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Medicine, Nursing and Health Sciences

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Biomed Benchmark

News from Biomedical Science at Monash – November 2006, Issue 2

Protein research leads to Life Scientist of the Year award

The discovery of how a protein called MENT helps condense DNA so that it fits inside the cell nucleus has contributed to Monash researcher Associate Professor James Whisstock being awarded the 2006 Science Minister's Prize for Life Scientist of the Year.

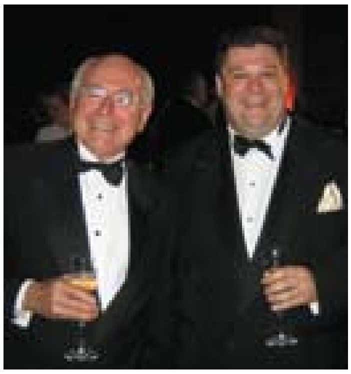
Dr Whisstock received one of the nation's most highly-regarded awards for his work on the structure and function of a specialised family of proteins called serpins. The prize is presented to a scientist in the early stage of his or her career for world-class scientific research.

In humans, mutations in serpins can disrupt the normal folding of these proteins or cause them to aggregate. This leads to the development of diseases such as emphysema, liver cirrhosis, certain dementias and thrombosis. One focus of Dr Whisstock's research is understanding how serpins aggregate and how to prevent this process.

Associate Professor James Whisstock, awarded the Life Scientist of the Year

Recently, Dr Whisstock's group was the first to find serpins in bacteria and he hopes that the study of these proteins and how they avoid aggregation will provide important insight into how to combat human disease.

Further, Dr Whisstock has now found that although some serpin aggregations contribute to disease, aggregations of the serpin MENT play an important role in DNA packaging and is fundamentally involved in condensing DNA to fit inside the nucleus.



Associate Professor Whisstock with the Prime Minister, The Honourable John Howard PM at the award ceremony in Canberra

This is the second time in three years that a Monash University scientist has received the Science Minister's Prize for Life Scientist of the Year. Professor Jamie Rossjohn, also from the Department of Biochemistry and Molecular Biology, was awarded the prize in 2004.

New Head of School

Professor Christina Mitchell, newly appointed Head of School

Professor Christina Mitchell has been appointed as the new Head of the School of Biomedical Sciences.

Prior to her appointment in June, Professor Mitchell was Head of the Department of Biochemistry and Molecular Biology (1999-2006). In the last five years, under her supervision, the department has been ranked Number 1 in Biochemistry departments in Australia according to the Go8 ranking. Trained as a physician and scientist, Professor Mitchell is currently working to identify novel proteins that regulate cell growth. Her research is helping to understand the processes of cancer and degenerative diseases.

Professor Mitchell's research is particularly focussing on the signalling mechanisms in cancer cells and trying to understand how abnormal signalling can lead to the spread of cancer. Her Cellular Signalling Laboratory has recently cloned three new enzymes that play important roles in cancer and have assisted in understanding how cancerous cells function.

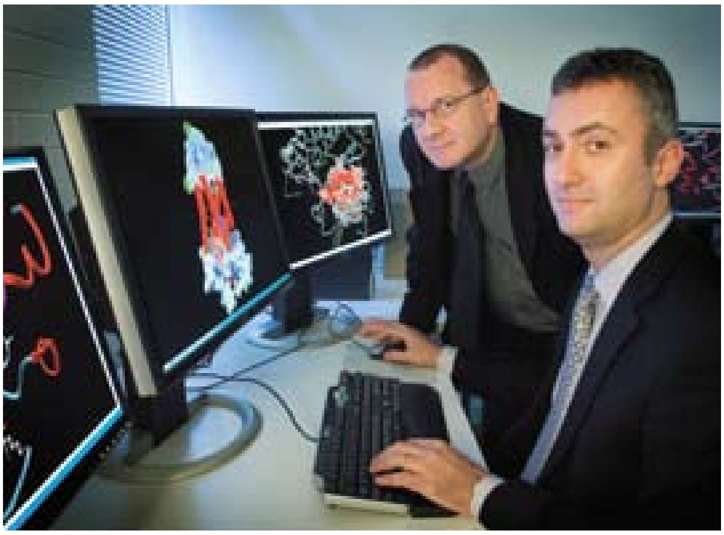
Professor Mitchell has published 80 original peer-reviewed research articles and seven reviews/book chapters in highly prestigious international journals. Currently she serves on the advisory committee to the Victorian State Government with respect to Science and Biotechnology (BREAP) and the NHMRC Research Fellowship committee (2005-2006).

Discovering new drugs

In April 2006, Monash University welcomed Professors Arthur Christopoulos and Patrick Sexton as leaders of the Drug Discovery Biology Laboratory.

The laboratory investigates the molecular nature of the most prominent class of drug targets – G protein-coupled receptors (GPCR), and how these can be used to understand how drugs work, and to develop new drugs. Current GPCRs under investigation by the group are potential targets for the treatment of neurological disorders such as schizophrenia, and depression, as well as other disorders such as diabetes, obesity, migraines and bone disease.

A receptor is a protein on the outside of a cell that receives signals from the outside world.



Professors Patrick Sexton and Arthur Christopoulos

GPCR's are the most common type of receptor and are targeted by nearly 50 percent of current therapeutic drugs.

The Drug Discovery Biology Laboratory is particularly interested in exploring new ways to target drugs to bind to GPCRs in an attempt to achieve greater selectivity of action.

In some cases, drugs will bind to the wrong area of the GPCR which will create 'side effects'. Professors Christopoulos and Sexton are also trying to understand GPCR function so that drugs will behave in a precise manner, enabling the reduction of side effects and an increase in drug effects.

"We are particularly interested in the relationship between drugs and GPCRs. As GPCRs are almost universally involved in both normal and diseased states, an understanding of these interactions may provide insights that could be applied in the treatment of many different diseases," says Professor Christopoulos.

"Researching the mechanisms of drug action tells us how individual cells react to certain drugs," says Professor Sexton. "An understanding of how cells respond will help with the identification and development of new therapeutics."

Heart smart: new drug improves blood flow

A new drug has been shown to improve blood flow, specifically in diseased arteries, reducing the risk of high blood pressure. The discovery was made by an international team of researchers from Monash University and Bayer HealthCare.

Professor Harald Schmidt, the Director of Monash University's Centre for Vascular Health, and Dr Johannes-Peter Stasch, Project Leader with Bayer HealthCare, describe the implications of the discovery as very promising. "We hope that the full potential of this new therapeutic principle can be translated soon into benefits for patients," Professor Schmidt said.

Bayer HealthCare, the company that discovered and developed the drug, has already begun clinical trials to assess its effectiveness in the treatment of acute heart failure.

"Current drugs used to lower blood pressure dilate blood vessels but don't target the actual cause of the problem. Our joint study suggests that this drug targets a newly discovered mechanism of the disease," Professor Schmidt said.

In the diseased blood vessel wall, radicals interfere with the ability of the cells lining arteries to control the contraction and dilation of the arteries and the formation of arterial blockages.

The Monash-Bayer research shows that these radicals destroy a key enzyme in the arterial wall and that the new drug reactivates the damaged enzyme," Professor Schmidt said.

Professor Schmidt and research colleagues will now try to further advance the diagnosis and therapy of heart disease and stroke.

"Vascular diseases are the number one cause of death worldwide. Yet we don't know enough about the causes to reliably identify and treat cases, let alone prevent these diseases," he said. "This discovery is an important step along the way."

Professor Harald Schmidt

Bacterium test for cystic fibrosis sufferers

Dr Cynthia Whitchurch has developed a technique which detects a highly contagious strain of bacteria effecting people with cystic fibrosis – a test that could save lives.

Dr Cynthia Whitchurch

Between 1991 and 1996, an infectious strain of the bacterium *Pseudomonas aeruginosa* killed five young children with cystic fibrosis (CF) who were attending a paediatric CF clinic in Melbourne. The bacterium has since been found to be widespread in patients attending CF clinics in eastern Australia.

The strain appears to be especially virulent, particularly in the very young, as it is resistant to multiple antibiotics, and can establish chronic infections that are difficult to eradicate. A team lead by Dr Cynthia Whitchurch, in collaboration with Dr David Armstrong of the Monash Medical Centre, has developed a technique that can check whether someone with CF has acquired the bacterium strain. They are also investigating why the strain is so easily transmitted.

Cystic fibrosis is a genetic lung disease that affects one child in 2500 in Australia*. CF sufferers produce thick mucus which blocks their lungs and provides a breeding ground for bacteria – making them more susceptible to infections. There is no cure for CF, and to reduce the risk of lung infection, patients rely on regular physiotherapy to clear their airways.

“There is a high risk of cross infection of this bacterium among CF patients requiring regular hospital visits,” Dr Whitchurch says. “CF sufferers are prone to lung infection caused by *P. aeruginosa* and some infections can ultimately be fatal.”

Hospitals already separate at-risk CF patients in order to minimise infection spread, and this new technique to test for the bacterium would be a valuable addition to their infection control protocols.

“Being able to test whether a patient has the strain will mean that staff can reduce the chance of exposure for patients who do not have it. This will not only help prevent infection of CF individuals but will also relieve the burden on hospital resources,” Dr Whitchurch says.

The technique, called a diagnostic PCR protocol, amplifies genetic sequences that are unique to the particular strain of *P. aeruginosa*. Dr Whitchurch hopes to develop the technique into a simple diagnostic tool that will be used to test for the presence of the strain in CF patients.

*www.cysticfibrosisvic.org.au

Helping to remember and learn

A type of brain cell that was thought to play only a supportive role in brain function may, in fact, be a ‘star’, according to a Monash neuroscientist.

Scientists know that 10 per cent of the brain consists of neurons, the cells responsible for movement and thinking. The rest are glial cells, and it has always been believed that a type of glial cell called an astrocyte provides mechanical and metabolic support for neurons, by maintaining the environment in the brain. Research now suggests that astrocytes, identified by their distinctive star shape, actually do a lot more.

Monash neuroscientist, Dr David Bowser is investigating the role of glial cells and how they function. He and other researchers believe that the actions of these cells, which have been ignored for decades, may have implications for learning and long-term memory, while also playing a role in diseased states.

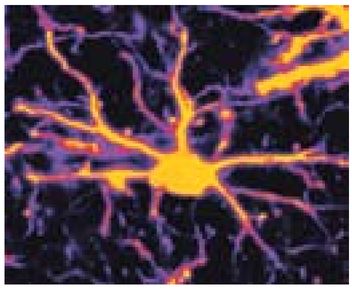
Dr David Bowser

“Neurons send messages to each other through synapses which connect them,” Dr Bowser explains. “We now think that glial cells can determine which neural connections get weaker and stronger over time because they actually influence the formation of the synapses.

“Which synapses are formed or deteriorate has an effect on learning and storing of memories and can be very important in some disease states.”

Neurons use a fast form of communication via quick electrical synapse impulses. Until recently, it has been thought to be the only form of communication within the brain. Scientists now believe that not only do astrocytes and neurons communicate with each other, but a type of communication between glial cells also exists. Glial cells use particular types of chemical signals rather than electrical ones to relay messages to each other and neighbouring neurons in a much slower and long-lasting form of communication.

“Slower forms of communication between cells are important. Astrocytes which are positioned to connect neural networks in the brain have a longer lasting influence on neurons. This is really important for regulating the networks, particularly in states of uncontrolled neural activity such as an epileptic seizure,” Dr Bowser says.



star-shaped astrocyte

Dr Bowser’s previous research demonstrated the importance of astrocytes in putting a “brake” on diseased states. Currently he is focusing on understanding how astrocytes release these chemical messages in the brain. Through the use of new state-of-the-art imaging techniques, he hopes to develop methods to accentuate or reduce the release of these chemicals in the brain.

Stem cells for MS research

Stem cells could fight the effects of Multiple Sclerosis.

Professor Claude Bernard and his team from the Monash Immunology and Stem Cell Laboratories at Monash University are working to generate stem-cell therapies for Multiple Sclerosis (MS) – to minimise disease inflammation, promote regeneration of brain tissue and subsequently eliminate the effects of the disease.

Recently, Professor Bernard has found that an MS-like condition in mice can be significantly suppressed by either inhibiting molecules known to cause inflammation, or by blocking a protein which normally prevents the nerve to regenerate.

At present there is no cure for MS. Although immune therapy is beneficial to a proportion of patients, some do not respond to any of the currently available therapies. Professor Bernard's group will endeavour to block the activity of these molecules, in order to help maintain and restore the CNS following immune damage in diseases like MS.

MS, a neurodegenerative condition, exists in several forms and in various degrees of severity. In the majority of cases, patients inexorably advance to a state of chronic disability.

Professor Claude Bernard

"This causes an enormous emotional as well as a financial burden on patients and families of MS suffers," Professor Bernard says. "We are investigating the ability of stem cells to reduce inflammation and at the same time replace the damaged cells to promote tissue repair and regeneration in the brain."

"Ultimately, the research will significantly improve the quality of life for MS suffers and will result in a reduction of costs associated with the care and dependence of patients to the community."

The project brings together senior stem cell scientists, Professor Alan Trounson, Associate Professor Richard Boyd and Professor Ban-Hock Toh, from Monash Immunology and Stem Cell Laboratories.

Eggs survive in older ovaries

In research that could have broad implications for women's fertility treatments, scientists have found that despite their age, female mice have a renewable egg supply in their ovaries.

The discovery, by Associate Professor Jeff Kerr from Monash's Department of Anatomy and Cell Biology and Professor Jock Findlay from Prince Henry's Institute of Medical Research, has sparked controversy among biologists and challenged the theory, held for more than 50 years, that female mammals are born with a finite number of oocytes (eggs).

Two years ago, international researchers speculated that mice could continue to produce eggs throughout puberty and adulthood. Although their speculation caused debate throughout the scientific community, the scientists could not produce evidence to confirm their idea.

Dr Jeff Kerr and Prof Jock Findlay

However, Dr Kerr and Professor Findlay's research gives support to the theory.

In the mammalian ovary, reproductive cells called oocytes (eggs) develop within ovarian follicles. In humans, the eggs are believed to die off from late in foetal life, after birth and into adult life. When egg numbers decline towards zero, females can no longer reproduce – resulting in the condition we know as menopause.

Dr Kerr, Professor Findlay and their colleagues have found that the total numbers of eggs in young and normal healthy adult female mice do not decline over time and that overall egg number is maintained for longer than previously thought. Their research suggests that mice have a source of renewable oocytes, Dr Kerr said.

"The mechanism behind renewable oocytes is still unknown," he said. "Although other scientists have suggested that the new eggs come from stem cells in the bone marrow or the ovary, we really don't know and further experimentation is needed to find out."

Professor Findlay said the phenomenon of egg regeneration in mice did not necessarily mean the same happened in humans. "But the mechanism could provide direction for ovarian stem cell research and help women with fertility conditions," he said.

One in six Australian couples faces some form of infertility. Due to the limitations and sensitivity of human ovaries, few studies have been conducted into the factors that influence egg survival, growth or death in relation to fertility.

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