

VC says farewell and tours new buildings

On 24 June, Vice-Chancellor Professor Richard Larkins visited the School and met our talented researchers. He was accompanied by Chancellor Dr Alan Finkel; NHMRC CEO, Professor Warwick Anderson; Deputy Director of Florey Neuroscience Institutes, Professor Geoffrey Tregear; Faculty Dean, Professor Steve Wesseling; Head of School of Biomedical Sciences, Professor Christina Mitchell; and researchers Professors Rob Pike, James Whisstock and Stephen Bottomley.

The guests toured the 'Crystal Palace', home to the largest fully-integrated crystal production facility in the world.

"The RIGAKU Crystallation robot can deliver incredibly small volumes of protein and quickly screen thousands of samples for the growth of crystals for structural studies," says Associate Professor Matthew Wilce, Director of the Crystal Production Unit. "The results are available to researchers remotely via a web-based interface."

The \$4 million instrument, which was funded by the Australian Research Council, Australian Regenerative Medicine Institute, Grollo Ruzzene Foundation and Monash University, will shortly open for business and support Monash scientists initially and external clients later.

Professor Bottomley then led guests through the Protein Production Unit. His staff produce and purify recombinant proteins for biophysical and structural studies, antibody production, and targets for vaccine trials.

With the move to the new home in building 16, the facility staff can increase production output and now purify proteins in a low-temperature environment. They will also provide a high-throughput cloning service, and express proteins in insect and mammalian cells.

The guests also met staff in buildings 76 and 77. School Infrastructure Manager Dr Isabel Roberts hosted

a tour of the central administration area. The Vice-Chancellor praised the shared-services model, which he proposed for the School and actively supported. He also met with the following scientists, who discussed their research: Professor Tony Tiganis, Associate Professor Moira O'Bryan, Professor Julian Rood, Dr Dena Lyras, Dr Fasseli Coulibaly and Dr Travis Beddoe.

Following the tour, Vice-Chancellor Professor Larkins attended his farewell party, which was hosted by the Dean.

Superbug debugged

An international team of scientists led by Monash researchers have uncovered how a superbug kills hospital patients worldwide. And, in doing so, they've upturned prevailing dogma. Of the two toxic proteins produced by the bacterium *Clostridium difficile*, they have shown that toxin B, not toxin A, causes intestinal disease.

For their efforts, team leader Professor Julian Rood and lead author Dr Dena Lyras from the Department of Microbiology have had their work published in the prestigious journal *Nature*.

The research focuses on *C. difficile*, a superbug that infects hospital patients undergoing antibiotic therapy. The antibiotics destroy the 'good' bacteria in the gut and allow this 'bad' bacterium to thrive in the colon, where it triggers an immune response and chronic diarrhoea, which is difficult to treat.

In the US, more people die from *C. difficile* associated disease than all other intestinal infections combined, with most deaths involving elderly people. If this superbug invades Australian hospitals and replaces less aggressive strains here, it will seriously threaten our healthcare system.

C. difficile produces two toxic proteins, toxins A and B. In their study, the Monash team constructed genetically-engineered mutants of *C. difficile* that produced only toxin A or toxin B, which colleagues in Chicago injected into animal models.

The results showed that bugs that made toxin B still caused disease, unlike mutants that made toxin A. This disease causing protein is also detected in infected patients.

Why do these findings contradict previous studies? Dr Lyras explains: "We work with whole bacteria, which reflects what really happens in an infection, rather than working on

purified toxins alone as most of our peers have done."

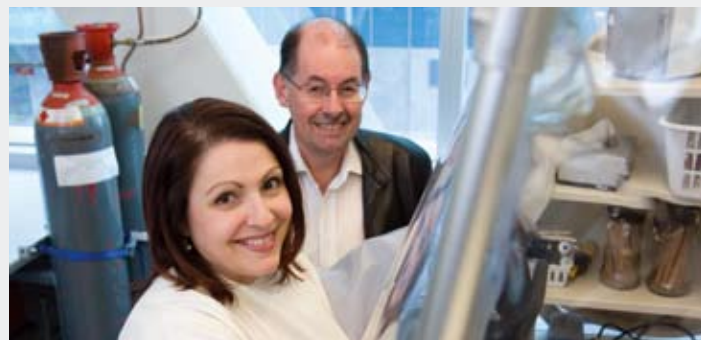
"We're one of only three labs in the world that can do these complex experiments."

Professor Rood agrees. "Taking a toxin away from the bacteria and analysing it has considerable merit," he says, "but it only tells part of the story."

"*C. difficile* diagnosis, treatment and prevention now will need to focus on toxin B."

What's next for the dynamic duo? They plan to nail how pesky *C. difficile* spores lodge in the gut and block that process — and hopefully prevent infection — a challenge they both relish.

"We work on bugs that other people think are too difficult to study, then crack their genetics and figure out how they cause disease," Professor Rood says.



Dr Dena Lyras (left) with Professor Julian Rood



Swimming for science



Zebrafish

They swim gracefully, their shimmering, striped bodies catching the light. But these zebrafish are no decoration. They are helping Monash scientists understand what happens during development and disease. And the FishCore facility where they reside is open for business.

The centre, which is managed by the Australian Regenerative Medicine Institute, is the largest of its kind in Australia. It houses 1000 fish tanks in the quarantine room and can accommodate around 5500 tanks in the main facility.

The water is also recirculated and treated with the latest filtration, sterilisation and monitoring systems to keep the fish disease-free and happy.

Professor Peter Currie, deputy director of ARMI, is a proud parent. "The facility is for everyone to utilise and take advantage of the attributes that zebrafish have, which may complement their own research," he says.

"Zebrafish breed prolifically, lay and fertilise eggs externally, and are optically transparent so you can see all the organs forming. Also, in one afternoon, you can generate all the transgenic zebrafish lines that you need from a genetically-engineered DNA construct."

In Professor Currie's case, these fish allow him to study how muscle forms normally in the embryo and in muscle diseases such as muscular dystrophy where genes are mutated. Also, with the genetic tools available, he can look at how zebrafish embryonic muscle stem cells respond to injury in real time.

"It's really amazing to see a transparent embryo growing and moving under microscope," Professor Currie says.



FishCore aquarium manager Julian Cocks. Photograph by Paul Philipson

From a practical perspective, the fish facility will allow researchers to access the latest zebrafish technologies. Scientists can either collaborate with Professor Currie's team and receive high-end technical support or use the centre independently following some training.

While the high-tech set up of the FishCore facility dazzles visitors, the stars of the show are the stunning zebrafish, growing and multiplying, swimming for science.

Drugs and stroke

Stroke is a devastating disease. In Australia, it is the second-highest cause of death after coronary heart disease and leading cause of disability. Yet there are limited treatments – other than clot-busting drugs that must be given early when stroke symptoms first strike. So the rush is on to better understand this brain disorder and minimise its impact.

PhD student Claudia McCarthy and Associate Professor Rob Widdop from the Department of Pharmacology and researchers at the University of Melbourne are closing the knowledge gap. They have shown that Angiotensin II type 2 receptor, or AT₂R, can protect the brain following a stroke, work that was published in the journal *Stroke*, and the subject of an invited presentation by Claudia to the British Hypertension Society in Cambridge.

In the landmark study, she administered molecules that inhibit or stimulate AT₂R to conscious

rats five days before a stroke, and three days afterwards. They were monitored for behavioural and motor function changes throughout this period, and brain tissue was tested for abnormalities.

What did Claudia see?

"Our control animals were unable to perform motor coordination tasks 24 and 72 hours after a stroke," she says.

"However, with the AT₂R stimulation group, it's like they haven't had a stroke; there is less brain damage, behavioural symptoms were reduced, and our molecule protects neurons that would otherwise die."

"This is the first time that anyone has directly stimulated AT₂R and shown these neuroprotective effects."

Meanwhile, animals that received the AT₂R stimulator together with an AT₂R blocker fared badly on movement tasks, and sustained brain damage.

However, these rats received before and after injury doses of the beneficial molecule in the brain. What happens in real-world conditions? Claudia plans to give new AT₂R-targeting drugs, which can be given peripherally, to rats following a stroke. If this benefit is preserved, these compounds could be potentially used in the future after

a stroke, or in combination with blood pressure-lowering drugs as a prevention strategy.

Time will tell if this approach is viable.

For more information:
www.strokefoundation.com.au



Ms Claudia McCarthy

Sperm tales

Mention male fertility, or sperm development casually and conversations can stop. But not for two new scientists to the School of Biomedical Sciences, who study sperm development from its early beginnings as a stem cell in the developing testis to the mature and functional cell that can fertilise an egg.

Both Associate Professors Moira O'Bryan and Kate Loveland, who arrived from Monash Institute of Medical Research, are passionate about their calling and happy to talk.

"There is a general perception that female infertility is more common than male infertility," says Associate Professor O'Bryan. "It's not. If both partners are younger than 35, the infertility rate is about the same."

"And if a man is stressed, has an infection, broken limbs, or is exposed to environmental toxins, his sperm count will plummet and could take several months to recover."

While Associate Professor O'Bryan has worked with infertile men in the clinic, these days her team can be found scanning reams of microarray-generated data. The detectives at the Department of Anatomy and Developmental Biology localise mutations to key chromosomes, then scour databases for genes that cause infertility in genetically-modified mice with either faulty sperm, or none at all.



Associate Professor Moira O'Bryan

Using this approach, the team has identified two new genes with essential roles in male fertility.

The next step is to look for the mouse infertility genes in human males. To do this, Associate Professor O'Bryan's team can search a DNA database of 3000 infertile men, selecting donors who share the same sperm abnormalities as her mice. They will then check if these infertile men also harbour the same infertility genes as their mouse counterpart.

"With this information we can not only learn how sperm are made," says Associate Professor O'Bryan, "but we may be able to tell men why they are infertile, develop diagnostic

tests and perhaps design male contraceptives in the future."

Associate Professor Kate Loveland is also interested in male fertility. But her main research focus is testicular cancer, a disease where there is no cure.

The established scientist, who has a joint appointment at the Departments of Biochemistry and Molecular Biology, and Anatomy and Developmental Biology, works with male germ cells – immature sperm precursors that begin life in the fetus and mature at puberty.

These germ cells are also linked to cancer. Associate Professor Loveland explains: "They can form any cell and

retain a unique capacity to turn on certain genes that is unlike most cells in our body."

These attributes allow her to study the male germ cell to reveal the cause of testicular and other cancers. In particular, Associate Professor Loveland is interested in the reproductive hormone activin and its role during testis development.

Her team discovered that genetically-modified mice which lack activin have increased numbers of sperm precursors. However, in normal mice the hormone keeps this cell population in check.

"We've identified key target genes for this pathway in the developing testis, when spermatogenesis is kick-starting," says Associate Professor Loveland.

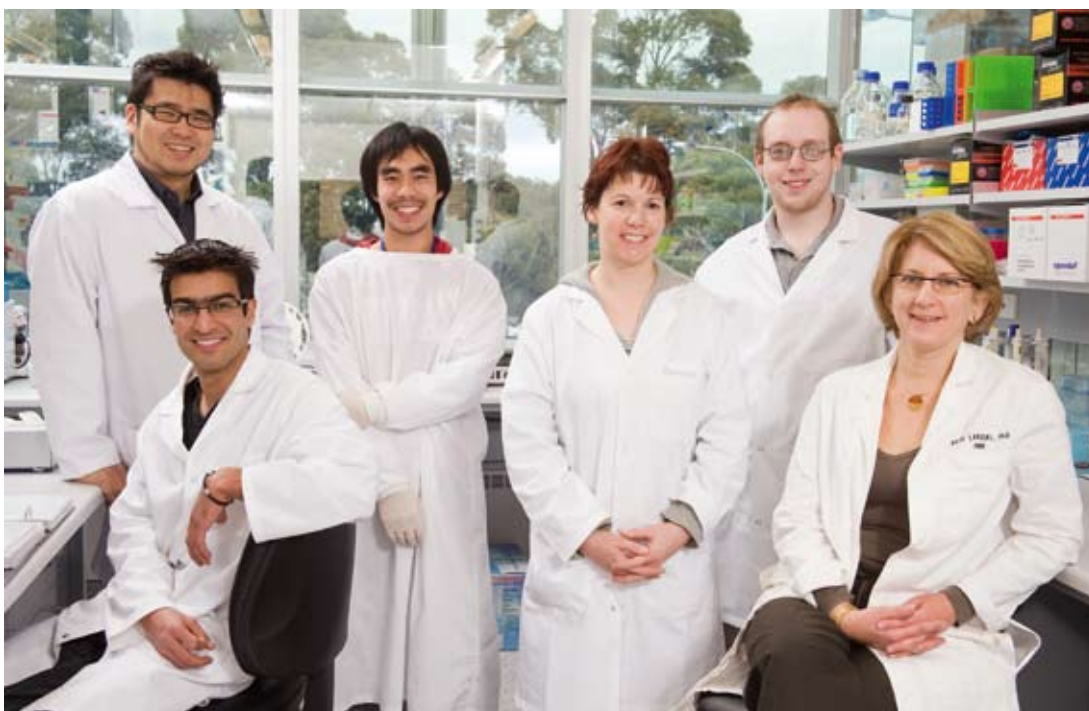
But what happens in men?

In healthy men participating in contraceptive trials, one particular activin receptor subunit is turned on when sperm development is temporarily interrupted. This also happens in the testis of men where testicular cancers are forming.

"This result is important because this particular receptor subunit allows not only activin, but some of its related family members to signal," says Associate Professor Loveland.

"We are now testing which genes that activin regulates in mice are also affected in men with diseased or dysfunctional testes. This will allow us to track the impact of this hormone in both normal development and metastatic disease."

However, the activin story doesn't end with the testis. This molecule and its partners may activate other cells, from virus-infected airways of asthmatic patients to specific blood cells in our bodies. It's Associate Professor Loveland's mission to unite research fields by revealing the common pathways by which activin works to drive key developmental switches in healthy and diseased organs.



Associate Professor Kate Loveland (far right) with her team

The fertile brain

Dr Jeremy Smith has always been interested in reproduction. He figured there were plenty of questions to answer, and infertility would remain an ongoing societal concern.

He was right. Dr Smith has spent ten years studying how hormones control reproduction, and together with Professor Iain Clarke, from the Department of Physiology, he is cementing the role of key molecules and cells in the brain that drive this complex process.

The duo have collaborated with colleagues in Scotland, the US, Spain and South Africa to highlight how a small protein called kisspeptin stimulates the reproductive system. Their work was recently published in *The Journal of Neuroscience*.

Kisspeptin acts through its receptor to stimulate brain cells that secrete gonadotropin releasing hormone, or GnRH, a chemical master switch that triggers the onset of puberty and regulates other reproductive molecules in males and females.

To prove this important function, Dr Smith and colleagues worked with inhibitors of kisspeptin. The Monash scientist administered a blocking peptide to female sheep, and showed that 'pulses' of brain

and pituitary gland hormones that control reproduction were markedly reduced. Overseas colleagues showed similar effects in mice, rats and monkeys – indicating that kisspeptin plays a critical role across species.

"These data show that kisspeptin is essential for driving the reproductive system," Dr Smith says.

"However, the question that remains is what drives kisspeptin? Sex steroids, nutrition and the environment are all key candidates."

A kisspeptin inhibitor could be potentially used to suppress reproduction in the lead-up to IVF, to treat hormone-dependent cancers in men and women, and delay early-onset puberty. Second-generation kisspeptin inhibitors that can be delivered to the body as a nasal spray or skin implant rather than injected into the brain are being developed.

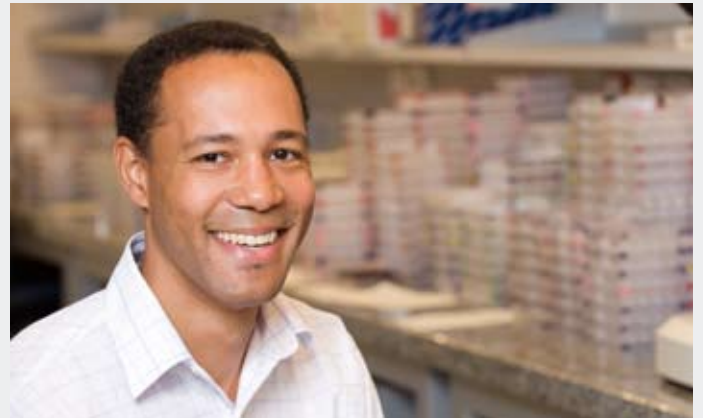
Professor Clarke, who has spent 30 years studying reproduction, is delighted with the research findings.

"This is the biggest advance in 20 years. It enables us to understand how the brain regulates the reproductive system."



Dr Jeremy Smith

Of insects, mice and man



Dr Fasseli Coulibaly

Take an unconventional global health research idea, apply for funding, and the chances of success are usually slim.

Enter the philanthropic Bill and Melinda Gates Foundation, which is paying 81 scientists worldwide \$US 100,000 each to test bold concepts. And Dr Fasseli Coulibaly, from the Monash Department of Biochemistry and Molecular Biology, is one happy recipient.

The 34-year-old French expatriate has devoted his research career cracking the three-dimensional structures of viruses: from birnaviruses of fish and poultry to poxviruses that affect animals and humans, and baculovirus that infects insects.

"Viruses have everything I want," Dr Coulibaly says. "You can study them at the molecular level and also have an impact on public health."

Now he is translating his passion to designing low-cost vaccines against HIV and potentially other human illnesses. But rather than use conventional vaccine vectors or carriers, Dr Coulibaly will use sugar cube-like crystals, called polyhedra, from an insect virus harmless to humans to try and coax the immune system into action, and thwart the threat when it appears.

"We want to prove that these polyhedra are better than existing ways of presenting foreign molecules to the immune system. We will be comparing polyhedra containing the HIV-1 Gag protein with soluble HIV-1 Gag alone," Dr Coulibaly says.

To achieve this goal, he has partnered with Associate Professor Johnson Mak, an HIV assembly expert from the Burnet Institute, who has supplied the HIV gag gene for the vaccine. The challenge for the Monash team is to produce in insect cells a crystalline vaccine that contains enough HIV-1 Gag for testing in mice. Associate Professor Rosemary Ffrench, an immunologist, also from the Burnet Institute, will check if mice mount immune responses to the candidate vaccines.

The stakes are high but Dr Coulibaly is cautious. "It would be fantastic if we could make a promising HIV vaccine," he says. "It's challenging and it might not happen. But it is one of our long-term goals."

If Dr Coulibaly's novel vaccine is a star performer, the health applications would be extraordinary. And future funding for ongoing research would be assured. He has a year to find the answer.

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