to fighting human disease (see page 53).

NZBIO support

The Wilkins Centre is an active member of NZBIO, a national organisation representing bioscience based industries in New Zealand. NZBIO's functions include acting as an advocate for the industry, interacting with government agencies and providing national and international networking opportunities.

In 2009 the Centre provided additional support to enable preparation of the report 'Sight 2009: The importance of New Zealand's human therapeutics sector in future economic growth' by the NZBIO Special Interest Group for Human Therapeutics. This report shows the significant contribution of the sector to the national economy and makes recommendations for promoting future growth.

Science education

Supporting high-quality science education in New Zealand schools not only encourages the next generation of scientists but also helps others to understand and value science. In 2009 the Wilkins Centre was involved in numerous science education initiatives, including:

- BioEd 2009 Conference - The Wilkins Centre sponsored two secondary school teachers to attend the Christchurch conference: Gail Bergman of Hamilton Girls' High School and Ally Jerram of Marlborough Girls' College. Ms Jerram reported that the event, based on the life and legacy of Charles Darwin, was a rare and exciting opportunity to listen to real scientists and to mix with people from around the world with a common passion. She says that the cost of such events is usually prohibitive for teachers from small provincial towns, and that attending the conference has greatly enhanced her teaching.
- 2009 Asian Science Camp - The Wilkins Centre co-ordinated a New Zealand delegation to the camp in Japan. It sponsored two Year 13 secondary school students and one secondary school science teacher to attend the camp (see story in Research Highlight Section).
- NZ Biotechnology Learning Hub – Wilkins Centre investigators David Ackerley and Margaret Brimble featured in research stories and videos on this national website in 2009. The hub provides teaching resources for primary and secondary schools and helps to link modern biotechnology to the school curriculum (along with sister site 'The Science Learning Hub').
- LENSscience (Liggins Education Network for Science) – Several Wilkins Centre investigators participated in this classroom-based programme that provides schools with access to research scientists, to maximise student potential with high quality learning opportunities for both students and teachers.
- Rotary National Science and Technology Forum – Wilkins Centre scientists Jodie Johnstone, Chris Squire and Paul Young once again ran a practical laboratory session for around 150 students at this national residential programme for outstanding all-round science, maths and technology students about to start Year 13. In the practical session students got hands on experience with purification of green fluorescent protein.
- Incredible Science – This is an open day for primary and intermediate school students interested in science that is hosted by The University of Auckland and attracts over a thousand children. Wilkins Centre staff and students helped to set up and run a display called 'Scientists of the Future' where kids could see what scientists do in their labs all day and try using some science equipment themselves to look at tiny fish under a microscope and extract DNA from cauliflower. See the Incredible Science website for a video featuring Wilkins Centre students Kristina Burkert and Dan Verdon <http://www.incrediblescience.co.nz/id/80/>



Public engagement

The Maurice Wilkins Centre actively engages with the public by sharing news of its research and successes and providing commentary on topical scientific issues. It communicates with New Zealanders through the news media, public lectures and presentations, and visits by schools students.

In 2009 the Centre members successfully generated significant national and regional media coverage on a number of scientific topics:

- The national Drug Discovery Symposium convened by the Centre in September captured the interest of national media. Associate Professor Rod Dunbar, Wilkins Centre Director, appeared on television to discuss the potential for drug discovery to be a very valuable, knowledge based industry in New Zealand's economy. The topic was also reported in national and regional newspapers.
- Professor Hunter was awarded New Zealand's top science prize, the Rutherford Medal in November. As a result he appeared in television and radio interviews and was profiled widely in New Zealand print media. Professor Hunter was also presented with a 'World Class New Zealand' award in March, which also featured in national media.
- The Wilkins Centre sponsored the visit of stem cell research pioneer Professor Sir Martin Evans who presented the Maurice Wilkins Lecture to an audience of over 300 university staff, students and members of the public. As a result, he also made numerous appearances in national media including a feature story in the Weekend Herald.
- A new type of anticancer drug developed by Wilkins Centre investigators Jeff Smaill and Adam Patterson, which is showing promising activity against lung cancer, received coverage in both international and national media following the first public announcement of this work at a major international cancer conference.
- Local print media featured stories on the students and teacher awarded Maurice Wilkins Centre travel scholarships to attend the 2009 Asian Science Camp and on Wilkins Centre student Zoe Wilson, who won a place at a prestigious international symposium.
- Wilkins Centre Director, Associate Professor Rod Dunbar, was a featured guest interviewed by Kim Hill on National Radio. The conversation ranged from his research into vaccines for cancer, to the challenges of developing successful cancer therapies in New Zealand and the importance of promoting research and development in this country. The interview was subsequently replayed as part of Radio New Zealand's 'Great Encounters' series.

Wilkins Centre investigators also participated in visits from school students and gave presentations about their research to the public.

Service

Wilkins Centre investigators support both the national and international science communities through service in leadership roles and on many advisory boards and panels.

National roles

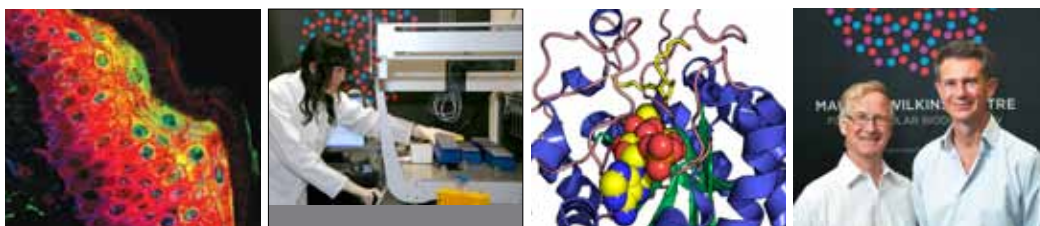
In 2009 Wilkins Centre investigators have served in advisory and governance roles in the following New Zealand organizations;

- Royal Society of New Zealand
- Marsden Fund Council and Panels
- NZ Health Research Council
- Rutherford Foundation
- National Heart Foundation Science Panel
- Allan Wilson Centre for Molecular Ecology & Evolution
- NZBIO
- Queenstown Molecular Biology Meetings Organisation
- Nuffield Medical Research Fellowship for Oxford University
- Logan Campbell Medical Trust
- New Zealand Bioinformatics Institute
- MoRST Oxygen Group
- Sustainability Council of New Zealand

International roles

In 2009 members of the Wilkins Centre have served in over 35 advisory, editorial and governance roles in international organizations based in the United States of America, Belgium, Australia, the United Kingdom, Holland, Canada, France, Sweden and Norway.





Organisational Development

Research Seeding Programme

A major new research strategy launched in 2008 is a contestable programme to seed very early stage research collaborations involving Wilkins Centre investigators from different scientific disciplines. In March 2009 the second phase of this programme was launched with fully funded Wilkins Centre PhD scholarships being offered in the multidisciplinary training category of the programme.

Three rounds of the programme were held in April, August and December. A total of \$1.40 million was awarded to seed 23 new projects including support for 12 new PhD students.

Projects funded were:

New initiatives

Development of a novel multiplex fluorescent reporter gene system: Ackerley and Horvat, Victoria University of Wellington; Smaill and Patterson, The University of Auckland

Analysis of the effects of stromal-targeting agents on the tumour infiltrate: Ching, Henare, Dunbar, Print, Palmer and Browett, The University of Auckland

Insect virus polyhedra nanocrystals as a vehicle for vaccine delivery: Taylor and Metcalf, The University of Auckland

Immune responses in lymph nodes: Ronchese, Hermans and Ma, Malaghan Institute; Dunbar and Bogle, The University of Auckland

Tissue engineering to develop grafts for treatment of tendon injuries: Cornish, Anderson, Shim, Naot, Reid, Hunter, Kim, The University of Auckland

Protein misfolding networks in yeast: Atkinson and Bellows, Victoria University of Wellington; Maass, ESR Ltd; Furneaux, IRL Ltd

Access to advanced equipment

Binding sites within PI3 kinase (p110 α subunit): Buchanan, Rewcastle and Flanagan, The University of Auckland

Characterisation of granulovirus particles: Metcalf and Middleditch, The University of Auckland

Analysis of changes in lymphatic fluid in diabetes: Phillips, The University of Auckland

Characterisation of NY-ESO-1, a peptide for cancer therapy: Harris and Greenwood, The University of Auckland

Identification and cloning of Sox-2 specific cytotoxic T lymphocytes from the blood of patients with glioblastoma: Hermans, Malaghan Institute; Dunbar, The University of Auckland

Multidisciplinary training

- *Structure-aided design of chemical inhibitors of human rhinovirus:* PhD student Katrin Schunemann. Supervisors: Brimble and Fraser, The University of Auckland; Wilson and Connelly, The Scripps Research Institute, USA
- *Molecular mechanisms for inhibition of TrpD, a TB enzyme:* PhD student Tammie Cookson. Supervisors: Parker, Canterbury University; Lott, The University of Auckland
- *Characterisation of adrenomedullin:* PhD student Maggie Au. Supervisors: Brimble, Aitken, Dingley and Harris, The University of Auckland
- *PI3K characterisation and analysis in metabolic diseases:* PhD student Hayden McEwen. Supervisors: Grattan, University of Otago; Shepherd and Rewcastle, The University of Auckland
- *Development of novel inhibitors of the IDO enzyme for cancer therapy:* PhD student Simon Fung. Supervisors: Ching and Squire, The University of Auckland
- *Characterisation of the structures of the calcitonin receptor:* PhD student Joseph Gingell. Supervisors: Hay, Lott and Baker, The University of Auckland



- *Vaccine design for lectin targets*: PhD student Paul Haseler. Supervisors: Brimble, Squire, Williams, Flanagan, Dunbar and Baker, The University of Auckland
- *Synthesis and functional characterisation of advanced glycation end products (AGEs) and AGE-modified target peptides*: PhD student Meder Kamalov. Supervisors: Brimble and Cooper, The University of Auckland
- *Inhibition of the NeuNAc synthases from *Neisseria meningitides* and *Campylobacter jejuni**: PhD student Dmitri Joseph. Supervisors: Parker, University of Canterbury; Arcus, Waikato University
- *How vaccine formulation parameters can impact on the immune response*: PhD student Silke Neumann. Supervisors: Hook, Rades, and Kemp, University of Otago; Dunbar and Brimble, The University of Auckland; Hermans, Malaghan Institute
- *Imaging and modelling lymph node structure at high resolution in 3D*: PhD student Inken Kelch. Supervisors: Dunbar, Bogle, Phillips, Sands and LeGrice, The University of Auckland
- *Structural characterisation of the enzyme alanine racemase from *Staphylococcus aureus**: PhD student Emma Scaletti. Supervisors: Krause and Cook, University of Otago; Brimble, The University of Auckland

New Investigators

In 2009 the Wilkins Centre once again expanded its national network of investigators and seventeen new Associate Investigators accepted invitations to join the Centre:

- Professor Andy Mercer, Department of Microbiology and Immunology, University of Otago
- Professor Colin Green, Department of Ophthalmology, The University of Auckland
- Professor Dave Grattan, Department of Structural Biology and Anatomy, University of Otago
- Professor Ian Reid, Department of Medicine, The University of Auckland
- Professor Jill Cornish, Department of Medicine, The University of Auckland
- Professor John Windsor, Department of Surgery, The University of Auckland
- Professor Kurt Krause, Department of Biochemistry, University of Otago
- Professor Peter Lobie, The Liggins Institute, The University of Auckland
- Professor Rob Smith, Department of Chemistry, University of Otago
- Associate Professor Lai-Ming Ching, Auckland Cancer Society Research Centre, The University of Auckland
- Dr Sarah Hook, School of Pharmacy, University of Otago
- Dr Gavin Painter, Industrial Research Ltd
- Dr Dave Larsen, Department of Chemistry, University of Otago
- Dr Mik Black, Department of Biochemistry, University of Otago
- Dr Marc Jacobs, Auckland Bioengineering Institute, The University of Auckland
- Dr Wayne Patrick, Institute of Natural Sciences, Massey University
- Dr Tony Hickey, School of Biological Sciences, The University of Auckland



Equipment & facilities

The purchase of equipment through the 2007 allocation of CoRE capital equipment continued in 2009 with purchase of 15 of the 17 items on the equipment list finalised at the end of the year.

Significant equipment items installed in 2009 included the new computer controlled robot that will be used to screen potential drugs and an advanced confocal laser-scanning microscope which will be used by researchers at the Auckland Bioengineering Institute to look at molecules and cells in human tissues (for further details see www.mauricewilkinscentre.org.nz). In addition a fluorescence spectrophotometer and recombinant protein production equipment were installed at The University of Waikato to support the work of Wilkins Centre researchers based there.

In 2009 The University of Auckland also provided funding to increase the automation of the Wilkins Centre protein crystallisation facility. An automatic imaging system was installed that is used to visualise crystallisation experiments at programmed times and store the resulting images. These images can be accessed from anywhere in New Zealand via the internet so that researchers can monitor their crystallisation experiments from their desk, whether they are in Auckland or Dunedin.

While primarily used by Wilkins Centre investigators, the capital equipment purchased has also provided valuable services for many New Zealand biotechnology companies and researchers based at CRIs and Health Boards. In 2009 the Wilkins Centre client list included:

- Androgenix Ltd
- Pathway Therapeutics Ltd
- Proacta Ltd
- Symansis Ltd
- Plant and Food Ltd
- The University of Waikato
- Massey University
- University of Canterbury
- AgResearch Ltd
- Middlemore Hospital

Human capability

The multidisciplinary, and collaborative nature of Wilkins Centre research provides an excellent training environment for younger scientists and students – our future science leaders.

PhD student support

The Wilkins Centre supports a large cohort of PhD and MSc students within its associated research groups by providing funding for working expenses and travel as well as for access to specialised research equipment and facilities. In 2009 the Wilkins Centre provided full or partial scholarship support for 14 PhD students and 1 MSc student from this cohort.

There were 10 Wilkins Centre-associated PhD students who completed their studies in 2009.

Personnel Exchanges

In order to maintain a world class research programme it is important that Wilkins Centre investigators and students keep up to date with international developments in their research fields. The Wilkins Centre provides support for staff and students to travel to conferences and to visit other laboratories in New Zealand and overseas to learn new skills and techniques.

In 2009 the Wilkins Centre Research Seeding Programme provided support for Victoria University PhD student Claire Horvat to carry out experimental work at The University of Auckland. Under the supervision of David Ackerley at Victoria University, Claire is working on developing new anti-cancer enzymes from bacteria, and as part of her research, uses prodrug compounds developed by Jeff Smaill and Adam Patterson at the Auckland Cancer Society Research Centre. "The Wilkins Centre support has been great. I've been able to take my research a step further and learn a whole new skill set."

Wilkins Centre research fellow Dr Catherine Lloyd spent four weeks at the European Bioinformatics Institute with the BioModels Database team. The CellML model repository being developed by Wilkins Centre investigator Peter Hunter and his team at the Auckland Bioengineering Institute has aims that are very similar to the BioModels Database. Visits like Dr Lloyd's have played an important role in changing the once competitive relationship between the two groups into a collaborative one. Where possible, common standards and practices have now been adopted, making it easier to exchange models between the two databases. The Centre's recent presence at Systems Biology meetings in Europe has also increased awareness of CellML and European based research groups have started to develop their own tools to use CellML models.



Structural biologists in New Zealand are very fortunate to have good access to the Australian Synchrotron Facility. The Wilkins Centre, along with the New Zealand Synchrotron User Group, facilitates trips by research staff and students to the Australian Synchrotron to collect experimental data. Each trip generally involves both experienced synchrotron users and new users who are trained to use the synchrotron during the trip. Those who travelled to the synchrotron in 2009 were research fellows Dr Chris Squire, Dr Jodie Johnston, Dr Alina Castell, Dr Ghader Bashiri, Dr Neil Patterson and PhD students Richard Bunker and Aisyah Rehan.

Wilkins Centre workshops

The Wilkins Centre ran four technology-based academic workshops in September 2009. These workshops were designed to inform and educate members of the Wilkins Centre in the most up-to-date techniques and equipment available in New Zealand, and to provide an opportunity to discuss potential future collaborative projects between Centre investigators. The topics covered in the workshops were immunology, genomic and proteomic technology, molecular modelling and cell signalling. The workshops were well attended and the programme will be continued in 2010.

International experts

The Wilkins Centre enables visits to New Zealand by international scientists, so that they can share their knowledge and research experiences with the New Zealand research community and establish research links.

Visitors hosted in 2009 were:

- Professor Martin Evans (Cardiff University, UK)
- Professor David Knight (Cardiff University, UK)
- Dr Julia Archbold (Monash University, Australia)
- Professor Steve Kent (University of Chicago, USA)
- Professor Susan Gasser (The Friedrich Miescher Institute, Switzerland)
- Dr Matthew Call (Harvard Medical School, USA)
- Professor Rod Hubbard (The University of York, UK)
- Dr Alexander Wlodawer (National Cancer Institute, USA)
- Associate Professor Bridget Mabbutt (Macquarie University, Australia)
- Dr Zeti Hussein (Kebangsaan University, Malaysia)
- Dr Peter Kenny (Astra-Zeneca, UK)
- Professor Joe Trapani (Peter MacCallum Cancer Institute & Monash University, Australia)
- Dr James Whisstock (Peter MacCallum Cancer Institute & Monash University, Australia)
- Dr Clive Stanway (Cancer Research Technology, United Kingdom)
- Dr Ian Street (Australian CRC for Cancer Therapeutics, Australia)
- Dr Ethan Shevac (National Institutes of Health, United States of America)
- A delegation from the People's Government of Guangdong Province led by Mr Song Hai, the Vice Governor (China)



External funding

Many of the research projects within the Wilkins Centre research programme are supported by additional grants from other funding sources. The Wilkins Centre also targets a proportion of its research budget to seed and develop new projects to the point where they are successful in securing competitive funding.

NZ funding

In 2009 Wilkins Centre investigators were awarded new grants worth more than \$18 million from New Zealand funding agencies for research projects to be carried out over the next one to six years. Success with major funding agencies is illustrated by the following:

- Health Research Council (8 grants, \$13.5 million)
- Marsden Fund (1 grant, \$0.9 million)
- Foundation for Science, Research and Technology (4 grants, \$3.6 million)

International funding

In 2009 Wilkins Centre investigators secured new funding from the following international sources to fund future research:

- Ludwig Institute for Cancer Research (USA)
- Human Frontiers Science Programme (Europe)
- Association for International Cancer Research (UK)

Governance and management

Governing Board

Over 2009 the Governing Board met on three occasions. During the year the Board had oversight over the change of Directorship of the Wilkins Centre from the Founding Director Professor Ted Baker to Associate Professor Rod Dunbar. In 2009 the Centre's management team made a number of changes to the format, style and content of its annual report and annual plan, in consultation with Board. In addition the Board continued to monitor the progress of the Centre in extending its national network of investigators and its profile among the wider public. The Board routinely reviewed progress of the Wilkins Centre research programme and compliance with its budget.

The composition of the Board was changed at the end of 2009 with Professor Richard Bellamy retiring and Professor Grant Guilford, the new Dean of Science at The University of Auckland, joining the Board.

W J Falconer CNZM

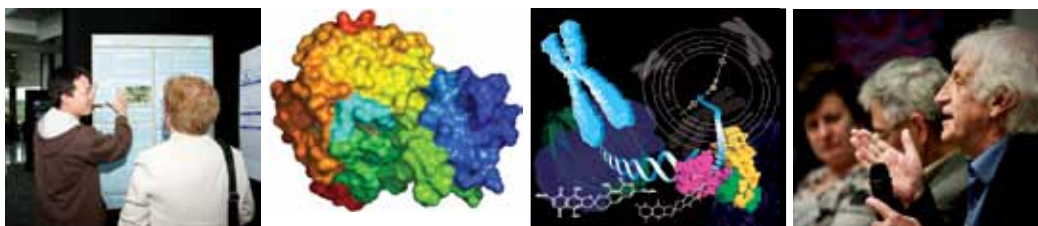
Chairman

Management Committee

The Wilkins Centre Management Committee, made up of the Wilkins Centre Principal Investigators and management staff, met seven times during 2009.

Members of the Governing Board, Scientific Advisory Board and Principal Investigators are listed in the Directory at the end of this report.





Research Outputs

Publications

In 2009 research outputs from Wilkins Centre investigators included over 300 peer-reviewed scientific papers published in international journals, and 2 patents. Research directly supported by the Wilkins Centre generated the following 80 scientific papers.

Papers and Reviews:

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9. Cairns, M. J., Carland, M., McFadyen, W. D., Denny, W. A., & Murray, V. The DNA sequence selectivity of maltolato-containing cisplatin analogues in purified plasmid DNA and in intact human cells. *Journal of Inorganic Biochemistry* (2009) **103**(8): 1151-1155.
10. Carley, S., & Brimble, M. A. A novel approach to the CDE ring system of pectenotoxin-4 triggered by VO(acac)₂-induced epoxy-acetalization. *Organic Letters* (2009) **11**(3): 563-566.
11. Chaussade, C., Cho, K., Mawson, C., Rewcastle, G. W., & Shepherd, P. R. Functional differences between two classes of oncogenic mutation in the PIK3CA gene. *Biochemical and Biophysical Research Communications* (2009) **381**(4): 577-581.
12. Cho, H. Y., Blum, R. A., Sunderland, T., Cooper, G. J. S., & Jusko, W. J. Pharmacokinetic and pharmacodynamic modeling of a copper-selective chelator (teta) in healthy adults. *Journal of Clinical Pharmacology* (2009) **49**(8): 916-928.
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Patents

Patents awarded

1. **Baguley, B.C., Deady, L.W., Denny, W.A., Rodemann, T. Rogers, M.L.** *New polycyclic carboxamide derivatives having antitumor activity useful in the treatment of cellular proliferation disorder e.g. neoplasm, tumor and cancer.* **2009: USA**
2. **Denny, W.A., Atwell, G.J., Yang, S., Wilson, W.R., Patterson, A.V., Helsby, N.A.** *New nitrophenyl phosphate compounds useful in cancer therapy, gene-directed enzyme-prodrug therapy and antibody-directed enzyme therapy.* **2009: USA**
3. **Harris, P. W. R., Brimble, M.A., Sieg, F.** *Synthetic analogues of neural regeneration peptides.* **2009: PCT**

Patents pending

1. **Dunbar P.R., Horlacher O., Feisst V.** *Cell marker of melanocyte cell lineage and uses thereof.* **2009: PCT**
2. **Fraser, J. D.** *Use of SSL-7 for detection and isolation of IgA and complement C5.* **2009: PCT**



Presentations

The significance of our research is demonstrated by Wilkins Centre investigators being invited to give more than 63 international and national presentations in 2009. The presentations included invited lectures at conferences and seminars at academic institutions in the USA, Japan, the UK, Germany, Australia, China, France, Turkey, Singapore, Switzerland, Canada, Korea, the Czech Republic, Austria, the Netherlands and New Zealand, as shown in the diagram below.



Presentation highlights

Significant presentations given by Wilkins Centre investigators in 2009 include:

- Ted Baker was invited to give keynote lectures on X-ray crystallography and its contributions to biology, chemistry and physics at three international crystallographic meetings during 2009 in Canada, Turkey and China. He originally gave the lecture at the International Union of Crystallography Congress meeting in Japan in 2008 and it was so popular that the union asked him to repeat it three more times in 2009 at its North American, European and Asian meetings.
- Ted Baker was also invited to give the opening address at the '9th International Conference on Lactoferrin: structure, function and applications' in China.
- Bill Denny presented a plenary lecture at the Lorne Cancer Conference (Australia) entitled 'Drug development projects targeting cancer-specific enzymes.' This conference is a world class annual cancer research meeting with presentations by leading international cancer experts.
- Margaret Brimble was invited to give a plenary lecture at the 'Intersect 09: Chemistry meets Biosciences, Materials and Medicine' symposium at La Trobe University (Australia). The title of her lecture was 'Synthesis of Therapeutic Peptides and Vaccine Components'.

- Peter Shepherd was invited to speak about 'Effects of isoform specific PI kinase inhibitors on glucose metabolism' at the 34th European Symposium on Hormones and Cell Regulation.
- Garth Cooper was invited to give a lecture at The Royal Society of Chemistry Symposium on the Chemistry and Biology of Peptides at the University of Oxford (UK).
- Peter Hunter was invited to give a plenary lecture at the International Conference on Computational Bioengineering in September on the topic 'FieldML.'
- Wilkins Centre investigators Bruce Baguley, Mik Black, Bill Denny, Rod Dunbar, Cris Print and Franca Ronchese were all invited speakers at the Joint NZ-Singapore Cancer Symposium, held at Biopolis in Singapore in November. The meeting was organised by Wilkins Centre investigator Peter Lobie (The University of Auckland) and Neal Copeland (A*STAR). This symposium aimed to serve as a platform for researchers from both countries to network and form collaborations.



Collaborations

The Wilkins Centre contributes to and benefits from an extensive network of national and international collaborations that has been built up by our investigators over a number of years. The research funded through the Centre has both strengthened these existing links and helped to establish new collaborations.

The international and national reach of these collaborations is shown in the diagram below.



New academic collaborations

In 2009 new collaborations have been set up between the Wilkins Centre and the following organisations:

- The New York University School of Medicine (USA)
- Arhus University (Denmark)
- Integrated Biotherapeutics (USA)
- A*STAR (Singapore)
- Hong Kong University of Science and Technology (China)
- The European Bioinformatics Institute (UK)

Uptake of Wilkins Centre research and expertise

The primary focus of the Wilkins Centre is on finding new therapies for human disease. The Centre drives the translation of its research and expertise from the laboratory to development phase through a variety of partnerships with commercial and non-profit organisations, in New Zealand and overseas.

The creation of spin-out companies is an important pathway for the development of Wilkins Centre research, and often brings in international partners and funds. Wilkins Centre investigators maintain close links with such companies and further research is regularly contracted back to their research groups. The Centre has close links with spin-outs Proacta Inc, Pathway Therapeutics Ltd and Symansis Ltd.

The Wilkins Centre also partners with established companies, and the knowledge and expertise that its investigators have developed in scientific fields vital to the biotechnology and pharmaceutical sectors are highly sought after. Examples of contract research and the provision of facilities to industry are outlined on page 27 of this report and Wilkins Centre investigators also act as consultants for a number of national and international companies. In 2009 the expertise of Wilkins Centre investigators was sought by:

- Paraco Ltd
- Connovation Ltd
- Landcare Research Ltd
- Industrial Research Ltd
- AFT Pharmaceuticals Ltd
- Eli Lilly and Company (USA)
- Proacta Inc
- Pathway Therapeutics Ltd
- Bomac Laboratories Ltd
- Symansis Ltd
- Neuren Pharmaceuticals Ltd
- Aquapharm Biodiscovery Ltd (Scotland)
- InvivoGen (France)
- Androgenix Ltd
- InSyGen Therapeutics Ltd
- EBoz Ltd

The establishment of partnerships with international non-profit organisations is another way in which the Wilkins Centre achieves uptake of its research and expertise.

For example, researchers associated with the Centre and based at the Auckland Bioengineering Institute are paid to work on the 'Human Physiome Project', along with European collaborators, under the European Commission Framework Programme. Auckland research leader Professor Peter Hunter says "research funding agencies in Europe and the US now request that models use the CellML standard developed in Auckland."

Other international organisations Wilkins Centre investigators are involved with include the Global Alliance for TB Drug Development and the TB Structural Genomics Consortium.



Awards and Honours

- **Top Scientist**

As already highlighted earlier in this report, in 2009 Professor Peter Hunter was awarded the top science prize in New Zealand, the Rutherford Medal. In addition he was also awarded a 'World Class New Zealand' award in March, was appointed Chair of the Marsden Fund Council and was awarded an Honorary Doctorate by the University of Nottingham.

- **Invitrogen Life Science Award**

Wilkins Centre investigator Dr Debbie Hay was presented with the 2009 Invitrogen Life Science Award at the Queenstown Molecular Biology Conference in September. This award is presented annually to an emerging New Zealand based researcher who has published excellent research using molecular biology, in high-ranking international journals.

Dr Hay, a Senior Lecturer in the School of Biological Sciences at The University of Auckland, received the award for her work on the calcitonin family of peptides, which contains several physiologically and clinically relevant peptides. These are important hormones in clinical medicine and Dr Hay has used molecular analysis to help guide development of new medicines that target them.

- **Oxford Professor**

In April 2009 Wilkins Centre investigator Professor Garth Cooper began a part-time appointment as Visiting Professor in Pharmacology (Discovery and Experimental Therapeutics) at the University of Oxford in the UK. The initial term of the appointment is for three years, with the expectation that it will continue for the duration of his career.

The visiting professorship will facilitate a joint research programme in cardiovascular therapeutics, in which workers in Oxford will contribute to the exploration of mechanisms of new experimental therapies for cardiovascular disease and diabetes currently under development in the Wilkins Centre.

Professor Cooper's appointment is expected to stimulate the exchange of students and post-doctoral fellows between the Wilkins Centre and the Department of Pharmacology at the University of Oxford.

- **Rutherford Fellowship**

The Rutherford Foundation of the Royal Society of New Zealand awarded Dr Nicola Jackson the inaugural Freemasons Roskill Foundation Postdoctoral Fellowship to undertake postdoctoral research at the University of Cambridge.

Nicola completed her PhD in Molecular Medicine and Pathology at The University of Auckland in 2008 and then worked as a Wilkins Centre Postdoctoral Fellow until leaving for Cambridge. Under the supervision of Professor John Fraser, she investigated the antibiotic-resistant superbug, *Staphylococcus aureus*. Her PhD also involved a collaboration with Professor Ted Baker and Heather Baker in the Structural Biology Group.

Nicola will join a team of scientists within the Department of Pathology at the University of Cambridge, led by Professor John Trowsdale and Dr Adrian Kelly, whose research is focused on understanding how pathogens interact with their host's immune system. This opportunity will allow Nicola to broaden her interest in host-pathogen interaction and to apply the knowledge gained from her PhD to another important human pathogen, *Salmonella enterica*.

- **Rising Star**

Hae Joo Kang completed her PhD in 2009 and was awarded a The University of Auckland Best PhD Thesis award. Her PhD focussed on discovering the three dimensional structure of the major protein that makes up the pili of *Staphylococcus aureus*. In October, Hae Joo was also presented with the "Rising Star" award at the 2009 Conference of the Asian Crystallographic Association in Beijing.

- **International Winner**

Zoe Wilson, who is studying for a PhD in organic chemistry, was selected to attend the 39th St Gallen Symposium in Switzerland in May 2009. She was one of 200 international students across a range of disciplines invited to attend the symposium, from more than 1,000 essay entries received.

Zoe's winning essay "Can a researcher be an island?" highlighted the importance of inter-disciplinary collaboration between scientists. The symposium, at the University of St Gallen, brings together international decision makers in business, academia, politics and society, with outstanding students and members of the media. It aims to promote the sustained success of companies and societies in a globalised world.

- **Best Student Presentation**

Mridula Dogra received the award for best student oral presentation at the Webster Centre for Infectious Diseases symposium in April 2009. Supervised by Dr. Nuala Helsby, Mridula's PhD work focuses on studying the metabolism of a novel anti-tuberculosis drug, PA-824, which is currently in Phase II clinical trials.



Financial Report 2009

Operating Fund - TEC CoRE grant

	<u>\$ 2009</u>	<u>\$ 2008</u>
<u>Income</u>		
CoRE grant ^a	-3,972,800	-3,373,067
Equipment User charges ^b	-220,980	-226,958
Balance from previous year ^c	-1,781,293	-1,559,186
Total Income	-5,975,074	-5,159,211
<u>Expenditure</u>		
Salaries ^d	1,234,620	1,195,280
Overheads	861,831	909,174
Project costs ^e	631,530	478,742
Student support (PhD and other) ^e	199,819	206,588
Travel	85,492	93,592
Depreciation	615,536	494,543
Total Expenses	3,628,828	3,377,919
Income less expenditure^f	-2,346,245	-1,781,293

Capital Expenditure Fund

Income

Balance of TEC grant 2002	-10,596
Balance of TEC grant 2008	-712,278

Total Income	-722,874
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Expenditure

Capital expenditure 2009	655,313
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Funds carried forward to 2010^g	-67,561
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Notes

- a) This financial report is for the period 1st January to 31st December 2009 and covers the second six months of the Wilkins Centre Year 7 (CoRE grant 2008 to 2014) and the first six months of Wilkins Centre Year 8 (CoRE grant 2008 to 2014). This report only details income and expenditure relating to the CoRE grant funding that the Wilkins Centre receives from the Tertiary Education Commission. It does not contain details of external operating funding to Centre investigators from other funding agencies.
- b) These equipment user charges are collected by the Wilkins Centre from users of the large items of capital equipment purchased with funding from the Centre capital equipment fund. The charges are used to offset the operational costs of the equipment.
- c) This brought forward balance is unspent funding from previous years of the Wilkins Centre that will be used to fund research initiatives in future years.
- d) Summary: Wilkins Centre supported research staff FTEs 2009
- | | |
|-------------------------|-------|
| Principal Investigators | 0.50 |
| Research Fellows | 8.09 |
| Research Technicians | 5.05 |
| Total | 13.64 |
- e) These costs include the costs of subcontracts for Associate Investigator's research projects during 2009. Expenditure in direct costs was significantly less than budget in 2009 due to the deferment of the first round of the flexible research seeding programme to December 2008 and fewer PhD scholarships being taken up in 2009 than planned. Corresponding increases in expenditure are forecast for 2010 to 2013 now that this programme is operational and the majority of the PhD scholarships have been taken up.
- f) This balance of funding will be used to fund initiatives supporting the Wilkins Centre research programme in the period 2010 to 2012.
- g) This balance will be used to complete the capital equipment purchase programme in 2010.



Directory

Governing Board members

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Prof Gary Hook

Mr John Loof

Prof Iain Martin

Prof Emeritus George Petersen

Ms Maxine Simmons

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Prof Suzanne Cory

Dr Jilly Evans

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Maurice Hugh Frederick Wilkins

1916 – 2004

The Centre proudly takes its name from the New Zealand born Nobel Laureate Maurice Wilkins. He is most famous for his work at King's College London where he began spectroscopic studies on nucleic acids which eventually led to the use of X-ray crystallography to define the Watson-Crick model of DNA. For this work, he was awarded the Nobel Prize in 1962.

The Centre for Molecular Biodiscovery was founded in 2002. It was renamed the Maurice Wilkins Centre in 2006 with the support of Maurice's widow, Mrs Patricia Wilkins, and their family.

