

## Doubling of PhDs at ANZAC

At least 50 postgraduate students will be enrolled next year in the Discipline of Medicine at Concord Campus, double the number of only three years ago.

Vicky Skleparis, the Postgraduate Administration Officer for Concord campus, says a postgraduate website is now being built for this record number of Concord students.

The site will be purpose built as a resource for people interested in taking up postgraduate study through the Sydney Medical School's Concord Clinical School and for students already enrolled in course work or a research program.

The website will contain contact details, practical information on aspects of candidature, more general information relevant to local postgraduate students and links to useful sites.

## More good news

**Dr Julie Redfern** from the Vascular Biology and the Choice Study Research group was awarded the prestigious 2009 Young Tall Poppy Award for NSW. Julie was one of 18 finalists with outstanding scientific research and a passion for communicating science to the wider community. The award is run by the Institute of Policy and Science and recognises early career researchers who have achieved significant scientific milestones.

## Achievements recognised by NHMRC Grants

The outstanding work being undertaken by the ANZAC Research Institute has been recognised and rewarded by an exceptionally successful response with our applications for project grants to the National Health and Medical Research Council.

Six of our 11 grant applications were successful, resulting in total funding of \$3.8 million in new NHMRC grants over the next 4 years. The upshot of this success means an additional \$1M for next year, giving a total of over \$3.5M for all NHMRC research projects in 2010. The six successful projects are outlined below.

### Androgen receptor mechanisms in female reproductive physiology

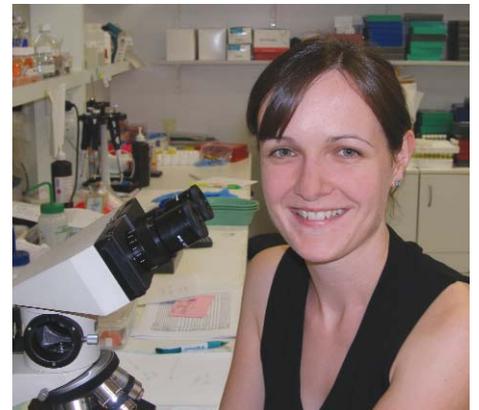
– Dr Kirsty Walters

One in every six Australian couples has problems with infertility, and in half those cases it's the woman who has difficulty in conceiving. Therefore, says Dr Kirsty Walters, it's important that we enhance our understanding of ovarian and uterine functions.

"Basically my project looks at the role of androgens, which are classically known as male hormones," says Dr Walters. "They play a really important role in males. In females it has always been thought that androgens had only a harmful role during adult life but until recently it wasn't suspected that androgens have an important role. So we've found a previously unsuspected role that androgens play in regulating female fertility."

Working with mice Dr Walters has discovered that females where androgen activity has been completely blocked have lower fertility, apparently because fewer eggs are being ovulated.

"The indications that if we can find out the mechanisms then we might be able to



isolate the factors that regulate female fertility and other androgen associated disorders in humans such as polycystic ovary syndrome," she says.

"That's a relatively common condition among women where they don't ovulate - the follicle grows but the egg is never released and the follicle turns into a cyst which is associated with harmful, excessive levels of androgens in women."

Dr Walters came to the ANZAC Research Institute from Scotland in 2005. The NHMRC grant of \$500,000 over three years will enable her to advance her research.

# More good news

**Prof Garth Nicholson** and **Drs Marina Kennerson** and **Patsy Polly** were awarded a \$345,000 grant over two years from the Muscular Dystrophy Association for their study entitled “Analysis of structural and regulatory elements of CMTX3 candidate genes.” This study will explore new mechanisms of axonal degeneration by identifying the gene causing an X-linked form of Charcot Marie Tooth (CMTX3) Neuropathy. Using bioinformatic resources and next generation deep sequencing we will examine the entire genomic structure and regulatory elements of the known candidate genes in the CMTX3 interval. These experimental approaches will improve a systematic screen for identifying structural and regulatory mutations as a cause for CMTX3. Discovery of this gene mutation will provide a means to determine mechanisms causing axonal degeneration and therapeutic treatment strategies.

**Prof David Handelsman, Amanda Idan** and **Leo Turner** were awarded \$US200,000 by the World Anti-Doping Agency for a one-year project on “Detection of indirect androgen doping with GnRH analog (Leuprolide).” This study is examining a new form of indirect androgen doping with the aim to deter it through developing new detection tests in conjunction with colleagues at the National Measurement Institute’s Australian Sports Drug Testing Laboratory. Indirect androgen doping is a new method devised to circumvent WADA’s effective banning of all known synthetic androgens. This form of cheating tries to use drugs that increase the body’s own testosterone production so as to increase muscle size and strength, motivation and ultimately elite sports performance.

## Aging, Nutrition and the Geometric Framework

– Prof. David le Couteur



We reported earlier this year in “Discovery” on the Concord Health and Aging in Men Project (CHAMP), a study which started in 2005

of more than 1700 men then aged 70 or older living in suburbs close to the ANZAC Research Institute.

As a spin-off from that study this project will examine issues of nutrition, obesity and dietary needs in old age. The NHMRC has granted \$750,000 over four years.

It will involve collaboration with Prof. Stephen Simpson, whose studies of insects already have shown nutrition has a profound effect on aging.

“Geometric Framework is a way of comparing the ratios of different things in your diet – fat to carbohydrate to protein in particular,” says David le Couteur.

“Steve found a certain ratio would promote reproduction in insects, and a certain ratio would promote longevity. We’re currently investigating that in mice. And now, by working with the cohort of men in CHAMP, we’ll be able to follow these men over several years and see if the same thing applies.”

Prof le Couteur says initial pilot analysis of dietary data supports a number of significant and surprising paradoxes in older people.

“One is that old men who are overweight and eat a low-protein diet and a high fat diet are healthier. So fatter is better, bigger abdominal circumference is better, higher blood pressure and high cholesterol is better. All those things that are bad in middle age because they lead to subsequent disease – by the time you get old actually seem to be beneficial for you.”

The purpose of this grant is to study those nutritional aspects, looking at things like the obesity paradox, and the effects of nutrition on frailty.

## The Sertoli cell: master regulator of hormone-induced spermatogenic development

– Dr Charles Allan



The vast majority of men will never have heard of the Sertoli cell, but it is a critical cell for sperm production, discovered more than a century

ago by an Italian scientist.

This project will determine the key roles of major hormones (testosterone, follicle-stimulating hormone, Vitamin A) in Sertoli cells, unique highly specialised cells found in the testis that provide essential nutritional and structural support for sperm production.

“Without it you don’t get sperm,” says Dr Allan. “The Sertoli cell is crucial during development of the testis; it stops the uterus from forming in males. It has hormone receptors. It is rightly understood as the nurse cell of the testes without which they don’t form or function properly.”

“We are trying to understand the role of these key hormones in the development of the Sertoli cell and in driving the full functional maturation of the Sertoli cell. Testis size is determined by Sertoli cell number, and sperm production capacity is determined by Sertoli cell number.

“The ultimate goal is to identify the genetic targets and regulatory factors, the key ones that control Sertoli cells and therefore control sperm production and these may allow us to have new strategies for treating male infertility or for contraception so we can either turn things on or fix things up or turn things off.”

The NHMRC has granted \$543,000 over three years for this project, which has already established that FSH (follicle-stimulating hormone) is the key player in driving Sertoli cell numbers.

## Geewiz facts

The cornea is the only tissue that can be transplanted without needing immune suppressing drugs. Why not others?

## Improving the use of chemotherapy by targeting the inflammatory response

– Prof. Stephen Clarke



Any one of us with friends or relatives who've had chemotherapy for cancer has probably heard at least once the complaint that "the chemo

really knocked me around." Predicting and preventing that severe adverse reaction is the aim of this project, funded by \$500,500 over three years.

Stephen Clarke and his team have demonstrated that patients who exhibit an inflammatory reaction to their cancers have difficulty in getting rid of drugs from their system - they clear those drugs more slowly and show more side effects from those drugs.

"We have established an animal model to investigate the whys and wherefores of that, how we might be look at an explanation for that on a molecular basis, and also how we might be able to predict and prevent that," says Prof. Clarke.

"We always knew that people who were really sick didn't handle chemotherapy very well but we didn't understand the mechanism. One of the things that happens as people get more advanced cancers is that inflammatory proteins increase, probably produced by other proteins that come from the tumour, and that has an effect on the liver's ability to get rid of the drugs."

Through collaboration with ANSTO part of the research now will involve labelling cancer drugs with radioisotopes so scanners can track where the drugs go and how they are cleared from the system.

The ANZAC Research Institute team leads worldwide investigations in this area. The work has already taken about 10 years and resulted in a number of papers being published.

"I think we're getting quite close and this will enable us to predict patients more likely to get toxicity," says Stephen Clarke. "But we're still a few years off finding ways of intervening to reverse the process."

## Role of osteoblast in mediating glucocorticoid-induced metabolic dysfunction

– Prof. Markus Seibel



Steroid drugs like prednisone and dexamethasone have been used medically for over 60 years. They are very valuable and widely used to

treat inflammatory conditions including asthma, arthritis, and autoimmune diseases, as well to suppress organ rejection after organ transplants. While they are tremendously valuable drugs, they cause serious side-effects such as osteoporosis, hyperglycaemia, excessive fat accumulation and muscle wasting which are major limitations on the use of steroids.

This research is examining the effects of such steroids on bone, blood lipids and body composition (fat, muscle) changes in an experimental setting using a special strain of genetically modified (transgenic) mice created to study the interruption of the harmful effects of steroids on bone. While in control mice the high doses of steroids cause bone loss (osteoporosis), increased cholesterol and triglycerides, and obesity, the transgenic mice were protected from the bone-wasting as well as the lipid effects and obesity of the high dose steroids.

These important new findings indicate that the effects of high dose steroids on the body's metabolism are, at least in part, due to effects on the osteoblasts, the bone forming cells. Our findings indicate that bone loss and metabolic disturbances, presently considered separate effects of high doses of steroids, may in fact be closely linked, both the products of steroid effects on the osteoblast.

Our research will create new knowledge about the primary target cells and how high doses steroids cause diabetes and osteoporosis, and may open new avenues for strategies to treat or event prevent them.

The NHMRC grant is worth \$788,900 over four years.

## Role of endogenous glucocorticoids in inflammatory arthritis

– Assoc. Prof. Hong Zhou



Inflammatory joint diseases like arthritis affect millions of people worldwide and in most patients these are usually chronic conditions

that cannot be cured. High doses of glucocorticoids (steroids) are used widely for their very effective ability to suppress inflammatory diseases as well as for their immune system modifying effects. However whether the body's own glucocorticoid also influence the course of a disease like inflammatory arthritis (eg rheumatoid arthritis) is unknown.

Our experiments have used an experimental model of inflammatory arthritis where we found that disrupting steroid messages in osteoblasts had a greatly dampening effect on the autoimmune arthritis in mice. These new and important findings strongly suggest the unexpected fact that the body's own steroids and the osteoblast play a crucial role in mediating and maintaining joint inflammation in autoimmune arthritis.

Using our genetic modified animal models we will further investigate the primary target cells and the mechanisms of early autoimmune arthritis. The NHMRC grant of \$662,600 over four years will enable us to advance our project to identify the mechanisms underlying these hormonal effects with the aim of finding new targets for efficient treatment for arthritis.

## Gee whiz facts

The gender gap in life expectancy with Australian men living 5-7 years less than women has not narrowed in the last century. But why?

