Lab+Life SCIENTIST

CAN YOUR MICE TRAIN THEMSELVES?

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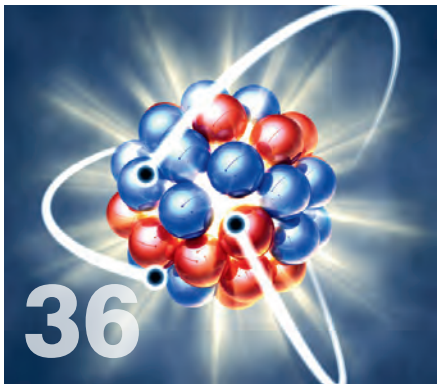

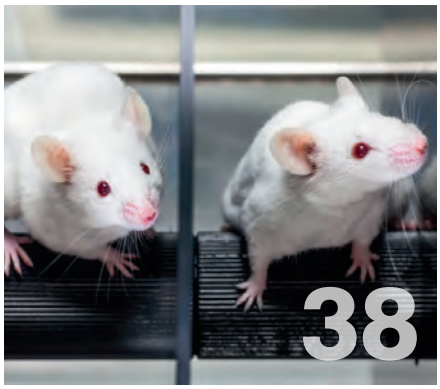

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An unclear path with significant challenges and rewards

Welcome to *Lab+Life Scientist*'s final issue for 2017. US scientists recently made the first ever attempt to edit a gene inside the human body, with the hopes to cure Hunter syndrome, a rare genetic disorder.

CRISPR was earlier used to correct mutation implicated in a heritable heart condition in preimplantation human embryos using the CRISPR-Cas9 genome editing technique. The technology has been used in a variety of applications — to make superbugs kills themselves, turn bacteria into a molecular tape recorder, improve crop efficiency and provide sustainable biofuel. It holds great promise for medical sciences; however, with different regulatory frameworks around the world there are fears about potential misuse of technology.

This issue features items on a range of topics, from lab automation to cryo-electron microscopy and exon skipping. The lead article provides insights on the current state and future of cryo-EM from Professor Richard Henderson, the winner of 2017 Noble Prize for Chemistry. Henderson is visiting Australia in February to present at the 43rd Lorne Conference on Protein Structure and Function (5–8 February). The conference is a part of the five-event series to be held in Lorne, Victoria. Other conferences are: 22nd Lorne Proteomics Symposium (2–5 February); 29th Lorne Cancer Conference (9–11 February); 38th Lorne Genome Conference (12–14 February); and 7th Lorne Infection and Immunity Conference (15–17 February). The annual three-week conference series will feature a number of leading international and local experts across a range of fields. Two other Lorne presenters covered in this issue include: Professor Steve Wilton, the Foundation Chair in Molecular Therapies at Murdoch University and Director of the Perron Institute for Neurological and Translational Science and co-head of Molecular Genetic Laboratory, and Dr Michael Gantier, an ARC Future Fellow, Research Group Head, Nucleic Acids and Innate Immunity at the Hudson Institute in Melbourne.

In this issue we also learn about a high-throughput system to study mouse behaviour and physiology at a much faster rate than that achieved via manual methods. The system aims to deliver large, standardised datasets, a reduction in the number of experimental animals and time savings through complete automation.

There is also an article about a new 'LabBag' — an all-in-one system in the form of a transparent bag that provides a cheap, fast and sterile way for scientists to grow, differentiate and freeze stem cells. Inside this bag, artificially produced stem cells are able both to grow and to form 3D aggregates in a sterile environment. These cells can be used by the pharmaceutical industry as patient- or disease-specific test systems for drug development and research into active ingredients. To learn more, go to page 17.

Regards,
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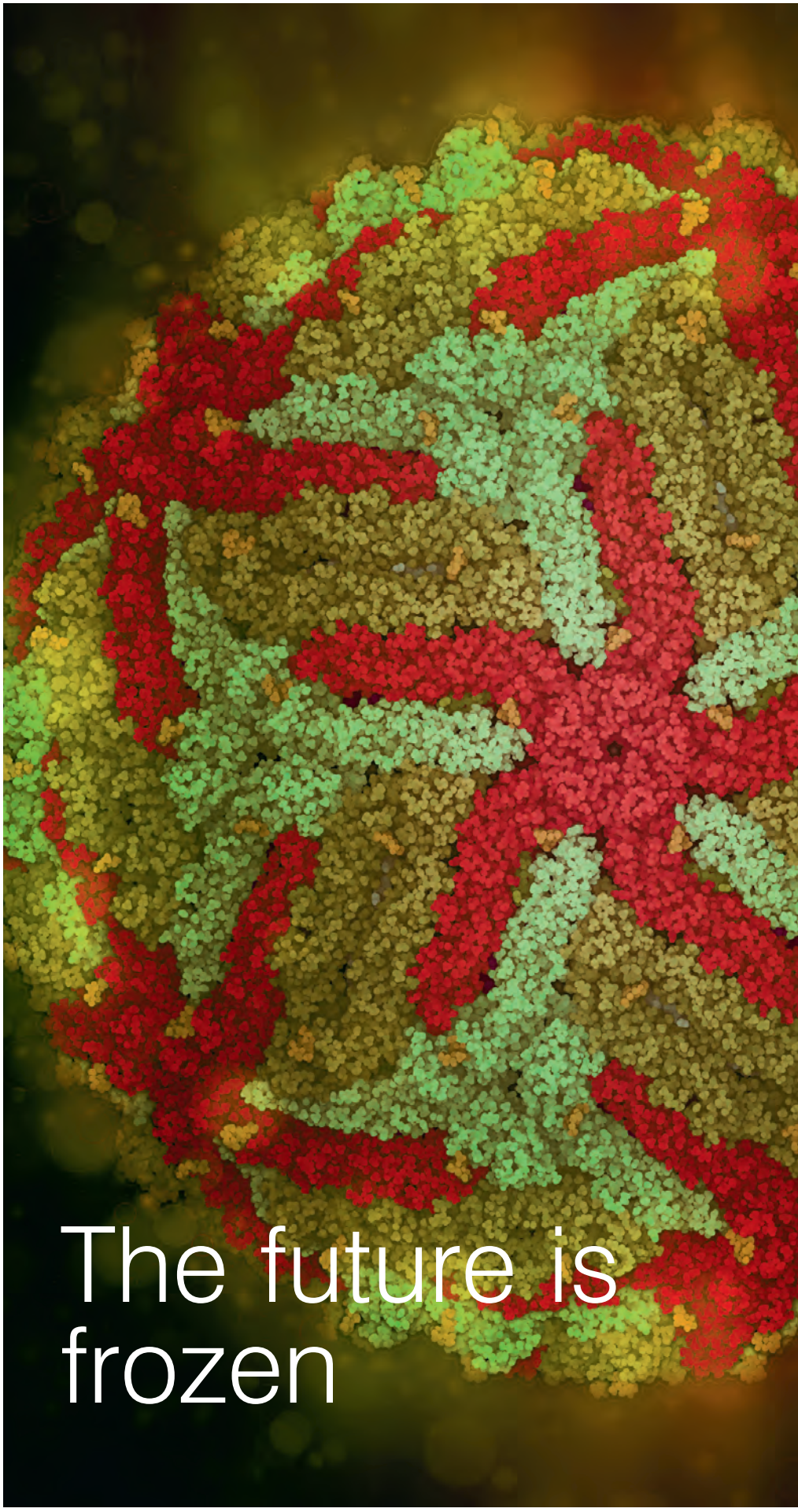
Mansi Gandhi

The future is frozen

Cryo-electron microscopy (cryo-EM) may not yet have revolutionised the world of medicine but it has definitely transformed the field of structural biology.



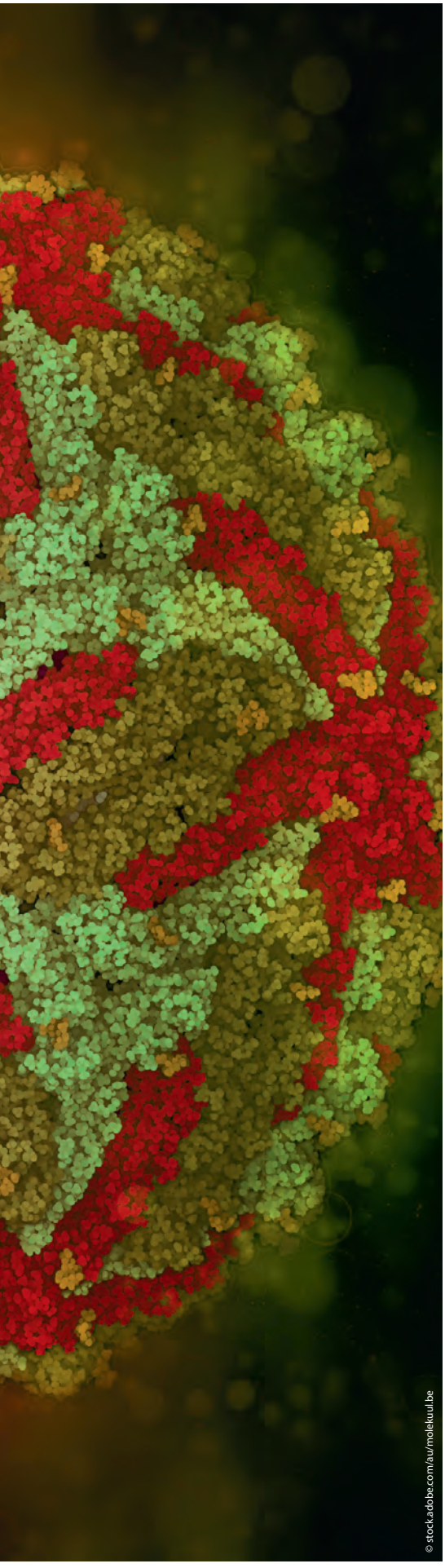
In October, Scottish physicist turned molecular biologist Professor Richard Henderson from MRC Laboratory of Molecular Biology, Cambridge, UK, along with Jacques Dubochet, University of Lausanne, Switzerland, and Joachim Frank, Columbia University, New York, was awarded the 2017 Nobel Prize for Chemistry "for developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution".

The technique allows researchers to freeze biomolecules mid-movement and visualise processes they have never previously seen, which is decisive for both the basic understanding of life's chemistry and for the development of pharmaceuticals, according to The Royal Swedish Academy of Sciences. Their technology has moved biochemistry into a new era, according to the academy.

Professor Henderson will soon be visiting Australia to present at the 43rd Lorne Conference on Protein Structure and Function, to be held from 4–8 February in Lorne, Victoria. Henderson will provide an overview of the current state of cryo-EM, and discuss "how there are still many improvements that can be made before the approach reaches its theoretical limits".

Making a near-perfect method

Recent years have seen major technology advances in cryo-EM but there is still a long way to go. "Although the field of single particle electron cryomicroscopy (cryoEM) is already producing many valuable structures that cannot be obtained by any other method, there are still a number of significant improvements that we expect to



Biochemistry is now facing an explosive development and is all set for an exciting future.

make the method even more productive," said Henderson.

"We expect the main developments to be (a) bigger, faster and better electron imaging detectors, (b) more robust and reliable quarter phase plates and (c) a reduction in beam-induced specimen motion which blurs the images, obtained by improvements in the specimen supports," he said.

"Our goal is to make cryo-EM into a near-perfect method limited only by fundamental physics, such as radiation damage, which is the only fundamental limitation," said Henderson.

Over the last 20 years, the great improvement of the power of conventional synchrotron X-ray beam lines has been one of the most exciting developments in structural biology, Henderson said. "These X-ray sources have been made brighter and more automated and have been equipped with more efficient X-ray counting detectors, so that macromolecular crystallography is now producing over 10,000 new structures deposited in the Worldwide Protein Data Bank (PDB) each year, from a wider range of specimens using smaller and smaller crystals. There are now 135,000 macromolecular coordinate datasets deposited and downloadable by anyone who wants to use them from the PDB."

Molecular medicine

In the past few years, cryo-EM has been used in a variety of scientific studies, from Zika virus to antibiotic resistance. Biochemistry is now facing an explosive development and is all set for an exciting future, according to the academy.

When asked about how cryo-EM could transform the future of health and medicine, Henderson said, "I'm afraid cryoEM has not (yet) transformed health and medicine. It is still too early and the method has only been operating to produce really high-resolution structures since around 2013."

X-ray crystallography took 30 years to become useful for "structure-based drug design" — from 1959 when we had the first (myoglobin) protein structure until 1990 when it was adopted by many pharmaceutical companies, said Henderson.

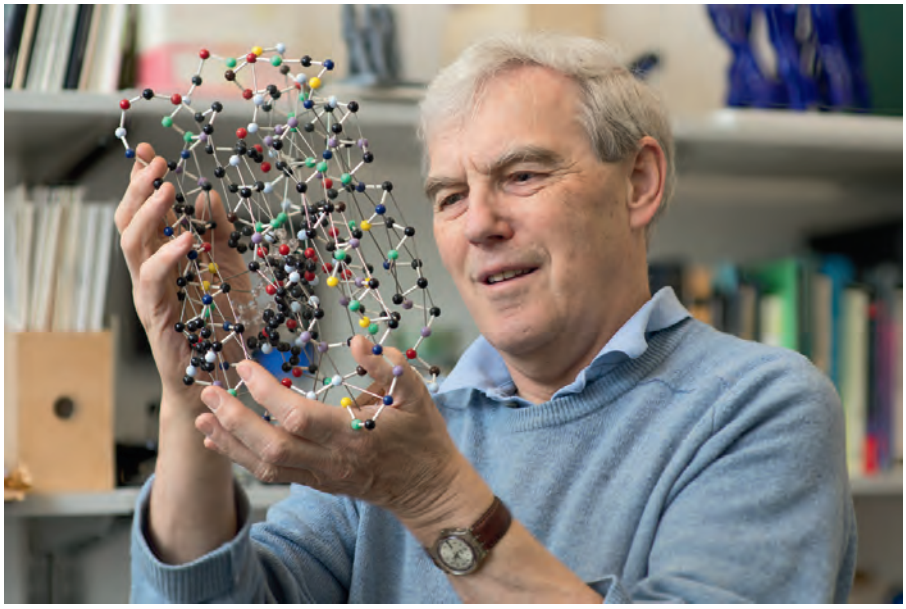
"CryoEM will not take so long, because numerous pharma companies have already started to use it. In the slightly longer term, cryoEM will be used to help to develop many new drugs — drugs that either activate or inhibit a particular disease-related process — to either cure or ameliorate the problem."

The cost challenge

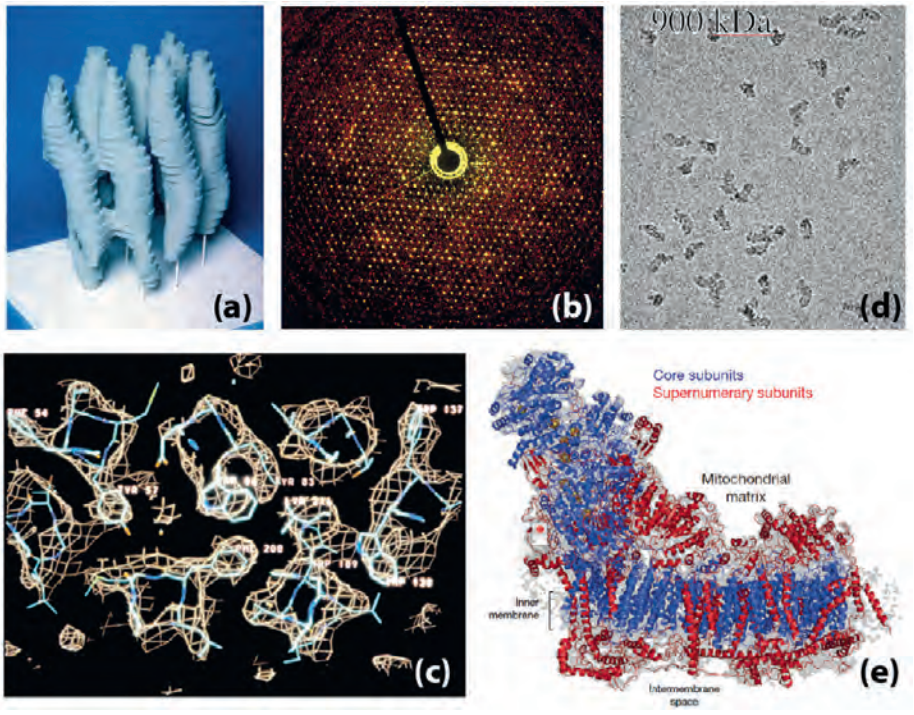
Cost, however, is one of the major factors limiting the spread of cryo-EM. "We are hoping to make cryo-EM less expensive — to democratise it," said Henderson.

In a paper published in Cambridge University Press Journal *Quarterly Review of Biophysics*, Henderson and his colleague Kutti R Vinothkumar discuss the need for affordable cryo-EM. "At present, the performance advantage of 'high-end' cryoEM ('high' because of the large associated capital and running costs of a 300 keV facility) means that those groups and institutions that have access to the best equipment have an enormous advantage over those without such access," the authors said in the paper.

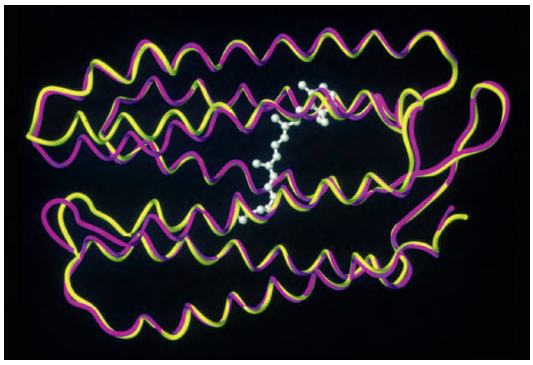
"Since an installation with equipment that can deliver the best quality images can cost £5m (AU$8.7m) with annual running cost including management in the range of ~£250,000 (AU$433,516), this acts a barrier to providing access for research groups that are not located in a major centre. One solution to the problem would be to provide national (eg, Saibil et al. (2015) for cryoEM in the UK) or international facilities best illustrated by the success and wide availability of third generation synchrotron sources for X-ray diffraction studies (eg, ESRF, SPring-8).



Richard Henderson looking at 1990 bacteriorhodopsin model. Image courtesy of MRC Laboratory of Molecular Biology.



(a) 1975 bacteriorhodopsin model, (b) bacteriorhodopsin electron diffraction pattern, (c) 1990 3D map plus model of bacteriorhodopsin (d and e) cryoEM image and molecular model of mitochondrial Complex I. Image credit: Gjonnes_collage.



Ground-state bacteriorhodopsin structure (purple) compared with a triple mutant (yellow) that resembles the trapped M-intermediate, from Subramaniam & Henderson, 2000. Image courtesy of MRC Laboratory of Molecular Biology.

"The preparation of suitable specimens for cryoEM also requires a lot of preliminary evaluation. Alongside the need for excellent biochemistry, there are many pitfalls along the route to producing a perfect cryoEM grid with a good distribution of single particles that are not denatured at the air–water interface, aggregated, stuck to the support film or suffering from preferential orientations.

"To overcome this list of typical problems requires (preferably) daily access to a cryoEM facility that is good enough for characterisation of any specimen preparation problems, and for collection of small diagnostic datasets. High electron energy is not necessary in such a diagnostic tool since good images can be obtained at 100 keV. However, the coherence of the electron source makes an enormous difference to the detail visible in the highly defocussed images that are needed to observe internal structure in smaller proteins. At present, it is not possible to interpret clearly images of protein assemblies of 150 k Da without the higher defocus that can be used with the much higher coherence of a field emission gun (FEG)."

Diagnostic cryoEM

Thus alongside the availability of state-of-the-art 'high-end' electron cryomicroscopes, the structural biology field also desperately needs an inexpensive diagnostic cryoEM, the authors said in the paper. "Such an instrument is needed for preliminary evaluations, and should be able to achieve good enough resolution to evaluate the intrinsic quality of the specimens once a suitable particle distribution has been obtained.

"This local characterisation of specimens and grids could then feed into and make the best use of regional, national or international resources where higher resolution cryo-microscopes with greater automation could be available.

"It is certainly unrealistic to expect every laboratory to be able to afford a state-of-the-art facility, which at present needs to include a 300 keV Krios or similar high-end instrument, plus a direct electron detector and possibly also a zero-loss energy filter.

"Given the cost of these higher voltage microscopes (due to the need for X-ray shielding and high voltage power supplies), it would be sensible to aim for a 100 or 120 keV instrument for the general market with a FEG electron source (500x brighter than a tungsten filament) and an efficient inexpensive detector at perhaps one tenth of the cost of the 'high-end' instruments."

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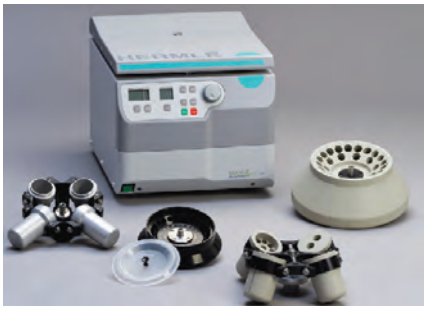

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Nanomanipulator enables UNSW researchers to probe the inner workings of cells

The mechanism of how cells work is key to understanding how tumours metastasize as well as tissue regeneration and other bodily functions. The process of mechanotransduction, or how a cell converts a physical stimuli into an electrical response, is fundamental to these understandings.

Dr Kate Poole, Group Leader — Cellular Mechanotransduction, University of New South Wales and her team are carrying out cutting-edge research into the molecules that are produced following exposure to a mechanical stimulus and how they interpret these molecules. Her team also works with the EMBL (European Molecular Biology Laboratory) Australia node for Single Molecule Science.

One of the challenging parts of Poole's research is to be able to 'poke' cells in a precise and repeatable fashion at the cellular level that replicates physiological conditions. To achieve this, she grows cells on a pillar array, akin to a microscopic bed of nails. She can then poke the cells using individual pillars using a piezo-controlled nanomanipulator that is gentle enough to apply a specific load without rupturing the cell membrane. Her focus is on two main areas: how cells in cartilage respond to mechanical stimuli, which has relevance to osteoarthritis, a degenerative condition that affects 1 in 11 Australians or over 2.1 million people; and how cells that migrate through the body sense the mechanics of their surroundings, which will provide insights into how cancer cells divide and spread.

Poole's current research at UNSW takes her postdoctoral work at the Max Delbrück Center for Molecular Medicine in Berlin to the next level. Poole's lab in Berlin used a Kleindiek MM3A-LM nanomanipulator and she said "the set-up worked incredibly well" and "there was no way that I was going to use anything that wasn't the Kleindiek". So, her lab in Australia is now equipped with two of the same nanomanipulators.

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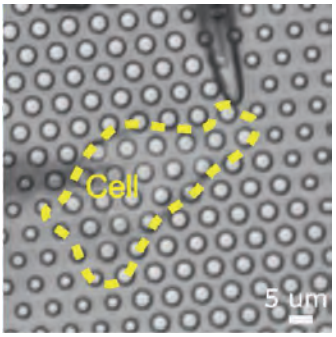

Kleindiek MM3A-LM manipulator tip (top) precisely 'poking' a pillar array (light circles) to stimulate a cell. Image courtesy of AXT.

Lead poisoning is the top risk factor for pre-eclampsia, says study

Griffith University researchers have found that lead poisoning is a major risk factor for pre-eclampsia, a disease which kills over 75,000 women internationally each year and is responsible for 9% of all foetal deaths.

Pre-eclampsia is a silent killer in which pregnant women develop high blood pressure and protein in their urine due to kidney malfunction, potentially leading to cardiac and/or kidney failure and eventual disability or death. Previously established risk factors include obesity, prior hypertension, older age and diabetes mellitus; now, the Griffith researchers have added to this list.

Published in the journal *Environmental Research*, the Griffith study reviewed the results of 11 previous international studies that measured blood lead levels of pregnant women who experienced pre-eclampsia and control groups of women who did not experience pre-eclampsia.

"We found that the link between high blood lead levels and pre-eclampsia is twice as strong as the risk from diabetes and is as big a risk as chronic high blood pressure," said Dr Arthur Poropat from Griffith Health.

"There is a clear dose-response relationship between maternal blood lead and pre-eclampsia: doubling the blood lead level results also doubles the risk of pre-eclampsia. Even relatively low levels of lead increase the risk of the condition."

Dr Poropat said women are exposed to lead in many ways, including through lead paint, lead-contaminated soils, lead water pipes, shooting lead bullets at firing ranges and other sources. They can even be exposed by handling or washing their spouse's lead-contaminated clothes.

"Fortunately, most people in Australia are not at risk of lead poisoning as they are not commonly exposed to lead via their occupation or the environment," Dr Poropat said. "However, there are certain well-documented risk areas within the country, including the industrial regions of Broken Hill (NSW/SA), Mount Isa (Qld) and Port Pirie (SA).

"Regardless of where women are located or their lifestyle, women should be aware of the risks associated with lead poisoning if they are preparing to become pregnant or are currently pregnant.

"Following exposure, the body struggles to get rid of lead, and 90–95% of the lead becomes stored in human bones. Tragically, when mothers' bones release calcium during pregnancy to help the foetus grow, lead is also released from the bones, resulting in the mother exposing herself and her foetus to lead.

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Too sterile for science? Gut bacteria transplants boost health in lab mice

Have you ever wondered why experiments in lab mice, such as vaccine studies, turn out very differently in humans or other animals? According to US researchers, the problem lies with the test subjects' gut bacteria.

All mammals depend on their microbiota, the collection of microorganisms they host in and on their bodies. Evolution shapes each animal's microbiota, favouring populations of microorganisms that help the animal survive their environment and diseases they encounter.

But laboratory mice aren't random house mice. They are carefully bred, fed and raised in tightly controlled conditions so that each mouse has predictable traits and genetics. This is a great advantage in basic biology research, but creating that predictability means that a controlled environment, and not the survival pressures of the outside world, shaped the microbiotas of laboratory mice.

"We hypothesised that this might explain why laboratory mice, while paramount for understanding basic biological phenomena, are limited in their predictive utility for modelling complex diseases of humans and other free-living mammals," said Stephan Rosshart, a postdoctoral fellow at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and first author on the new research.

Rosshart and his colleagues decided to give laboratory mice back what they have lost: a naturally co-evolved wild mouse gut microbiota. To achieve this, the researchers trapped more than 800 wild mice from eight locations to find healthy, suitable candidates for a gut microbiota donation. They then tested and compared the gut microbiomes of the wild mice (*Mus musculusdomesticus*) and a common strain of laboratory mice, called C57BL/6, from multiple sources.

Writing in the journal *Cell*, the researchers confirmed that C57BL/6 mice had distinct gut microbiomes from wild mice.

The researchers engrafted the microbiota of wild mice to pregnant, germ-free C57BL/6 mice, which are raised in a sterile environment and don't have microbiomes of their own. For a control group comparison, the researchers also engrafted microbiota from regular C57BL/6 mice into a separate group of pregnant, germ-free mice. Four generations later, the mice still carried either the wild microbiomes or the control laboratory microbiomes passed down from their foremothers.

When exposed to a high dose of influenza virus, 92% of the laboratory mice with wild microbiomes survived, whereas only 17% of laboratory mice and mice in the control group survived. In other experiments, the laboratory mice with wild microbiomes had better outcomes in the face of induced colorectal tumours, whereas the other mice had a greater number of tumours and more severe disease. The beneficial effects of the wild microbiota were associated with reduced inflammation in both models.

With more work and evaluation needed for definitive results, the researchers hope to improve and expand on the method of using natural microbiomes in laboratory mice.

Biotron compounds demonstrate antiviral activity against hep B

Australian biotechnology company Biotron has announced that several of its compounds have demonstrated significant antiviral activity against hepatitis B (HBV) in recently completed preclinical studies. The studies were completed in the USA in cell culture models that are considered 'industry standard' and are well recognised by potential pharma and biotech partners.

The World Health Organization estimates that 257 million people are infected with HBV and that up to 900,000 die every year from the disease, for which there is no cure. Pharmaceutical companies such as Gilead, Janssen and Merck currently have active programs developing drugs to treat HBV, as do US biotech companies such as Alnylam, Arrowhead and Arbutus.

"Although Biotron's work on its HBV compounds is preclinical, the interest level in the development of HBV treatments is at an all-time high," said Biotron Managing Director Dr Michelle Miller. "We are seeing evidence of this in the number of early-stage deals and collaborations being currently being undertaken in the sector. We believe this may provide Biotron with an early-stage development opportunity with an appropriate partner."

The news comes two weeks after Biotron revealed it has received an R&D Tax Incentive refund of $1.6 million for the 2016–17 financial year. The refund results from expenditure on the company's antiviral drug development programs.

"Whilst Biotron is fully funded for its current activities, which include the current Phase 2 HIV-1 trial (BIT225-009), this R&D cash rebate will strengthen the company's cash position and support commercialisation activities," Dr Miller said.

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How crop genome controls the time a seed wakes up

Scientists at La Trobe University and the University of Western Australia have made a seed germination breakthrough.

"Scientists and crop breeders have been interested in seed dormancy and germination for a very long time," said La Trobe University's Dr Mathew Lewsey. "They breed carefully to control it in many crops because it affects their yields enormously."

Lewsey and his colleagues' research, published in the journal *Genome Biology*, is beginning to decipher how a crop's genome can control the time that a seed wakes up.

With the knowledge gained from this research, Dr Lewsey hopes to perfect the genome-editing technology necessary to produce new plant cultivars that germinate differently, giving farmers the ability to precisely control when their crops are ready for harvest.

"We want to be able to control when seeds wake up and how quickly they do it," he said.

Dr Quentin Gouil, also of La Trobe University's Centre for AgriBioscience, said the boon for food security around the world would be incredible for staple foods such as rice, corn and wheat.

"The production of beer and spirits would also benefit from this level of control, along with medicines such as morphine and codeine," said Dr Gouil.

"Farmers and brewers can produce higher quality products if they know exactly when their seeds will wake."

Colleague Dr Reena Narsai, from the ARC Centre of Excellence in Plant Energy Biology at La Trobe University, is excited about the opportunities that could arise from this research in coming years.

"Our next move is to transfer our findings from the model research plant *Arabidopsis* into crop plants such as barley and rice," she said.

"New cultivars of plants that germinate as growers want would be permanently modified so that when those plants are propagated, their seeds and the offspring from those would all have the new behaviour.

"We will look to generate varieties that have accelerated or slowed down germination and will study how they control the genetic switches that turn this off and on."

The study was conducted by researchers from the La Trobe University Department of Animal, Plant and Soil Sciences at the Centre for AgriBioscience, the ARC Centre of Excellence in Plant Energy Biology and the University of Western Australia.

Monkey business pays off for award-winning microbiome researcher

Dr Michael Montague from the University of Pennsylvania has been declared the winner of the 2017 Microbiome Awards, sponsored by assay technology company QIAGEN.

The annual awards program seeks to provide extraordinary scientists with recognition for their scientific work in the field of microbiome research. The judging panel consists of independent, distinguished representatives from various institutions and universities who are currently leading the field of microbiome research.

Dr Montague's award-winning project aims to examine how varying degrees of social interaction impact the gut microbiome in rhesus monkeys. It will also explore how the diversity of gut microbial communities influences levels of peripheral and central serotonin.

Dr Montague will first measure female social behaviour, followed by shotgun sequencing of gut microbiomes from faecal samples and serotonin collection from whole blood and cerebrospinal fluid. Socially integrated females who interact more frequently in pairwise grooming are expected to possess more diverse gut microbiomes and lower serotonin levels.

The ramifications of serotonin in modulating behaviours such as mood, arousal and pain signal its importance to not only the brain-gut-microbiome axis but also for understanding various human disorders, including autism, depression and anxiety, that arise from defective signalling or abnormal metabolism of serotonin.

As main sponsor of the award, QIAGEN has donated prizes of up to US$65,000 in value to Dr Montague. He will receive a research package consisting of a two-year licence to Microbial Genomics Pro Suite; analysis of 250 samples using the Cosmos ID Genomics Platform; NGS library prep of 96 samples using any NGS library prep kit or US$3000 in NGS library prep services; sample prep of 400 samples using any DNA or RNA isolation kit or US$3000 in sample prep services; and a QIAcube instrument.

Applications for next year's Microbiome Awards will open in May. The 2018 awards will include a new category for students in the process of completing their PhD.

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Reversible 'master switch' for developmental genes discovered

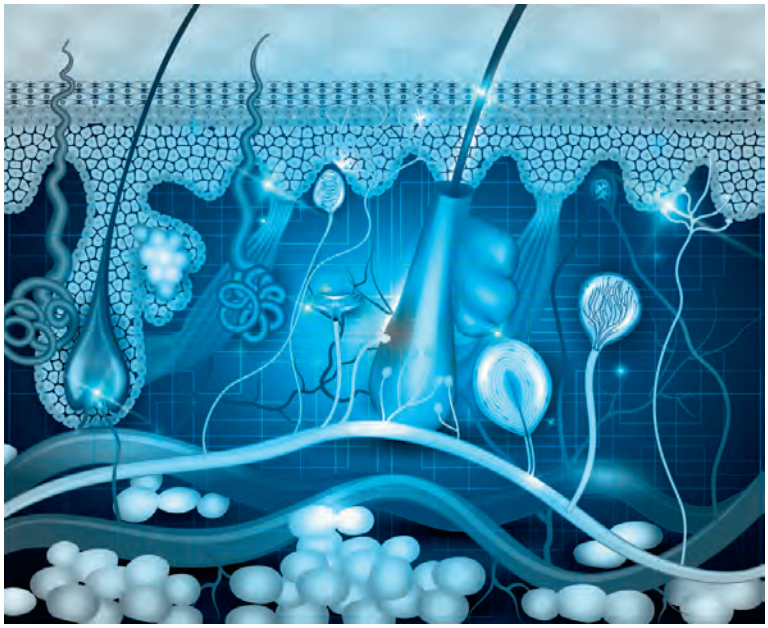
Researchers from Brigham and Women's Hospital (BWH) have identified a reversible 'master switch' on most developmental genes in the common fruit fly, a powerful model organism for studying how human genes are organised and function.

The human genome contains billions of DNA 'letters' that can only be read as words, phrases and sentences with the help of proteins that, metaphorically, mark the DNA with punctuation. Together, the DNA-protein combinations form chromatin, which provides the essential annotation for gene transcription.

However, it is still not understood how the annotation and readout of a single genome differs across cell types. The differences are crucial for normal development and are mutated in cancer. Currently, it is thought that different combinations of proteins act at each of the thousands of genes, and deciphering the numerous complex patterns is a difficult task.

Led by principal investigator Mitzi Kuroda, the BWH researchers identified a reversible master switch that sat on potentially all developmental genes in their model organism, the fruit fly. Their bivalent master switch model provides a conceptually simple explanation for how each developmental step is made along the path to different cell types, dependent on cell type-specific proteins, but acting through this common module.

According to the researchers, the fly model is likely to extend and synergise with seminal work by Harvard Medical School Professor Brad Bernstein and colleagues on the regulation of key developmental genes in mammalian embryos. It has been published in the journal *Genes & Development*.



Scientists grow genetically modified skin using stem cells

Scientists have reconstructed a fully functional epidermis, covering approximately 80% of the total body surface area, for a seven-year-old boy with a genetic skin disease called Junctional Epidermolysis Bullosa (JEB). The findings are reported in *Nature*.

JEB is a severe, often lethal, genetic disease that causes the skin to become fragile. Mutations in the genes LAMA3, LAMB3 or LAMC2 affect a protein called laminin-332 — a component of the basement membrane of the epidermis — leading to blistering of the skin and chronic wounds, which impair the patient's quality of life and can lead to skin cancer.

After all established therapies had failed, the medical team from Ruhr University Bochum, Germany, in collaboration with Prof Dr Michele De Luca from the Center for Regenerative Medicine at the University of Modena, opted for an experimental therapy — the transplantation of genetically modified epidermal stem cells. Obtained from the patient via skin biopsy, these stem cells were processed in Modena. The researchers transferred the intact gene into acquired stem cells. During this process, so-called retroviral vectors were deployed, ie, virus particles that had been specifically modified for gene transfer.

The genetically modified stem cells had been cultivated in a clean room laboratory and subsequently turned into transgenic transplants. The transplants were applied to the boy's arms and legs, entire back, flanks, and partially to the stomach, neck and face as well. "Overall, 0.94 square metres of transgenic epidermis were transplanted onto the young patient in order to cover all defects, accounting for 80% of his entire body surface," said Associate Professor Dr Tobias Hirsch, Plastic Surgeon from Bochum Children's Hospital.

Over the course of the next 21 months, the regenerated epidermis firmly adhered to the underlying dermis, even after induced mechanical stress, healed normally and did not form blisters.

Through the process of clonal tracing, the authors found that the human epidermis is sustained by a limited number of long-lived stem cells which are able to extensively self-renew and can produce progenitors that replenish terminally differentiated keratinocytes.

Because of its large scale, the case is considered unique on a worldwide level. "Transplanting 80% of the skin and providing intensive medical care to the patient over a period of eight months was extremely challenging," Tobias Rothoeft and Tobias Hirsch pointed out. "The close collaboration between the departments in Bochum and the University of Modena's expertise have been the key to success. This makes us very proud."

A miniature laboratory in a plastic bag

Fraunhofer researchers have developed an all-in-one system in the form of a transparent bag that provides a cheap, fast and sterile way for scientists to grow, differentiate and freeze stem cells. It is believed that the cell models produced in the 'LabBag' can be used for toxicity tests and drug development.

Scientists worldwide are looking for ways to heal diseases using stem cells, which offer the potential to develop new types of therapies and drugs. Stem cell material also holds the key to researching diseases in a way that was not possible before. However, if researchers are to achieve meaningful and transferable results, there must be an increase in the cell material to be examined. In addition, the latest studies show that 3D cell models reflect the conditions in the human body much more accurately — and the generation of these cell aggregates takes place primarily under sterile conditions in droplet-shaped nutrient solutions.

Now, the Fraunhofer Institute for Biomedical Engineering IBMT, the Fraunhofer Institute for Surface Engineering and Thin Films IST, and the Fraunhofer Institute for Process Engineering and Packaging IVV have pooled their expertise to develop a miniature laboratory in the form of a plastic bag. Inside this bag, human induced pluripotent stem cells — in other words, artificially produced stem cells — are able both to grow and to form 3D aggregates in a sterile environment. These cells can be used by the pharmaceutical industry as patient- or disease-specific test systems for drug development and research into active ingredients.

Hanging droplets without manual pipetting

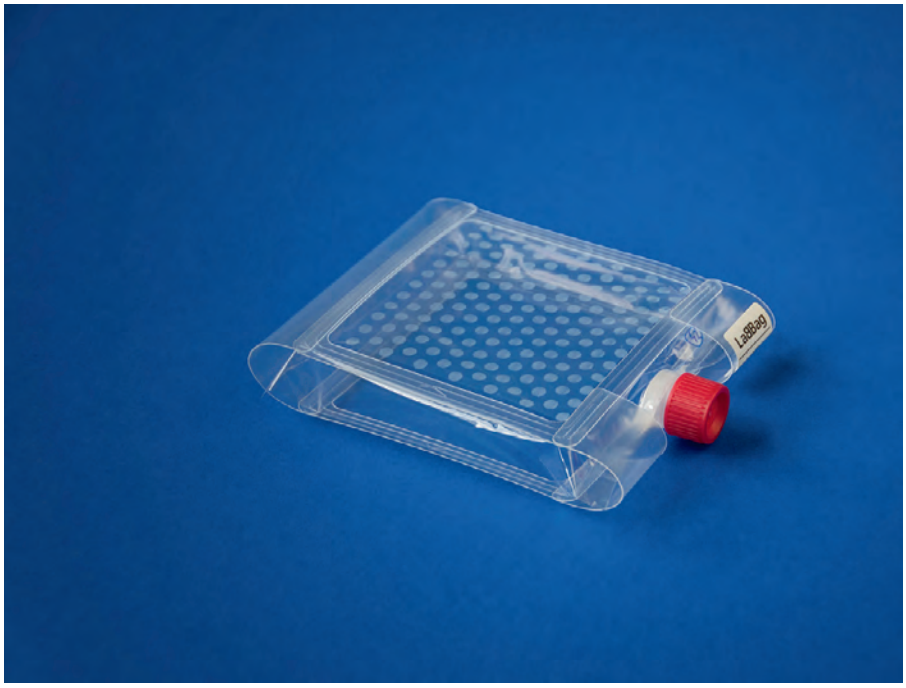
Until now, stem cell aggregates have been generated by using pipette feeder robots — which are expensive to purchase and maintain — or by means of manual pipetting, which is labour- and time-intensive. Manual pipetting in petri dishes requires a lot of practice, and there is also the risk of contamination.

The 'laboratory in a bag' developed by the Fraunhofer researchers aims to reduce the costs of labour and materials while also significantly increasing cell yield and process reliability. Simply by shaking the transparent bag, it takes just a few seconds to produce several hundred hanging droplets of nutrient solution, virtually automatically. The droplets function as mini bioreactors in which cell aggregates are able to form.

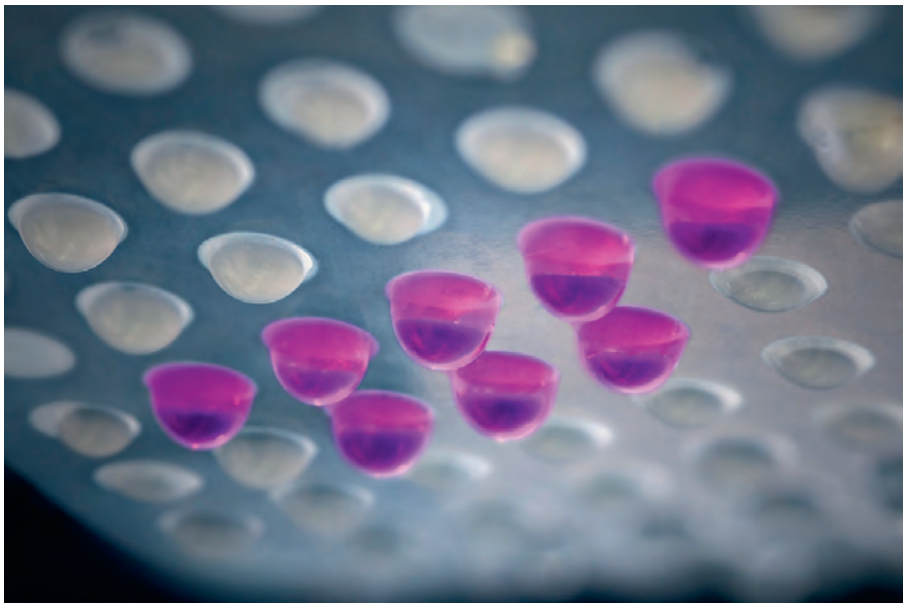
First, the nutrient solution containing the stem cells is poured into the bag. The bag is rotated once and then returned to its initial position. During this process, the droplets remain suspended on round hydrophilic spots. The cells sink to the bottom of the droplets, where they bind together and fuse to form a defined 3D aggregate.

"We have coated the polymer film of the bag with two different coatings," explained Dr Michael Thomas, project manager and scientist at Fraunhofer IST, whose team is responsible for the coating of the polymer film. "A hydrophobic, water-repellent base layer ensures that the nutrient solution containing proteins flows over the surface and doesn't stick to it. However, the second layer consists of 150 hydrophilic round spots, each with a diameter of 5 mm. The solution gets 'caught' on these spots, thus creating the droplets."

To functionalise the surface of the film in such a specific way, the researchers make use of atmospheric pressure plasma processes. In this method, physical plasma is generated in a gas gap between two electrodes by applying alternating voltage. This plasma is then used to treat the surfaces of a wide variety of materials.



The mini laboratory is 150 mm long, 120 mm wide and 20 mm high. The screw cap is made using 3D printing. Hydrophilic spots are visible on the upper interior surface of the bag. ©Fraunhofer IST



3D cell models can form in the hanging droplets. ©Fraunhofer IST

The resulting cell models can even be frozen in the bag — unlike with manual pipetting, where material must be transferred into a separate cryogenic vessel. The cryopreservation process — that is, the freezing of cells — falls within the remit of Fraunhofer IBMT, which is additionally responsible for growing stem cells and for characterising and analysing the 3D aggregates.

"We are focusing on growing induced pluripotent stem cells (iPS), since these have the potential to develop into any cell in the body as well as into any tissue or specific type of tissue," said Dr Julia Neubauer, a biologist at Fraunhofer IBMT. "Unlike embryonic stem cells, they don't provoke any ethical controversies either."

Stem cells become specialised in their shape and capabilities so as to accomplish certain tasks, and this makes it possible to develop patient-specific drugs. Dr Neubauer and her colleagues are focusing on the differentiation into heart muscle cells, and have actually already differentiated iPS cells into cells of this type successfully.

High-quality 3D cell models in 72 hours

Every drop has a volume of approximately 20 µL, and the size of the 3D cell model is around 400 µm. By varying the diameter of the spot on the surface of the bag, the size of the aggregates can be adjusted so as to achieve a targeted expansion of the biological portfolio. At present, Dr Neubauer and her team need roughly 72 hours to produce aggregates in hanging droplets

"We describe our LabBag as a mini GMP laboratory — where 'GMP' is short for 'good manufacturing practice', for which it meets all the requirements. The closed, sterile nature of the system makes the risk of contamination very small. Ultimately, we can produce better cell models for drug research and thereby avoid experiments on animals," Dr Neubauer said. The team plans to integrate sensors for controlling the process.

Fraunhofer IVV and its branch lab were responsible for creating the bag. They took charge of the choice and development of the materials used, including the seal, as well as of designing the bag and its underlying technology.

"We conducted a lot of tests relating to issues such as permeability, the quality of microscopic analysis, biocompatibility, and resistance to temperature and chemicals," said Dr Cornelia Stramm, a scientist at Fraunhofer IVV. "After all that, we decided on polymer films. Previously we had identified 15 groups of polymers, and we examined eight of these."

"The list of requirements for the LabBag was very demanding," added Andrea Liebmann, from the branch lab. "It needed to be highly transparent and adequately retain its shape; it had to be sealable and stackable; it needed to be capable of being sterilised and undergoing cryogenic freezing. The bag also had to offer single-handed operation (self-opening) and good accessibility for the exchange of nutrient solutions. To satisfy these high requirements, we developed a partially automated test rig to produce the bags."

The mini GMP laboratory thus offers the pharmaceutical industry — as well as smaller laboratories with no clean room technology — the opportunity to grow high-quality cell models for drug research without incurring high investment costs. Since it is cost-efficient to make the LabBag, it represents an attractive alternative to traditional approaches.

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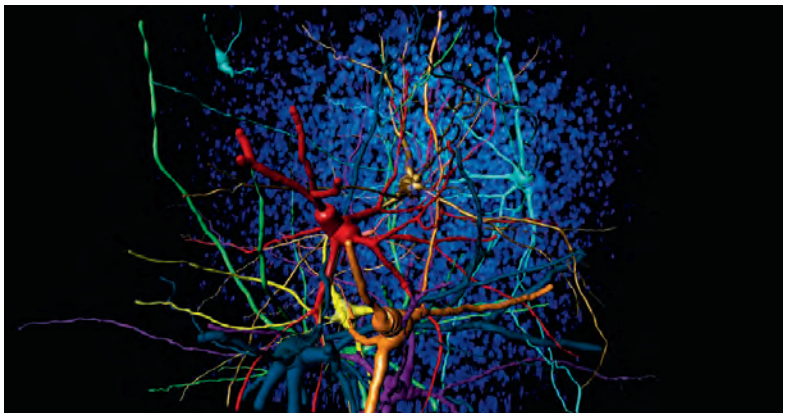
Abcam currently offers over 10,000 recombinant RabMAb antibodies that provide low-background, high-specificity, high-affinity (10^{-12} kD possible) and diverse epitope recognition, with recombinant technology adding high consistency and reproducibility, improved specificity and animal-free production.

In addition to the benefits of recombinant RabMAb antibodies, Abcam validates each one in key applications (WB, IHC, ICC/IF, IP and flow cytometry) and species (human, mouse and rat). They are affinity purified to remove any impurities that could otherwise lead to non-specific signal.

Abcam provides over 3000 directly conjugated recombinant RabMAb antibodies, including popular dyes and enzymes. The company further includes knockout validation via CRISPR technology for a growing number of antibodies.

Abcam Australia Pty Ltd
www.abcam.com



3D/4D image analysis software

Bitplane, a specialist in 3D/4D image visualisation and analysis software, has launched Imaris v9.0. Available for Windows and Mac, the Imaris product line offers what is claimed to be the most powerful and versatile 3D and 4D imaging analysis software solution on the market for researchers in life sciences, medicine and related fields.

Eight modules can be integrated to match the researcher's imaging needs. From data visualisation, analysis, segmentation and interpretation of 3D and 4D microscopy datasets to publication, Bitplane's Imaris products provide a user-friendly and integrated solution.

With Imaris v9, more imaging modalities along with tissue clearing and expansion techniques enable the acquisition of large (hundreds of GBs to TBs) and complex images. Until now, the automated analysis of these images was difficult or impossible. Imaris 9 enables more analysis possibilities for these images with a Billion Triangle Surface rendering model, as well as improved image handling for faster processing of surfaces.

The software includes the ability to interactively render massive surfaces, create surfaces from huge images and load complex surfaces in seconds. It also comes with enhanced volume rendering modes.

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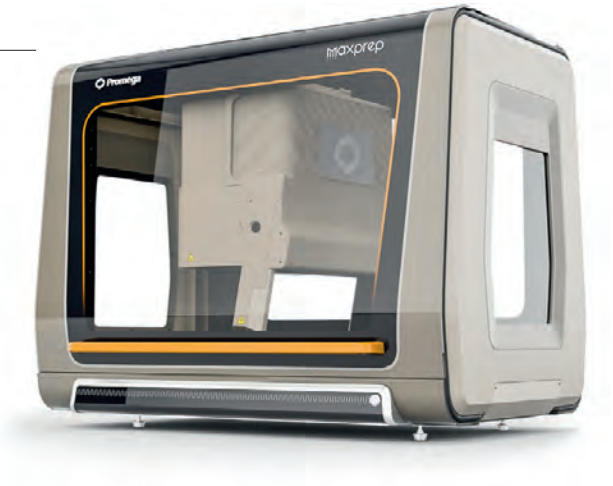


Modular automated nucleic acid preparation system

Promega has developed a modular automated liquid handling and purification system for its Maxwell nucleic acid preparation, which is said to offer labs more compared to large all-in-one instruments. The configurable system works with existing Promega Maxwell RSC instruments with a software upgrade and introduces additional components.

The Maxprep Liquid Handler provides automation for sample preparation of the Maxwell RSC cartridges and trays as well as post-extraction sample preparation for fluorescent quantitation, sample normalisation and a variety of PCR reaction set-ups. The Maxwell RSC 48 Instrument works with convenient, individual prefilled cartridges to process any number of samples from one to 48 without the risk of wasting reagents.

Promega Portal Software allows Maxwell RSC and Maxprep instruments to work together to transfer sample tracking information from one device to the next to build a complete nucleic acid preparation workflow. Data can also be imported into a laboratory information management system (LIMS). Individual instrument modules working together as part of a system provide a number of benefits compared to complete all-in-one workflow systems.

The system offers flexibility and scalability that matches laboratories' changing throughput requirements and budgetary constraints, allowing them to start with a modular workflow to address current sample processing needs and grow the system as needed. It also has functional redundancy, which ensures laboratory workflow is never disrupted, and efficiency that makes smart use of lab space, with compact modules that can be positioned where space permits.

The Maxwell RSC 48 and Maxprep Liquid Handler are supplied with preprogrammed methods that allow for the system to be used by anyone in the lab, regardless of prior instrumentation experience.

Promega Pty Ltd
www.promega.com

The science behind a better brew

A good beer is all about the yeast, but can next-generation sequencing lead to a better brew?

Beer is one of the most heavily quaffed beverages on Earth, and its popularity is only growing, with new breweries sprouting up like mushrooms. But how do you make a great beer with just the right flavour, consistency, aroma and colour? The answer is in the yeast — the microbe that makes grain, hops and water into beer.

"You can take things like flavour profiles, alcohol percentage, the cloudiness, the colour of the beer — yeast genetics are a big contributor to all those things," said Brian Steffy, senior lab manager at Illumina.

But what do we really know about yeast? Until recently, not much. Modern brewing originated in the 1700s, but it's largely been moved forward through trial and error. To learn more, an international group of scientists, yeast producers and beermakers applied next-generation sequencing to yeast — and the results could lead to better beer.

The project began when Steffy ran into Loren Miraglia from Encinitas Brewing Science in Southern California. Miraglia had an interesting yeast strain he wanted to get sequenced. They discussed it over a beer or two, and Steffy suggested they sequence 96 strains, rather than just one.

Miraglia didn't have 96 strains, but White Labs, a yeast producer based in San Diego, did. So White Labs supplied the yeast, Illumina did the sequencing and Synthetic Genomics conducted the analysis. Two Belgian universities collaborated as well. The results were published in the journal *Cell*.

The paper focused on how the domesticated yeasts used to make beer, bread and wine diverged from wild yeasts, and the findings could take some of the guesswork out of beermaking. Knowing a yeast's precise genotype, and the phenotypic traits they confer, could boost quality control.

"A lot of brewers struggle with consistency," said Steffy. "If you scale up, the beer never really tastes the same. A lot of that could have to do with the yeast. Maybe it doesn't handle bigger batches. You can make choices that are going to serve you well if you're planning to scale up."

Furthermore, the genomic information could give brewers greater control over their beer, allowing them to target yeast(s) that produce the most desirable traits.

"Predicting the type of beer you're going to make before you make it," said Steffy. "Right now, it's a lot of hit and miss."

The *Cell* paper produced a lot of genotype data, while White Labs has spent years accumulating phenotype data. Now they have to associate the two datasets to identify the genes that produce specific traits.

To memorialise the research, White Labs created a beer in its honour — the White Labs Frankenstout, created with all 96 strains from the study. Meanwhile, Steffy is content with the memory of having worked on such a fun project, which just happened to play to Illumina's strengths.

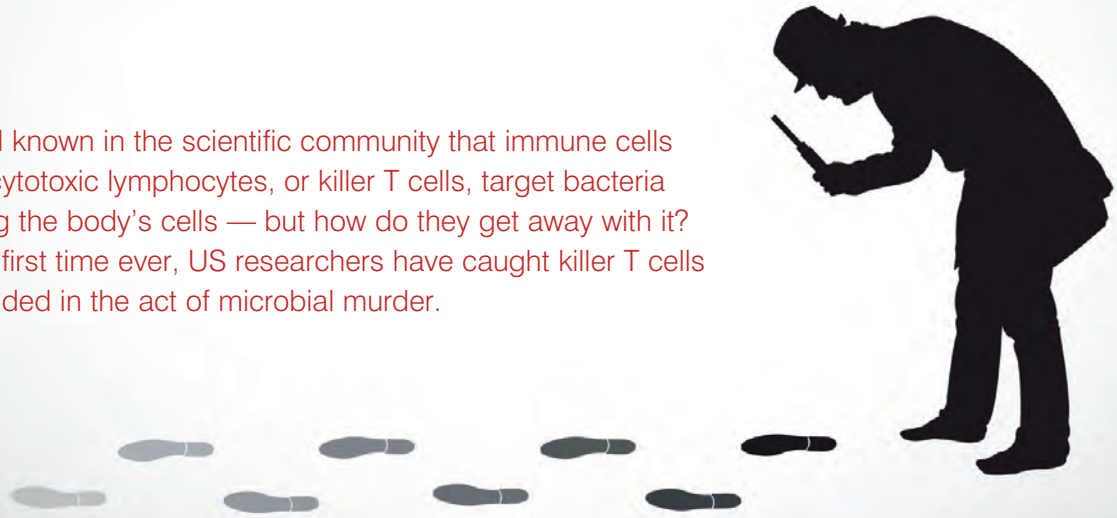
"We're a genetics company," he said. "We can support many applications."

Illumina Australia Pty Ltd
www.illumina.com

It was the killer T cells,

on the cell surface, with granzyme B

It is well known in the scientific community that immune cells called cytotoxic lymphocytes, or killer T cells, target bacteria invading the body's cells — but how do they get away with it? For the first time ever, US researchers have caught killer T cells red-handed in the act of microbial murder.



Bacteria can quickly evolve resistance against antibiotics, yet they have not so readily been able to evade killer cells. And although killer T cells can trigger bacterial death by inflicting oxidative damage, it has not yet been understood how killer cells destroy bacteria in environments without oxygen.

Now, researchers from Boston Children's Hospital, the Wistar Institute and the University of Michigan have discovered that killer T cells act methodically, shooting deadly enzymes into bacteria to 'program' a complete internal breakdown and cell death. The process inflicts bacterial cell death regardless of whether the environment contains oxygen or not.

As explained by Judy Lieberman, co-senior author on the study from the Boston Children's Program in Cellular and Molecular Medicine, the scientists tested killer T cells against three very different types of bacteria: *Escherichia coli*, *Listeria monocytogenes* and *Mycobacteria tuberculosis*. Using a combination of proteomics and computer modelling, the researchers were able to see how the multipronged attack targeted multiple processes. The results were published in the journal *Cell*.

"To see which proteins were destroyed by killer cells, we measured their protein levels before, during and after they were attacked," Lieberman said. Proteins are critical to life because they direct the use of nutrients and production of cellular machinery that bacteria need to survive.

"Each strain of bacteria has about 3000 proteins, and we saw that — in all three bacterial species — about 5–10% of those proteins were slashed by the killer cells' death-inducing enzyme, called granzyme B," Lieberman explained. "If you made a list of the proteins that bacteria absolutely needed to survive, it would be a small list — interestingly, this seems to be identical to granzyme B's hit list."

To deliver granzyme B, killer T cells seek out surface markers on the body's cell surfaces that might indicate a bacterial invader has taken up residence inside the cell. The killer T cells then latch onto the infected cell and use an enzyme to create a small pore in the cell's surface, through which they inject granzyme B.

Once granzyme B gets into the cell, it passes into the invading bacterium and essentially destroys critical proteins for cell survival as well as its ribosomes, the pieces of bacteria's cellular machinery that actually make proteins. It's almost as if the bacteria's internal factory of life not only loses the blueprints for the parts it needs to make, but also suffers a catastrophic mechanical failure of its assembly line.

"This enzyme breaks down multiple proteins that are essential for the bacteria to survive," said Sriram Chandrasekaran, co-senior author from the University of Michigan. "It's essentially killing several birds with one stone."

Importantly, no matter how many times the researchers exposed the bacteria to granzyme B, the bacteria did not develop resistance to its fatal attack. The researchers theorise that the only way bacteria can survive is to camouflage themselves so that the killer T cells cannot 'see' them or shoot granzyme B into them.

The research comes in the midst of the antibiotic resistance crisis, with Chandrasekaran noting that most drugs that treat diseases like tuberculosis or listeria, or pathogens like *E.coli*, are no longer effective.

The scientists are therefore hopeful that their work may lead to a new class of antimicrobial drugs that fight infections by mimicking granzyme B, going after bacteria in a similar way. They are also searching for the specific mechanisms by which bacteria might evade killer cells and investigating how similar 'death pathways' take effect in fungi and parasites, such as those that cause malaria.

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LIMS are crucial in many laboratory operations, providing numerous benefits in laboratory management. However, budgetary and time constraints are often a barrier that prevents labs from utilising an effective LIMS.

Offering a compact infrastructure, intuitive interface, SaaS platform and extensible features, Lims1 Emergent contains all the essentials of a cost-effective LIMS. Features such as sample life-cycle management, data automation, integration, calculation and reporting capability are built in to the core Lims1 Emergent package.

The product is modular in nature and can be easily implemented by a laboratory from day one, allowing the lab to realise improved productivity immediately. The software-as-a-service platform also alleviates the need to manage in-house infrastructure. As the laboratory grows, it can easily add modules and transition to a full Lims1 system when the time is right.

The modules available in the Lims1 Emergent system are: web access capability for external clients; batch assignment, including quality control samples; a data pipe to integrate with computerised laboratory instruments; invoicing and accounts; notifications and scheduling; and equipment calibration.

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Izon Science's products are used for the isolation and characterisation of biological and synthetic nanoparticles. The Izon qViro-X is a system designed for size, concentration and aggregation data for bacteria, viruses and vaccines.

The product directly measures the size of individual nanoparticles in solution, to build up a profile of concentration (viral titre) against size and, therefore, the degree of sample aggregation. Results are available within minutes, and each measurement requires only 40 μL of sample fluid.

The system is suitable for: vaccinology and vaccine production; virus quantitation and stability assessment; gene therapy research (analysis of viral vectors); and microbiology and virology research (eg, virus-cell interactions).

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Phagocytosis assay kit

Cayman Chemical's Phagocytosis Assay Kit employs latex beads coated with fluorescently labelled rabbit IgG as a probe for the measurement of the phagocytic processes in vitro.

The engulfed fluorescent beads can be detected using a fluorescence microscope, allowing kinetic studies of phagocytosis at the single-cell level. In addition, the flow cytometric readout provides the advantage of visualising perturbations in phagocytosis on the population level and, when combined with antibody staining, of specific cell types within complex populations.

The product has been validated in human peripheral blood monocytes and human and mouse monocyte/macrophage cell lines. Uptake is assessed via flow cytometry or fluorescence microscopy in the far-red channel. Phagocytosis is detectable in 1–4 h at 37°C.

The kit provides enough Latex Bead-Rabbit IgG-DyLight 633 Complex for up to 500 samples.

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Automated system for the characterisation of biomolecule stability

The MicroCal PEAQ-DSC automated system is the latest innovation from Malvern Instruments in differential scanning calorimetry (DSC), a thermal analysis technique for understanding the stability of a protein or other biomolecule.

DSC measures the heat change that occurs in the biomolecule during a controlled increase or decrease in temperature. Understanding the factors that affect stability is critical in the design, formulation and optimisation of drug manufacturing processes.

The MicroCal PEAQ-DSC delivers unattended 24 h operation, together with streamlined workflows and automated data analysis to produce fast results. The temperature range reaches as high as 130°C, with scan rates up to 240°C/h. In addition, the system is network-ready, and has built-in automated cleaning and self-validation protocols. Dedicated instrument standards are available so that performance can be validated throughout a series of runs.

The MicroCal PEAQ-DSC is available with full documentation and software support for analytical equipment qualification, in line with USP and FDA guidance, as well as a comprehensive package to aid technical compliance to FDA CFR Part 11 and EU GMP Annex 11.

It is available in two versions: a standalone instrument that includes the DSC cell and a dedicated computer, or a fully automated system with the addition of a liquid handling robot. Either can be specified with the 21 CFR Part 11 software package.

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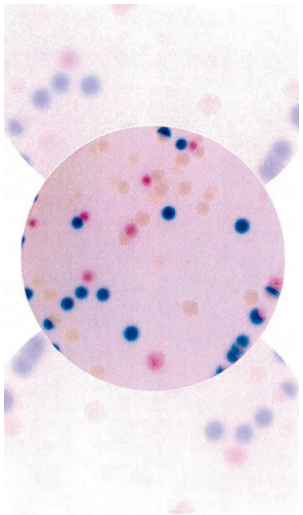

Mansi Gandhi

Skip, walk and jump

Rare diseases and the power of precision medicine

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When molecular biologists Steve Wilton and Sue Fletcher first started exploring dystrophin exon skipping for Duchenne muscular dystrophy (DMD), they faced a lot of scepticism.

Fast forward 20 years, and the drug developed by the researchers has altered disease progression — dramatically improving the quality of life of DMD sufferers. Strong support from the local Western Australian and US-based Muscular Dystrophy Association was a powerful motivator.

Caused by mutations in the DMD gene, the disorder affects 1 in 5000 males around the world, according to Muscular Dystrophy Western Australia. The disorder typically affects boys but girls can be carriers and in very rare instances present with the disease. Symptoms include delayed walking, inability of children to run and jump, followed by progressive muscle weakness and breathing difficulties.

The dystrophin gene has 79 exons spanning 2.3 megabases. In the severe forms of DMD, there is a protein truncating mutation so the end of gene message is missing — these kids have the most severe phenotype and typically become wheelchair bound before the age of 12, explained Wilton. One of the most common types of mutation in this gene is a deletion of one or more exons. If a deletion disrupts the reading frame, the result is Duchenne but if the deletion maintains the reading frame, the consequence is Becker muscular dystrophy, a milder form of the disease.

The drug developed by Wilton and Fletcher, now at Murdoch University, is designed to skip over the disease causing part of the gene message and reframe the message. For example, if a patient is missing exon 50, the reading frame is lost and the message is terminated in exon 51. Hence, by skipping exon 51, the early stop signal is 'skipped over' during splicing and the reading frame is restored.

This is the first splice switching drug to address the underlying genetic defect of Duchenne, and the first of its type to be approved by the US Food and Drug Administration (FDA), according to Wilton. The rights to develop the

drug have been licensed through the University of Western Australia to Sarepta Therapeutics, a Massachusetts-based commercial-stage biopharmaceutical company.

In September 2016, Sarepta received accelerated approval for Exondys 51 from the FDA. The drug has drastically improved the health and wellbeing of DMD sufferers during clinical trials, according to Wilton. A number of young boys suffering from DMD who would have been in a wheelchair are still walking, thanks to the treatment. The longer these boys stay out of a wheelchair, the progression of their disease has been delayed.

Exondys 51 is the first dystrophin-restoring drug that has shown a modest but unequivocal increase in the missing protein dystrophin, after treatment, according to Wilton. Exondys 51 will be relevant to about 1 in every 10 DMD patients, as DMD is caused by numerous different mutations in the same gene, but Professors Wilton and Fletcher have developed a panel of 'genetic patches' for other dystrophin spelling errors causing DMD. Over time, they hope that treatments should become available for the vast majority of DMD sufferers.

Sarepta also has second- and third-generation DMD drugs in the pipeline that are "going to be even more potent", according to Wilton. The researchers now have a proof-of-concept that they can change disease progression. Now, they are working on improving the treatment further.

When asked if CRISPR could provide a permanent solution, Wilton said that the gene editing has to be absolutely specific and as soon as there is a guarantee that there are no off-target effects, CRISPR could be one way of doing it. Our exon skipping approach cannot be regarded as a cure. We aim to reduce disease severity and progression by redirecting a DMD gene to make a semi-functional Becker-like protein, said Wilton. "What we are hoping for is either gene or cell replacement therapies become more efficient or CRISPR/Cas comes along and that the technology improves. I'm not going to say any of that cannot work, but right now we are able to buy more time for some DMD boys/young men with exon skipping."

Professor Wilton and his team are also applying these drugs to look into treating other conditions, including cystic fibrosis, multiple sclerosis and spinal muscular atrophy, the most common genetic cause of death under the age of two.

Professors Steve Wilton and Sue Fletcher (left) with DMD patient Billy Ellsworth and his mother Terri (right). Image courtesy of Murdoch University.

In November, Murdoch University researchers Wilton and Fletcher received significant funding from the National Health and Medical Research Council (NHMRC) to develop genetic therapies for rare diseases. Professor Wilton, the Foundation Chair in Molecular Therapies at Murdoch University and Director of the Perron Institute for Neurological and Translational Science and co-head of Molecular Therapy Laboratory with Professor Fletcher in the Centre for Comparative Genomics at Murdoch University, will lead the project, which will receive $800,000 over the next three years.

This project will build on two decades of research by Professor Wilton and Professor Sue Fletcher that has resulted in the first-ever treatment to have altered the progression of the fatal disease Duchenne muscular dystrophy, according to Murdoch University.

"We have exploited the fact that some genes linked to inherited diseases have sections that are potentially dispensable," Professor Fletcher said. Our technology — exon skipping — acts as a genetic whiteout that tricks cells into skipping over a genetic mutation, said Fletcher.

"This has resulted in a far better functionality of the dystrophin protein and improved function in DMD, and we believe these strategies can be applied to some other genetic diseases." Rare diseases affect around one in 12 Australians, but there are over 6000 known rare diseases, which means often there are only a handful of men and women with a disorder. Rare diseases pose challenges to researchers — they can't be studied through conventional trials, patient numbers are limited and getting an accurate diagnosis is difficult and costly. However, through research and personal advocacy, Professor Wilton has increased the profile of rare diseases.

The Murdoch research team will focus initially on eight genes that contribute to 46 serious inherited disorders. "This technology provides an exciting new platform to develop targeted therapies for a host of rare diseases that currently do not have successful treatments," Professor Fletcher said.

"We anticipate that several potentially therapeutic compounds will be developed during the course of this project." The Murdoch University team will work with long-term collaborators at UWA, Orthocell and Sarepta to develop the new therapies.

Murdoch University is also involved in six successful projects totalling over $5.5m led by UWA, TKI, Griffith University and Curtin University.

Wilton and Fletcher's research has received numerous awards, including the 2012 WA Innovator of the Year Award, 2013 Australian Museum Eureka Prize for Medical Research Translation, the 2014 LabGear Australia Discovery Science Award, and selection of Professor Wilton as a finalist in the 2016 Western Australian of the Year (Professions category).

Disposable gloves

Ansell's Microflex 93-850 gloves offer 2x more chemical splash resistance than leading brands of disposable gloves, according to the company, and exceed every known standard for barrier quality and consistency.

Workers who wear disposable gloves with pinhole defects are at greater risk of exposure — both because harmful materials can seep through pinholes, and because pinholes can cause gloves to rip and tear more easily. For robust protection, Microflex 93-850 gloves are manufactured using highly durable nitrile, with high tensile strength.

The Microflex 93-850 gloves are recommended for workers in demanding environments who need strong, comfortable disposable gloves that withstand rip-tear, and protect against chemicals, waste and other hazardous materials.

Ansell
www.ppe.ansell.com.au

Circular dichroism (CD) spectrophotometer

The Jasco J-1500 CD spectrophotometer allows researchers to carry out measurements with a high signal-to-noise (S/N) ratio, especially for highly absorbing materials found in the far-UV, by incorporating several of the latest advances.

CD spectroscopy is an essential tool for the structural analysis of biological samples from small organic molecules and nucleic acids to higher molecular weight proteins, polymers and polypeptides. It provides an indication of the percentage of the molecule that is in each conformation (α-helix, βsheet, βturn, etc), which can then be used with other analytical methods to determine the complete structure. Denaturation and other conformational changes, along with the thermodynamics of such changes, may also be studied within the spectral range.

The limit of detection of a circular dichroism (CD) spectrophotometer (or any spectrophotometer) is determined by its S/N characteristics: the better the S/N, the better its limit of detection. The Jasco J-1500 CD permits the measurement of a CD spectrum in the vacuum-UV region down to 163 nm. The enhanced light throughput and digital lock-in technology allows for a small signal in a noisy environment to be detected.

Additionally, the optimisation of the nitrogen purge efficiency helps to reduce the amount of oxygen in the optical bench so that it does not bury the sample signal. The quality of spectral data obtained, including data obtained at shorter wavelengths, is said to improve the accuracy of protein secondary structure analysis.

ATA Scientific Pty Ltd
www.atascientific.com.au

Spark-free laboratory refrigerators and freezers

LIEBHERR has designed and manufactured purpose-built laboratory refrigerators and freezers with spark-free interiors to eliminate ignition sources inside the unit, and ensure the safe storage of highly explosive and flammable substances in sealed containers. The LIEBHERR Spark-free Laboratory Refrigerators and Freezers with Comfort controller are certified to EU directive 94/9/EC (ATEX) and rated II 3G Ex nA II T6.

The Comfort electronic controller on the laboratory refrigerators and freezers allows highly explosive and flammable substances to be optimally stored, with temperatures set to 1/10°C accuracy. An integrated data memory logs min/max temperature and the last three alarm events, and can be connected to external temperature monitoring systems. Visual and audible alarms also alert users of cold chain breaches and these can be forwarded to email, phone via volt-free contact.

The LIEBHERR Spark-free Laboratory Refrigerators and Freezers with Comfort controller are eco-friendly and energy efficient.

Andi-Co Australia
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Sphere Fluidics

CytoMine™

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Cyto-Mine®: The Single Cell Analysis & Monoclonality Assurance System

Cyto-Mine® is the next generation platform that will transform biopharmaceutical discovery and cell line development workflows. It is specifically designed to automatically perform:

- high-throughput single cell encapsulation
- incubation then protein secretion assays
- rapid cell sorting
- dispensing of 'hit' single cells into individual wells of 96- or 384-well MTPs
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CapellaScience

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Lose the jargon, win the war

The fight against superbugs

University of Birmingham researchers have identified new mechanisms used by bacteria to resist antibiotics, just days after one of their number voiced her concern surrounding the EU and UK's action plans to fight antibiotic-resistant infections.

Published in the journal *Nature Communications*, their study was the result of a decade-long research project at the university.

Using novel experimental approaches, involving whole genome DNA sequencing never previously applied in this area of research, the team at the university's Institute of Microbiology and Infection identified strategies that bacteria use to protect themselves from antibiotics. The experts focused their research on *E. coli*, which can cause urinary and blood stream infections.

"We investigated a gene found in bacteria that is involved in resistance to multiple antibiotics," said Professor David Grainger, senior author on the study. "Although we have known about this gene for many decades, the 'nuts and bolts' of how it provides resistance to antibiotics has been difficult to pick apart.

"Our research identified previously unknown roles for this gene in controlling processes that provide drug resistance.

"We found two completely unexpected mechanisms that bacteria use to protect themselves from antibiotics. One protected their DNA from the harmful effects of fluoroquinolone antibiotics, and the other prevented doxycyline getting inside bacteria."

Dr Prateek Sharma, who did much of the experimental work, added, "The resistance mechanisms that we identified are found in many different species of bacteria. Therefore, our research could lead to the discovery of molecules that could be developed into new drugs that can treat bacterial infections."

The study was co-authored by Professor Laura Piddock, one of the UK's leading microbiologists, who only three days previously expressed her concern that confusing language and a lack of specific objectives are hampering the global fight against antibiotic-resistant infections. Professor Piddock has co-authored a report for the UK All-Party Parliamentary Group on Antibiotics calling for policymakers to focus on measurable objectives and simple language, a summary of which was published in *The Lancet Infectious Diseases*.

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The World Health Organization (WHO) submitted a European Strategic Action Plan on Antibiotic Resistance to the WHO European Regional Committee in 2011, highlighting seven strategic objectives as guidance to national governments in European member states to address antibiotic use and resistance. In response, the EU and the UK government set out to devise their own plans to address the recommendations in the WHO policy document.

But the evidence reviewed for the report suggested that although some EU member states successfully implemented many of the WHO recommendations, some appear to have been overlooked. In particular, there was a lack of evidence to suggest any activity to restrict non-prescription use of antibiotics by people or off-label veterinary use of certain new or critically important antibiotics to human medicine.

Likewise, it appears that little has been done to evaluate the need for incentives to stimulate discovery, research and development of veterinary medicines to increase the likelihood that drugs will reach the market at the rate required to combat AMR.

"The UK has taken significant steps to meet the objectives of the EU Action Plan, which in turn satisfies the WHO Europe Strategic Action Plan," said Professor Piddock.

"Yet there is an absence of objective and tangible outcomes by which to measure success of these plans and strategies. There is also a lack of consistency between the strategies in use of terminology, areas of compliance and recommendations, which makes it difficult to discern whether the EU and UK regional action plans have satisfied the overarching WHO Action Plan.

"The biggest weakness is the ambiguous nature of the words employed in the recommendations. This 'jargon' may limit the impetus for decisive government action in some areas and pose a challenge to finding evidence of fulfilment of the AMR strategy aims."

The report made the following recommendations for use in future action plans to combat AMR:

- Use more specific and measurable objectives, and outline the means by which all activities should be evaluated, in all future strategies.
- Demonstrate how all future strategies should comply/align with the WHO Action Plan.
- Develop a harmonised collection of educational tools to address the problems of AMR and antimicrobial stewardship practices for both the public and those working in the healthcare and veterinary sectors.
- Use simple language in all communications.
- Monitor the efficacy of education campaigns through online channels.
- Coordinate a review of progress in the discovery, research and development of new drugs, including for the veterinary sector.

Explosion-proof fridge

The storage of explosive and highly flammable goods requires precise, reliable and safe cooling. The Kirsch LABEX-Series is designed to ensure this.

Certified to ATEX standards, the unit's interior is intrinsically safe and the whole interior is grounded to avoid static loading. This ensures maximum user safety, combined with temperature uniformity and low deviation across the whole cabinet.

The LABEX-520 is supplied with five integrated shelves and 500 L capacity, so there is plenty of storage space for refrigerated goods. The interior is completely flexible and can be adapted as the user's needs change. The interior is explosion-proof and intrinsically safe, and a glass door is optional.

Optimised ventilation plates minimise interior temperature variation, while microprocessor-controlled temperature and thawing regulation maximises temperature stability. The unit is energy-efficient and offers a wide range of alarm features. It has an RS-485 interface for computer-based temperature documentation and a potential free contact for alarm transmission. A low-noise compressor is also part of the package.

A 180°, easy-to-read LED display shows the current temperature. The unit also features visual and acoustic alarms and a versatile shelving system.

Capella Science
www.capellascience.com.au

Multimode microplate reader

The SpectraMax iD5 Multi-Mode Microplate Reader is a high-performance, hybrid monochromator and filter-based optical system designed to provide a complete solution for the user's research needs.

Consisting of a hybrid monochromator and filter-based optical system, users can choose between the monochromator, filters or a combination of both to optimise and gain sensitivity in their assays. The optical system includes an ultra-cooled photomultiplier tube to -5°C, reducing background noise for good sensitivity and dynamic range.

The microplate reader features a large, high-resolution touch screen with embedded software, with no need for a dedicated computer workstation. Data can be viewed quickly using the large touch screen, exported to a USB drive or analysed using SoftMax Pro 7 Software. QuickSync technology automatically delivers data to the user's workstation.

A built-in near-field communication (NFC) reader enables the user to start custom protocols with a single tap. NFC tags paired to specific user profiles give direct access to personalised protocols and experimental results.

The reader features linear, orbital and double orbital shaking, simple-to-use temperature control (ambient to 66°C) supporting temperature-sensitive assays and detection of plate formats from 6- to 384-well.

Bio-Strategy Pty Ltd
www.bio-strategy.com

Fume hood in vented and ductless models

The Universal fume hood is suitable for laboratories where space is limited or when multiple hoods are needed. Offered in 24″, 30″, 35″ and 47″ widths, the fume hood is designed for light- to medium-duty fume removal and features sturdy dual-wall construction and a fully vertical sliding sash.

With durable, one-piece fibreglass construction, the hood is completely moulded of durable, chemical-resistant and fire-retardant fibreglass. The interior features seamless, one-piece construction with all coved corners for easy cleaning. The VaraFlow baffle efficiently directs air through the fume chamber.

The hood's fully adjustable sliding sash is made of 3/16″ thick shatterproof Plexiglas.

A full selection of accessories and components, including work surfaces, base cabinets, plumbing and electrical services, are available.

HEMCO Corporation
www.hemcocorp.com

New Malvern MicroCal PEAQ-DSC for Faster, more Accurate Characterisation of Biomolecule Stability

DSC is often referred to as the Gold standard technique for measuring the thermal stability of biological macromolecules. Most commonly used for measuring protein stability, DSC measures the heat change during a controlled increase or decrease in temperature which is associated with the making and breaking of hydrogen bonds. These bonds are broken when the biologic is heated and it unfolds which is detected by the calorimeter.

DSC provides fast and accurate determination of melting transition midpoint (Tm), and changes in enthalpy (ΔH). Any increase in Tm seen when comparing native and modified forms during formulation screening can be associated with an increase in stability.

Most other spectroscopic techniques used to measure protein stability rely on monitoring change in the environment of a particular amino acid, often a Tryptophan. There are a number of problems with this approach. Firstly, not all proteins have Tryptophan and the unfolding may go undetected. Secondly, even if they do have the Tryptophan, those techniques will only detect changes in the local environment of those amino acids. This may not be a good representation of the unfolding as a whole. This is particularly important for multi domain proteins. One or more of the domains may not have the Tryptophan and therefore the unfolding of a particular domain may go completely undetected. If this domain is important for the stability of the biologic, then all the data used to assess the developability of that molecule will be misleading. This is why many laboratories run MicroCal DSC measurements to validate their spectroscopic analyses.

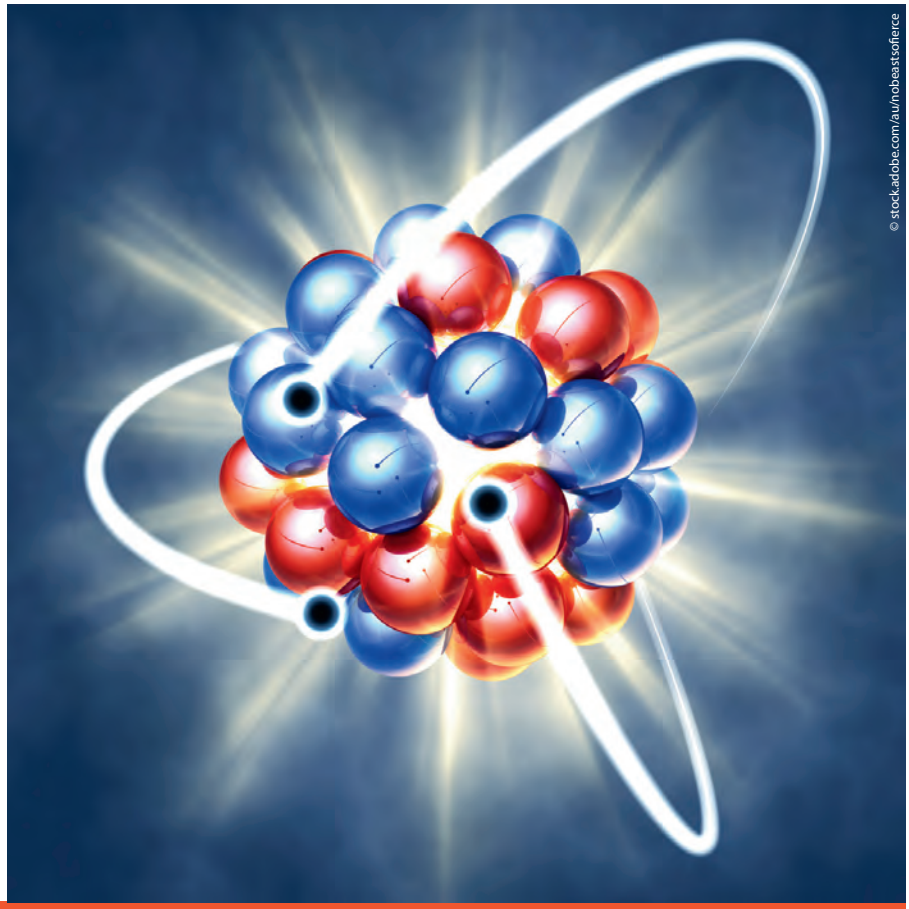
DSC is widely used for measuring the stability of proteins in a wide range of applications in the biopharmaceutical industry. The technique can be used for candidate selection, formulation, biosimilarity and process development studies. There is an increasing need in this environment to demonstrate high data integrity. The MicroCal PEAQ DSC has been developed to meet these needs.

The new Malvern MicroCal PEAQ-DSC Automated system is the latest innovation in Differential Scanning Calorimetry (DSC).

MicroCal PEAQ-DSC has smart algorithms for picking up even subtle features in DSC unfolding curves, to facilitate the identification of subdomain unfolding. The instrument can be used to study biologics in a broad range of buffers and formulations. It delivers unattended 24-hour operation, together with streamlined workflows and automated data analysis to produce fast results. The PEAQ-DSC temperature range reaches as high as 130°C, with scan rates up to 240°C per hour. In addition, the system is network-ready, and has built-in automated cleaning and self-validation protocols. The MicroCal DSC has low sample volume requirements and has features that support working in a regulated environment including software to support 21 CRF Part 11 Compliance.

MicroCal PEAQ-DSC is available in two versions: a standalone instrument that includes the DSC cell and a dedicated computer, or a fully automated system with the addition of a liquid handling robot.

For further details contact
ATA Scientific Pty Ltd
+61 2 9541 3500
enquiries@atascientific.com.au
https://www.atascientific.com.au/products/malvern-microcal-peaq-dsc-automated/



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Creating radioactive molecules

with photocatalysts

Princeton University researchers have pioneered a revolutionary new way of creating radioactive molecules. Led by Professor David MacMillan and published in the journal ***Science***, their work has the potential to bring new medicines to patients much faster than before.

Every new medication has to go through testing to confirm that it affects the part of the body it is intended to affect. As noted by Professor MacMillan, "Is it going to the right place? The wrong place? The right place and the wrong place?"

Tracing the path of a chemical that dissolves into the bloodstream used to present a serious challenge — one that radiochemists solved some years ago by swapping out individual atoms with radioactive substitutes. Once that is done, "the properties of the molecule — of the drug — are exactly the same except that they're radioactive, and that means that you can trace them really, really well", Professor MacMillan explained.

Unfortunately, this introduced a new problem: how to get the radioactive atoms into the drug in the first place.

"[This] is not a trivial thing to do," Professor MacMillan said. "People have developed long, sometimes month-long, two-month, three-month-long sequences just to get a tiny amount of a substance with a few radioactive atoms."

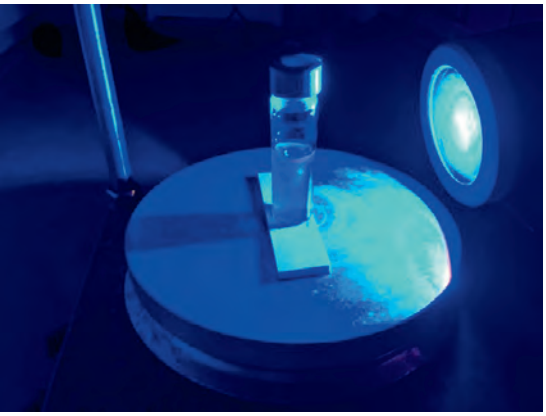
Now, Professor MacMillan and his colleagues have found another way, drawing on their work using blue LED lights and catalysts that respond to light, known as photocatalysts. "What we came up with was," Professor MacMillan said, "if you shine light on them, and you have a photocatalyst, could these photocatalysts actually remove the non-radioactive atom and then install the radioactive atom?"

It was a "wacky idea", Professor MacMillan admitted — but it actually worked.

The technique uses 'heavy water', which replaces the hydrogen (H) in H_2O with tritium, a radioactive version of hydrogen that has an extra two neutrons per atom. As explained by Professor MacMillan, "If you just let your drug sit in the radioactive water and shine light on it with a catalyst, the catalyst will remove the atom which is not radioactive — in this case, hydrogen — and replace it with tritium."

Attaching one of these atomic labels takes hours instead of months, and the technique works on many kinds of frequently used compounds. The researchers have already tested it on 18 commercially available medicines, as well as candidates in the Merck drug discovery pipeline.

For compounds that don't need radioactive tags, the same one-step process can swap in



A blue LED shines on a vial containing heavy water, a pharmaceutical compound and a light-activated catalyst. Image credit: David MacMillan/Princeton University.

> It was a "wacky idea", Professor MacMillan admitted — but it actually worked.

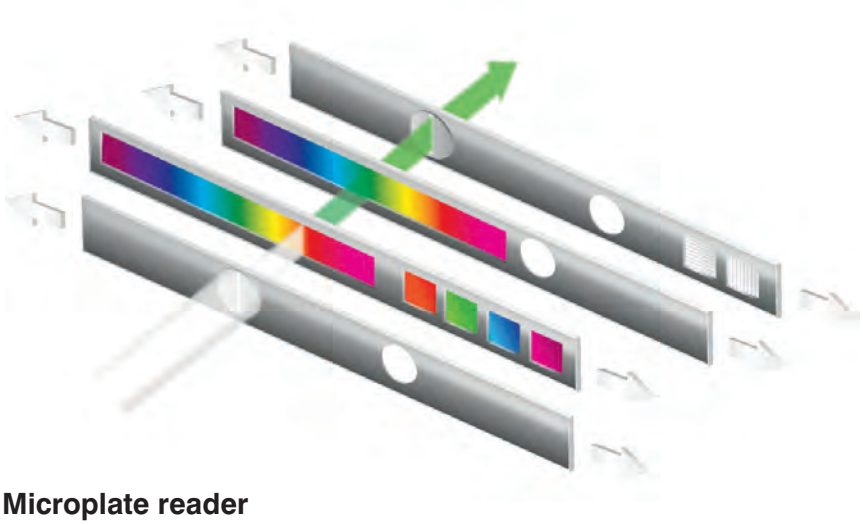
deuterium, a version of hydrogen with only one extra neutron. These 'stable labels' (with deuterium) and 'radio labels' (with tritium) have countless applications, in academia as well as drug discovery.

The simplicity of this new approach has another implication, according to Jennifer Lafontaine from pharmaceutical company Pfizer, who was not involved in the research. Because the previous process was so resource intensive, deuterium- or tritium-labelled molecules were often only created for chemicals that were "quite advanced in the drug discovery process", she said.

"This methodology could therefore open the door to earlier and expanded use of isotopic labelling in drug discovery, significantly enhancing our ability to study drug candidates on a deeper level and across a range of applications," said Lafontaine, who is senior director of synthesis and analytical chemistry for Pfizer.

The technology was developed in collaboration with Merck at Princeton's Merck Catalysis Center, where Princeton graduate student Yong Yao Loh and postdoctoral researcher Kazunori Nagao conducted research using the radioactive material. Professor MacMillan has dismissed suggestions that the process will be patented, saying "we want it to be available for everyone to use".

"Your average drug takes 12 to 14 years to come to market," said Professor MacMillan. "So everything that we can do to take that 14- or 12-year time frame and compress it is going to advantage society, because it gets medicines to people — to society — so much faster."



Microplate reader

Linear Variable Filters (LVFs) have variable coatings along their lengths that can reject or pass certain wavelengths of light. They consist of two quartz slides (a linear variable long pass and a linear variable short pass) which, when properly aligned, separate light into distinct wavelengths.

BMG LABTECH's CLARIOstar microplate reader features two LVFs: one for excitation and one for emission. A Linear Variable Dichroic Mirror slide is used to separate emission from excitation light, optimising the light path but also reducing background signal.

The optical system uses a free-air optical path to direct the light into the microplate well, reducing autofluorescence and increasing light transmission. The LVF monochromators also have continuously adjustable bandwidths ranging from 8 to 100 nm, with larger bandwidths allowing increased light for excitation and emission.

The technology offers flexibility and sensitivity for fluorescence and luminescence applications.

BMG LabTech Pty Ltd
www.bmglabtech.com

Illumination system for fluorescence microscopy

The X-Cite FIRE fluorescence illumination system by Excelitas Technologies is an arc lamp replacement for routine and advanced fluorescence imaging applications. It is claimed to have the broadest spectrum available in a white light LED for fluorescence microscopy and to rival traditional arc lamps for brightness, making it suitable for both compound and stereo microscopes.

In addition to its powerful output and broad DAPI to Cy7 spectral range, the product offers flexibility. Delivering light through a light guide alone or with a choice of more than a dozen microscope adaptors, the device can be installed on most new imaging systems or used to retrofit the microscopes labs have depended on for years.

Offering two models with a choice of UV wavelengths (365 or 385 nm), labs may choose the one that works with their preferred or existing DAPI filter sets. Each system includes intuitive fingertip control with speedDIAL, hands-free operation with a foot pedal, and USB and TTL inputs for automated applications.

The product's high power in 500–600 nm for TRITC and mCherry enables fast imaging time and good excitation for dim specimens. Power levels for TRITC, Cy5 and Cy7 excitation are said to rival that of arc lamps and can handle everything from routine imaging to demanding high-speed applications.

Designed for use with liquid light guides, the system is compatible with modern light-guide-only microscope designs and can also be combined with Excelitas microscope adaptors to replace traditional lamp houses.

SciTech Pty Ltd
www.scitech.com.au

Assay kits for monitoring nitrate and phosphate

The traditional method for measuring nitrate is the cadmium reduction method, which uses the toxic heavy metal cadmium. Chicago-based company NECi has developed a method to quantify nitrate that uses an enzyme. The method is said to be safer, greener, more accurate, sensitive and reliable.

Many researchers are investigating various aspects of nitrate, which sits in a central position in plant and algal metabolism, as well as in water pollution leading to eutrophication and impacts on species diversity in natural environments. Whether a team is analysing thousands of samples per day in an automated laboratory system or spot-checking levels on-site, NECi has a kit formulated for their needs. The company currently offers enzymes and enzyme-based test kits for the analysis of nitrate and phosphate in the laboratory or out in the field, and will soon be offering enzymes for the analysis of glycerol, galactose and ethanol.

The NECi assays are simple in design — a small volume of sample is mixed with a buffer containing the enzyme, a co-factor is added, then the reaction occurs. For the phosphate method, measurement at 360 nm using a UV-capable spectrophotometer or microplate reader yields results immediately following the enzymatic reaction. For the nitrate assay, Griess chemistry is carried out following the enzymatic reduction for the formation of an AZO dye and then absorbance is determined spectrophotometrically at 540 nm. The kits can also be used to perform total nitrogen and total phosphorus analysis.

United Bioresearch Products Pty Ltd
www.unitedbioresearch.com.au

GC gas calculation tool

Peak Scientific has created an online calculation tool to help laboratories that use gas chromatography (GC) to quickly find the optimal gas solution for their specific GC instrument.

The GC Gas Calculator consists of six simple questions regarding a user's GC instrument, such as the number and type of GCs, detectors, columns and injectors. These questions can be quickly and easily answered to calculate the gases, flows and purities required to support the user's GC applications and recommend a solution that will improve their lab workflow, determining a gas supply solution for the GC instrument indicated.

The user-friendly calculator is free to use and generates a simple report that Peak Scientific will provide to anyone who uses the calculator. It is available on the company's website.

Peak Scientific Instruments Pty Ltd
www.peakscientific.com

Cyclic AMP TR-FRET kit

Cyclic adenosine monophosphate (cAMP) is an intracellular signalling molecule that is a key mediator in a variety of pathways, including glycogen metabolism, gene regulation and olfactory sensory transduction.

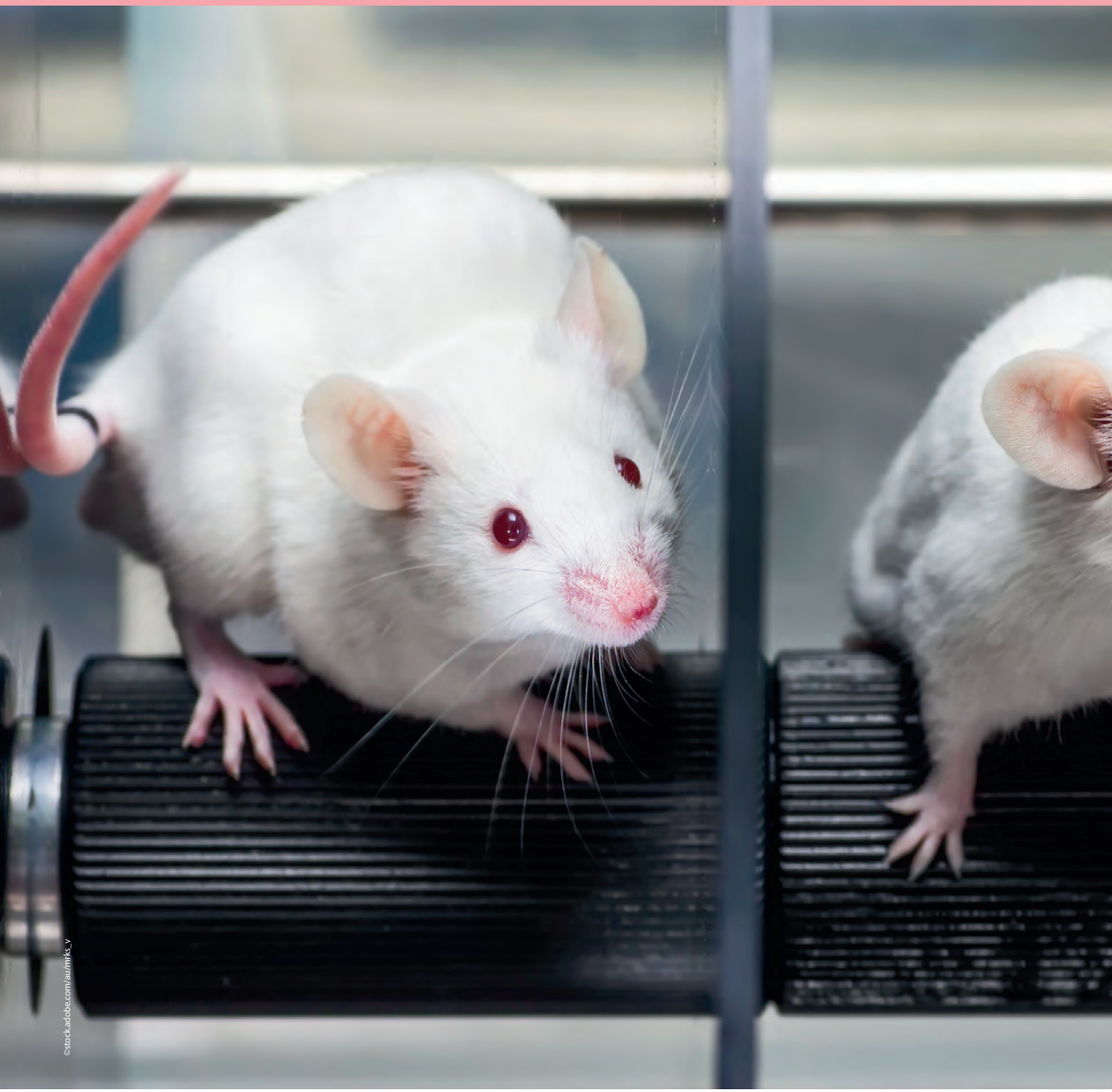
Cayman's Cyclic AMP TR-FRET Kit is designed to allow the user to detect and quantitatively measure the amount of cAMP present in cell-based assay systems. A europium (Eu) labelled monoclonal anti-cAMP antibody (donor) is paired with a fluorescence labelled cAMP analogue (acceptor). In the absence of any endogenous cAMP, it will produce a time-resolved energy transfer signal at 665 nm when excited at 340 nm. If cAMP accumulates in the well due to the activation of cellular adenylyl cyclase, this cAMP inhibits the formation of the labelled donor/acceptor complex, decreasing the amount of energy transfer signal produced, with the overall drop in signal being inversely proportional to the amount of cAMP accumulated.

The reagents supplied in the kit run up to 1000 assays in 384-well plates or 2000 assays in 1536-well plates.

Sapphire Bioscience
www.sapphirebioscience.com

Lauren Davis

When the cat's away, the mice will train



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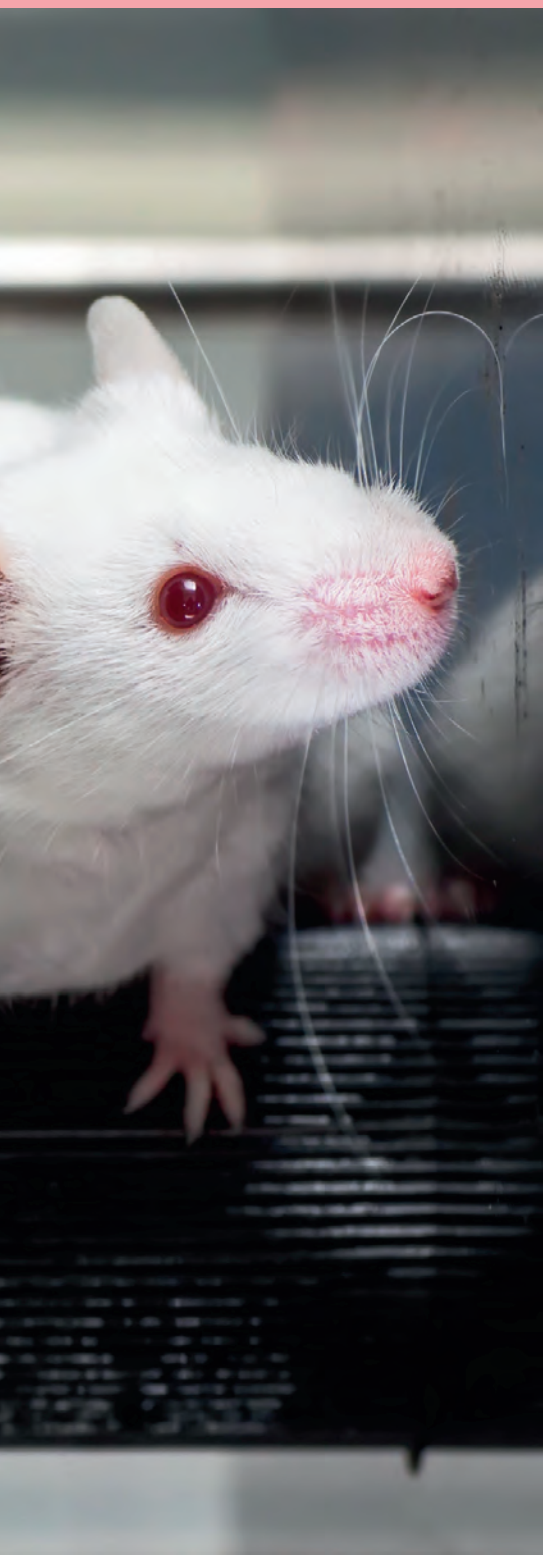
It's an almost inevitable part of working in a lab that, at one point or another, you're going to find yourself training mice — a necessary evil that can take up a substantial amount of time. But what if there was an easier way?



Seeking to move neuroscience research into the fast lane, researchers at Japan's RIKEN Brain Science Institute have constructed and deployed a high-throughput system to study mouse behaviour and physiology at a much faster rate than that achieved via manual methods. Described in the journal *Nature Communications*, the system aims to deliver large, standardised datasets, a reduction in the number of experimental animals and time savings through complete automation.

According to the RIKEN scientists, behavioural neuroscience — for example, studying vision or cognition — always entails training animals to do experimental tasks, like pushing a button to indicate a preference or demonstrate a memory. This training can take several months, making it a full-time job for one or multiple researchers, who must monitor their subjects using head-fixed assays in order to take tedious and labour-intensive brain recordings.

"However, the specificities of these paradigms and their integration with the growing array of state-of-the-art brain physiological recording systems differ greatly among and within laboratories due to the variability introduced by the experimenter's intervention," the researchers wrote. "This lack of standardization generates inherent reproducibility issues and eliminates the possibility of large, sharable data sets that could significantly accelerate the pace of scientific discovery and validation."

These problems have become particularly apparent in mouse studies, which is unfortunate as the mouse contains "the largest methodological toolbox for neural circuit research on behaviour", according to the researchers. In addition, mice can get stressed from being handled by experimenters, and training and experiments vary from lab to lab.

"It is hard to compare data across labs and even within the same lab, and we waste a lot of person-hours getting comparatively little data," noted Andrea Benucci, the leader of the RIKEN research group.

So what's the alternative? According to Benucci and his fellow researchers, the ideal mouse training system would feature the following:

- Self-head fixation for behavioural training and rapid exploration of several complex behavioural parameters with minimal experimenter intervention.
- High-throughput automated training.
- The capability to explore various sources of psychometric data.
- Flexible integration of multiple physiology recording/stimulation systems.
- The efficient generation of large, sharable and reproducible datasets to standardise procedures within and across laboratories.

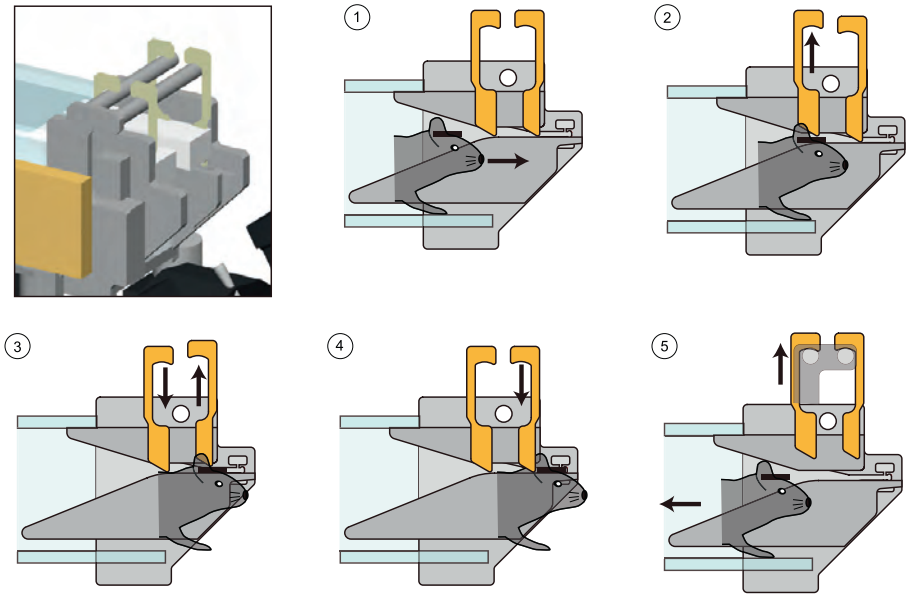
In order to realise his goal, Benucci collaborated with Japanese laboratory equipment manufacturer O'Hara & Co. The result was the creation of an automated experimental platform for mouse behavioural training, featuring full automation, voluntary head fixation and high-throughput capacity.

"The platform is scalable and modular allowing behavioral training based on diverse sensory modalities, and it readily integrates with virtually any physiology setup for neural circuit- and cellular-level analysis," the study authors wrote. "Moreover, its remote accessibility and web-based design make it ideal for large-scale implementation."

The researchers demonstrated their platform by training mice in two behavioural tasks: one visual and one auditory. For the visual task, the mice were trained to perform in a forced choice orientation discrimination task relying on binocular vision. They designed a 2D interactive visual task in which a circular grating placed in the central part of the visual field had a clockwise (c) or counterclockwise (cc) rotation relative to vertical.

For trial initiation, mice had to keep their front paws on a small wheel and refrain from making wheel rotations for 1 s (within ±15°). A stimulus was then shown on a screen for 1 s, during which time possible wheel rotations were ignored by the software (open loop). After this period, mice reported their percept of the stimulus orientation with c/cc rotations of the wheel for corresponding c/cc rotations of the grating stimulus, with the wheel rotation controlling the orientation of the visual stimulus in real time (closed loop). A correct response was a c (or cc) rotation to a cc (or c) rotated stimulus, resulting in a vertically oriented grating, the target orientation. After a correct response, the vertically oriented grating remained on the screen for an additional 1 s to promote the association between the vertical orientation and the reward. Correct responses were rewarded with a small amount of water, while incorrect responses were punished with a 5 s time-out stimulus consisting of a flickering square-wave checkerboard with 100% contrast. If there was no rotation crossing a near-vertical threshold of 10° for 10 s after the onset of the closed loop, the visual stimulus disappeared and the next trial started.

Mice performed three 20-minute sessions per day, discriminating orientations as small as 15°



Automated self-latching. Top-left panel shows a 3D rendering of the latching mechanism. Panels 1–5 show the sequence of steps leading to self-head fixation: (1) The head-plate (black bar on mouse head) is progressively restrained by narrowing rails (grey converging lines). (2) The forward motion of the head-plate mechanically lifts up the first pair of latching pins. (3, 4) The first pair of pins then lowers by gravity, and the continued forward motion of the animal similarly lifts up and down the second pair of latching pins, leading to the final self-head fixation (4). During 3, 4, small tilt and forward movements are allowed that reduce the probability of a 'panic' response due to a sudden head fixation. (5) When the task session ends, a computer-controlled servo motor actuator lifts up both pairs of latching pins and releases the animal. Original technical drawings edited by the study authors with permission from O' Hara & Co and provided by RIKEN.

from vertical. Eight out of 12 mice that entered the pre-training phase learned the task. Learning for the initial 45°/-45° orientation discrimination task took ~4 weeks, while it took on ~8 weeks to reach 75% accuracy with the smallest discrimination angle (±15°).

The second step saw the researchers train a group of mice in an auditory go-no-go task. They placed a speaker for auditory stimulation in front of the animal and enclosed the set-up in a sound isolation box to reduce ambient noise. Mice had to detect the occurrence of an 80 dB, 10 kHz pure tone played five times, which was presented in 70% of the trials (go stimulus). In the remaining 30% of the trials, the mouse was exposed to an unmodulated ~50 dB background noise (no-go stimulus). Mice had a 2 s window from the end of the go-stimulus to report the tone detection by rotating a small wheel at least 70° in either direction.

In hit trials (go responses to go stimuli), mice were rewarded with water in between trials. In miss responses (no-go responses to go stimuli), mice did not receive any reward or punishment. Similarly, in correct rejection trials (no-go responses to no-go stimuli), mice were not rewarded or punished. In false alarm trials (go responses to no-go stimuli), mice were punished with additional waiting time and shown a square-wave checkerboard with 100% contrast. Mice performed two sessions per day and learned the task over 12.5 ±3.5 days.

Finally, the scientists showed that they could image the mice once they had learned their tasks. Before commencing training, mice had been imaged using standard methods for retinotopic mapping to identify V1 and higher visual areas. Afterwards, a latching unit for physiology was connected to the mice's home cage, with the platform placed under a two-photon microscope. In typical two-photon imaging experiments, the researchers recorded from a volume 850 x 850 x 3 μm^3 of L2/3 neurons in the primary visual cortex. Using a common analysis for cell segmentation, they could identify ~200 neurons per volume. Using vascularisation landmarks, they could image the same cells over days or weeks, and segregated their responses as a function of the animal's choices or stimulus orientations.

"As a corollary of this cellular-level resolution, our semi-automated procedure can then be easily combined with a large variety of other imaging, optogenetic, and electrophysiology systems requiring a similar degree of stability of the neural target of interest," the researchers wrote. "In summary, the training setup combined with the latching unit for physiology is a convenient compromise for the relatively effortless integration of automated behavioral training with a large diversity of physiology systems."

The study authors thus demonstrated that the mice learned to engage in the behavioural training tasks at will, without any human intervention. A single system was able to operate around the clock, training four or more mice per day. And with multiple set-ups and mouse cages stacked in what resembles a row of server racks, the system has already been used to train 100 mice.

"Previously, training just one mouse took about 15 hours of a researcher's time," Benucci said. "Now, with 12 set-ups we are down to less than one-and-a-half hours."

Crucially, the mice learned to self-stabilise their heads, which is key for collecting high-fidelity physiology data and gives the system a great deal of experimental versatility. Furthermore, because the mice learned to self-direct and become familiar with the modular system, the experimental possibilities are said to extend beyond studying mouse behaviour to real-time brain imaging and physiology.

"Normally we see a decline in mouse performance or other incompatibilities when moving from highly trained behaviours to different types of experiments for brain recordings, but that doesn't happen with our system," said Benucci.

With the neuroscience platform having already been patented by RIKEN, Benucci now hopes it will be widely adopted nationally and internationally.

"Standard hardware and training protocols across labs that do not require the experimenter's intervention can go a long way to addressing data reproducibility in science, and in neuroscience in particular there is a pressing need for large, shareable datasets to validate findings and push the field forward," he said.

Process analyser series

Metrohm Process Analytics presents its latest range of online process analysers: the 2026 Titrolyzer and 2029 Process Photometer.

The powerful, compact process analysers are integrated solutions for 24/7 online analysis of critical chemical parameters in industrial processes and wastewater streams. Each single-method system is available in three basic configurations for monitoring up to two process streams, covering several market needs.

The 2026 Titrolyzer is suitable for titrimetric, ion selective or pH measurements. The 2029 Process Photometer performs photometric absorption measurements in the visible light range. A 7″ full-colour touch screen shows trend graphs and allows easy access to the user's data.

The process analysers are especially suitable for analysis in the chemical, petrochemical, semiconductor, food and beverage, potable water and environmental branches. Metrohm Process Analytics can offer process analysers that are configured for each specific application challenge. Sample dilution, extra reagents or even another sample stream can be added with the addition of peristaltic pumps in the modular wet part.

Strict separation of wet part and electronics ensures safe operation in harsh environments. The electronics part is housed within non-corrosive polyester-coated stainless steel. With an ingress protection rating of 66, each analyser is dust- and water-tight.

The company provides sample preconditioning systems including cooling, heating, pressure reduction, degassing, filtration and more. Information including results, remote control and status information can be communicated through discrete I/O (ie, analog outputs digital in/outputs), Modbus TCP/IP (Ethernet) or RTU (RS485) communication. Remote control is possible through VNC (Ethernet). Results can also be exported to USB.

MEP Instruments Pty Ltd
www.mep.net.au

Biologic stability measurement system

Unchained Labs has launched Hunky, a complete solution for quantifying biologic stability and predicting aggregation.

The product measures determined biologic stability by measuring ΔG, the amount of energy it takes to unfold a protein, letting scientists quantify exactly how much denatured protein they have in their samples. Its hands-off workflow and automated data analysis lets scientists see even small differences in their protein's stability.

Aggregation is a problem that usually shows up after it's too late. Hunky solves this by measuring ΔG at high and low protein concentrations to predict whether a protein aggregates from the native or denatured state. Scientists will know they have an aggregation problem right away and get insight on what they should do next.

AXT Pty Ltd
www.axt.com.au

Library prep kit for whole genome sequencing

Illumina has announced the Nextera DNA Flex Library Prep Kit for whole genome sequencing. It eliminates the need for sample preparation for whole blood and saliva and removes tedious steps in the library prep workflow, such as mechanical fragmentation of DNA, quantification and normalisation.

The product enables the direct input of blood and saliva samples, removing the need for ancillary equipment and reagents to extract DNA and quantify samples concentration prior to sequencing. It reduces hands-on touch points with On-Bead Tagmentation, which reduces total library prep turnaround time to less than 3 h.

The kit enhances library preparation efficiency with integrated DNA extraction protocols for blood, saliva, dried blood spots and direct colony. It enables the user to obtain consistent insert sizes and high coverage uniformity with minimal hands-on time and automation-friendly protocols. It supports a broad range of inputs (1–500 ng) from multiple types of genomes.

The assay platform has been designed to support the development of multiple products. It offers a fast, integrated workflow for a wide variety of applications, from human WGS to WGS preps for libraries of amplicons, plasmids and microbial, parasitic or fungal species, all compatible with any Illumina sequencer.

Illumina Australia Pty Ltd
www.illumina.com

Laser measuring microscope

Olympus developed the LEXT OLS5000 laser measuring microscope to perform three-dimensional measurement of the surface shape of a wide variety of samples using a technique that is non-contact and non-destructive. Succeeding the OLS4100 microscope, the OLS5000 offers improved measurement performance, delivering high-resolution imaging at speeds four times faster. Samples that were previously difficult to measure can now be imaged due to the expanded range of LEXT dedicated lenses and the OLS5000 range of frames.

The microscope scans laser light over the surface of a sample to provide enlarged images of micro-scale features and to perform measurements of surface area roughness, steps and other features. It measures surface area roughness precisely and with ease for enhanced productivity, making it suitable for a broad range of applications.

The device features 4K scanning technology and enhanced optics designed to enable the detection of near-perpendicular features and small steps at close to the nanometre scale. It also comes with intuitive software designed for usability with features including the ability to automate settings that previously had to be specified by the operator. The software functionality ensures that measurement variability between different users is decreased while maintaining a high level of repeatability.

The microscope can be used in R&D and quality inspection in a variety of applications, including semiconductors, electronic components, automotive, medical devices, material development, nanofabrication, advanced manufacturing and various additional engineering applications.

Olympus Australia Pty Ltd
www.olympusaustralia.com.au

Oxidative damage assay kits

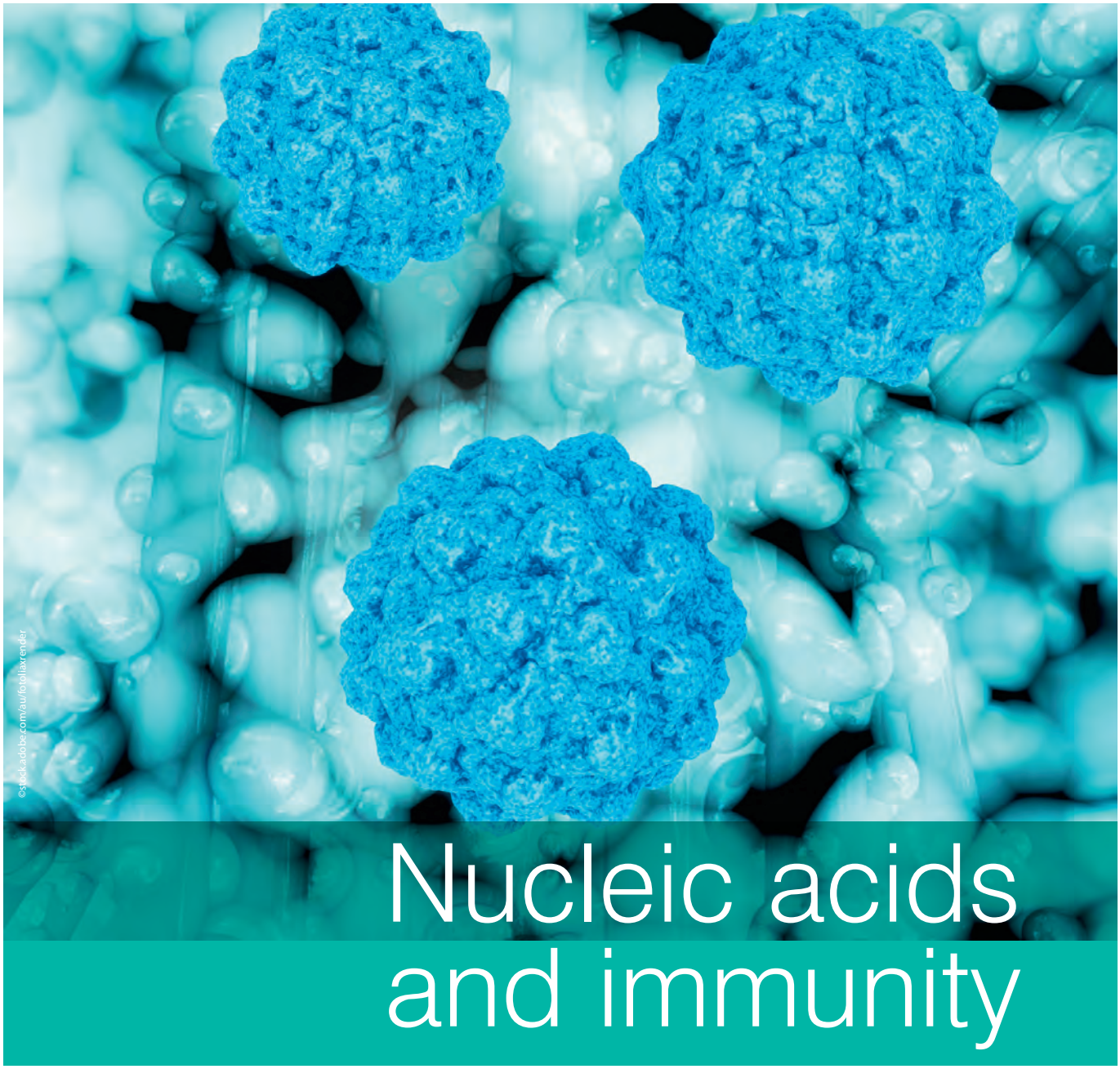
Cayman Chemical has a complete range of assay kits to measure direct and indirect biomarkers of oxidative damage. While direct measurement of reactive oxygen species (ROS) is preferred, indirect measurements are favoured by researchers due to the relative stability of damage markers compared to the transient ROS.

To quantify oxidative damage, it is best practice to measure multiple oxidative stress markers. It is possible to assess multiple biomarkers on the same molecule (eg, different markers of lipid peroxidation) or to examine one marker each on proteins, lipids and nucleic acids.

Cayman's range of oxidative damage assay kits includes kits to measure the following biomarkers: ROS (and reactive nitrogen species) — extracellular H_2O_2, $NO^{\cdot}$ metabolites, in vitro NOS activity, ROS, xanthine oxidase activity; DNA/RNA damage — 8-hydroxy-2'-deoxyguanosine, 8-hydroxy guanosine; protein oxidation (and nitration): methionine sulfoxide, S-Glutathionylated proteins, S-Nitrosylated proteins, nitrotyrosine, protein carbonylation; lipid peroxidation: 8-isoprostane, DHN-MA, lipid hydroperoxides, TBARS; and antioxidants — total antioxidants, ascorbate, catalase, glutathione, glutathione reductase, superoxide dismutase and thiol.

Sapphire Bioscience
www.sapphirebioscience.com

Mansi Gandhi



Nucleic acids and immunity

Dr Michael Gantier, ARC Future Fellow, Research Group Head, Nucleic Acids and Innate Immunity at the Hudson Institute in Melbourne, sheds light on the latest trends and developments in immunology and infectious disease research.

After completing a PhD on RNA interference in Dublin (Ireland), Dr Michael Gantier moved to Australia to join the laboratory of Professor Bryan Williams.

In 2015, he established his independent laboratory at the Hudson Institute of Medical Research, to study how nucleic acids control the interface between host and pathogens, and how this can lead to inflammatory diseases.

Dr Gantier is presenting at this year's Lorne Infection & Immunity Conference 2018 to be held from 14–16 February in Lorne, Victoria. He reflects on the latest developments in the field of infection and immunity and his lab's current research focus and future plans.

Lab+Life Scientist: What's your lab's current focus?

Michael Gantier: We are working on understanding how nucleic acids (ie, DNA and RNA) are involved at the interface between infection and immunity. In addition to carrying genetic information, DNA and RNA are also critical regulators of immune responses to pathogens. Being universally conserved across all forms of life, nucleic acids are used from prokaryotes to eukaryotes to signal infection, and mount rapid responses limiting the impact of the pathogen on the infected host. This system universally relies on the capacity of the host to distinguish its own nucleic acids from those of the pathogen.

The last decade has revealed that defective capacity to distinguish between host and

pathogenic nucleic acids was at the root of many infectious and auto-inflammatory diseases. In addition, nucleic acids can be differentially secreted in bio-fluids in chronic diseases, thereby presenting an unparalleled potential for diagnosis.

We are currently following up several projects that study the role and therapeutic potential of nucleic acids in infection and immunity. This includes: understanding how the immune system can also act to detect damaged or abnormal cells that have lost integrity of their normal genome, and the implication of this in the treatment of cancer cells, as well as in auto-inflammatory disease. In addition, my lab works on the development of small RNAs in circulation as biomarkers of chronic inflammation.

LLS: Were there any Eureka moments in your lab?

MG: My studies often seem to disprove what we originally intended to show (which I would not necessarily call Eureka moments!). However, it's really satisfying when you understand what is going on. Recently, we showed that a widely used genetic system, known as the Cre-Lox, had the capacity to trigger activation of a strong immune response. Because this system has been very widely used across the community for the past 20 years, we tried to understand what was going on, and discovered that Cre damaged DNA was released from the nucleus to activate an immune sensor called cGAS. This work is significantly important for a number of other studies since it means that some of the findings might have been misinterpreted. We also had a bit of a Eureka moment when we discovered that Acriflavine, a topical antiseptic used to prevent wound infections during WWI, could prevent viral infections and also potentially treat bacteria with antibiotics resistance.

LLS: What do you consider to be the top three developments in the world of infection and immunology in the recent past?

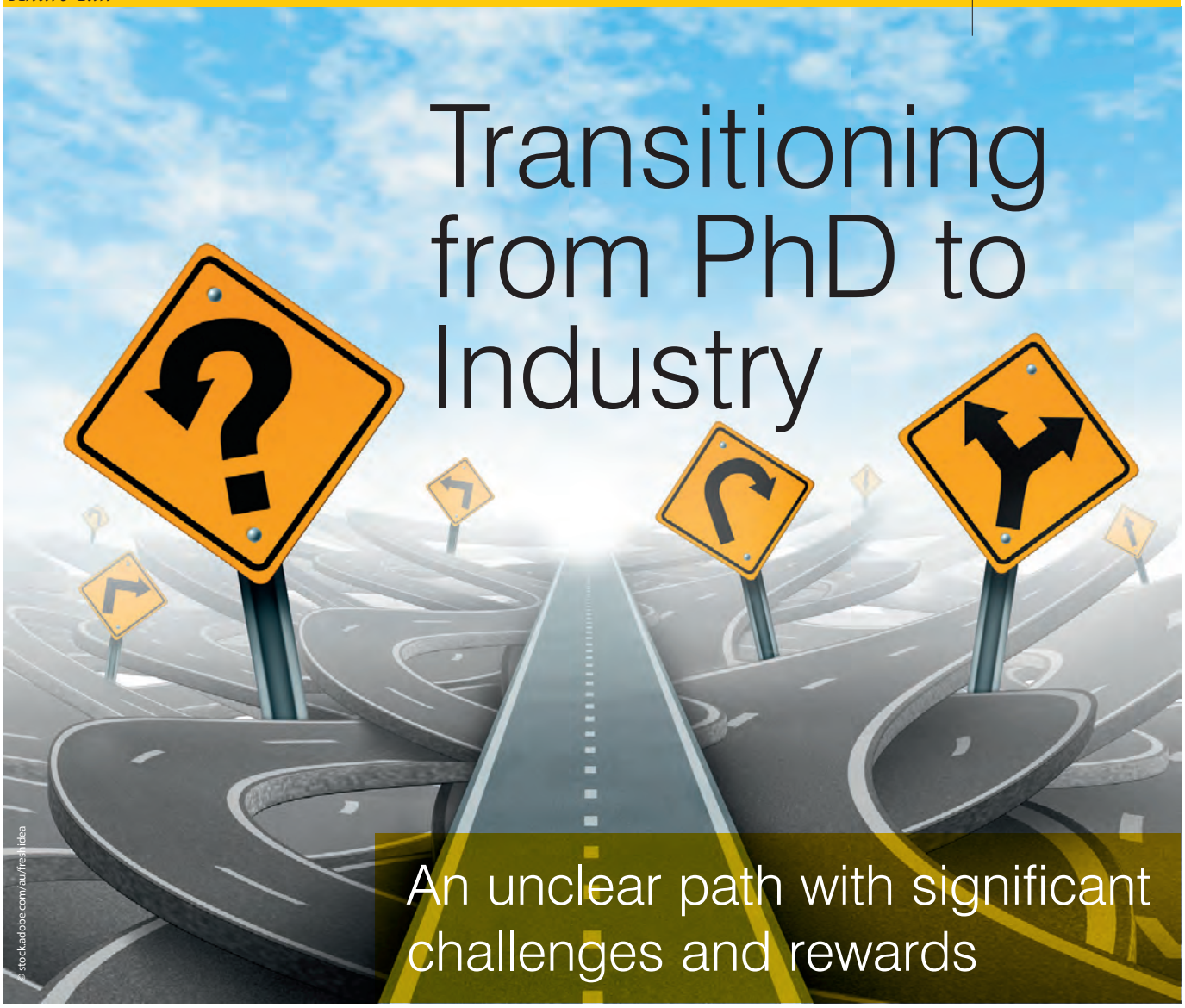
MG: The converging demonstration of the role of the microbiota affecting most aspects of the immune system would probably be my top pick. Then, I would say the discovery of the importance of nucleic acid sensing and its consequence in several auto-immune disorders (eg, interferonopathies), but I am biased! And also, although this would not be directly infection and immunity, the discovery of genome editing with CRISPR-Cas9 and others — which has many implications for our research, but also in the capacity to target latent infections (although viruses will probably evade these approaches very rapidly).

LLS: Could you provide a brief outline of your talk at Lorne?

MG: I will talk about our recent work on the detection of damaged DNA by the immune system — ie, how the type of damage seems to impact which sensor is activated, and how viral oncogenes can potentiate sensing. I will also present some of our latest work on the horizontal amplification of inflammation through cell-cell communication — which may present novel therapeutic opportunities for the treatment of autoimmune disorders such as cutaneous lupus, and limit disease flares in systemic lupus erythematosus.

*Andre Tan**

Transitioning from PhD to Industry



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An unclear path with significant challenges and rewards

My journey post-PhD was a baptism of fire. Though I had been intimately exposed to the early commercialisation activities of a technology to which I contributed during my PhD, I still found myself under-employed for a period of two years before landing a secure role.

It was depressing; I lived off the patience and generosity of my family which had already endured my PhD journey, while scraping money together by engaging as a consultant with various start-up companies on short contracts — something I didn't entirely want to do. I also went back to my retail job I had as an undergrad for a short period of time when my situation became dire. However, it taught me a lot about what not to do, and there were some fulfilling career rewards that money could never buy.

Lesson 1 — Run your post-PhD transition activities as a small business

With the very basic knowledge I'd gleaned about medical technology commercialisation, I used the reasonably large network I'd established during my PhD to seek out any opportunity to add experience to my CV. I was mostly unpaid, or paid very little for these engagements. However, my key goal was to break the "not-enough-experience-to-get-the-job-but-need-the-job-to-get-the-experience" vicious cycle and establish my reputation, so I endured the exploitation to maintain some cash flow, and leverage to other, bigger opportunities. I performed these engagements primarily as a sole trader consultant.

This meant learning how to operate as a small business and learning everything I could about the ecosystem and people I was talking to in order help them solve their problems. As a young consultant with a newly-minted PhD, life isn't easy. You don't have enough "grey hair" to be seen as an experienced consultant, and you'll be competing with other experienced people. It's also likely you've not had any real commercial experience. You're answerable only to yourself for finding new consulting and employment opportunities through networking activities to maintain cashflow, and only you can develop and maintain your own reputation.

To be successful:

- Adopt the start-up mindset to understand and solve your clients' problems

- Provide a point of difference against other competitor consultants
- Work your butt off to prove you're capable and worth re-/hiring for the next contract
- Behave like a professional (doing what you say you're going to do, and learning how to act professionally by asking and observing mentors, and people you respect)
- Know what's going on in your area as a matter of professional practice, and not because someone told you to
- Monitor and maintain cash flow
- Know your tax obligations intimately (or getting a good accountant)
- Network a lot (needed to manufacture serendipity for new opportunities and chance discussions/engagements)

Where academia often undervalues one's contributions, there is nothing wrong with earning money and acting like the CEO of a business — bills need to be paid.

Lesson 2 — Establish a diverse mentor network as your advisory board

No-one knows everything, including experienced CEOs. That's one reason why companies have Boards, and so should you. Not only do they (hopefully) demonstrate professional practices in the areas you're aligned with, they can act as your extended radar, seeking out new connections and informing you of potential opportunities, but they also steer you away from risk areas.

I am grateful for my mentors for their help with the following:

- Helping me to focus on my contractor responsibilities when my client was on shaky ground
- Alerting me to the full nature and scope of legal risks I was only partially aware of following some naïve decisions I made
- Listening and reflecting when other people close to me couldn't understand my post-PhD journey
- Providing me with the right connection at the right time, which put me on the path to a secure role

An IMNIS mentor is a great start, but additional mentors provide diversity in advice and guidance.

Lesson 3 — Unless you are a founder, carefully weigh up the pros and cons of working for pre-investment start-ups

Start-ups are trendy, sexy, and you learn lots by working in them. However, pre-investment STEM start-ups are especially risky unless you (or your legal advisor/generous mentors help you) put in place appropriate contractual protections for all parties.

Typically:

- Contracts are short — this affects the perception of your employability when HR managers at more established companies evaluate your CV, and form an impression that you can't hold a job. Sad, but true.
- The founders are often technical experts, but not necessarily commercial experts, or understand the difference between a technology and a product. Unless there is a strong management team, it's easy for such companies to lose their way, and you can potentially be forced to follow along.
- If you're an employee, you may have shares as part of an employee share option plan, as start-up pay can be lower than market averages. As a contractor, you're not entitled to anything outside of the contract value and benefits you've negotiated. I hazard a guess that shares for contractors would not typically be offered, and as a young STEM contractor, it's hard to command a high contract value. Low pay plus short contracts, with no long-term share options? Be wary!

It's slightly safer to work for a start-up company that has received some funding from professional investors (venture capital funds or angels, rather than or in addition to friends, fools and family). They generally undertake a level of commercial due diligence to ensure that the investment they intend to make into technology is sound, and that they get their money back at some point. Investors typically appoint a nominated representative to the Board of the company to ensure their interests are met. If the investors have sufficiently large equity share, they can exert their agenda and influence over the company. This situation may provide a more stable employer or contractor environment, as investors will typically focus company activities so milestones are met. As a young contractor or employee in a start-up, stability and the company's clarity of focus is essential for a regular wage and CV growth.

Though there are many other topics and details I could cover, I hope these 3 major lessons provide some foundations for your business acumen and your next steps, wherever they take you. Never underestimate your worth — a commercial mindset paired with the ability to break down and solve highly complex problems is a force to be reckoned with.

This article was originally published on Industry Mentoring Network in STEM (IMNIS), an ATSE initiative, under CC BY-ND 4.0.

**Andre Tan is a medical technology innovator, biomedical engineer and scientist. Between 2005 and 2014, he worked on developing a non-invasive, pain-free electrical stimulation treatment for chronic constipation at the Murdoch Children's Research Institute. Some of his involvement with this research led to the eventual launch of a medical device start-up, GI Therapies, in 2012. This exposure set the scene for his interest in medical technology innovation, regulatory affairs and commercialisation. Since completing his PhD through the University of Melbourne in 2014, he has worked across a range of pre-investment Australian medtech start-up opportunities, in both technical and commercial roles.*

Over the course of his postgraduate studies and early career, he has been involved with AusBiotech, the Australian Science & Innovation Forum and the Swinburne Design Factory in a variety of volunteer and mentoring capacities. He has also blogged extensively about his pre-PhD to industry transition, which can be found here.

Andre is currently the Business Development Manager for Zicom MedTacc, a medical technology accelerator based in Singapore. The primary focus of his and his team's role is to bring their portfolio companies and their technologies to Australia and New Zealand. He is currently seconded to one of the portfolio companies, HistoIndex, which is commercialising a next-generation tissue analysis system for more precise imaging and quantification of fixed tissue.

sCMOS camera

Thorlabs has announced the release of its 2.1 MP Quantalux sCMOS Camera, based on a high-performance 1 e^- read-noise imager. Suitable for demanding imaging applications, the monochrome sensor can image the full frame (1920 x 1080) at 50 fps with 16-bit resolution and offers a peak quantum efficiency of 61% at 600 nm.

Packaged in a housing that measures 2.38″ x 2.78″, the camera is equipped with passive thermal management for the sensor, reducing dark current without the need for a cooling fan or thermoelectric cooler. A USB 3.0 interface provides compatibility with most computers.

The company's goal in introducing the camera was to provide researchers and OEMs with a product for achieving low-light images without compromising on key specifications. In addition to the high performance, users can benefit from the ease of integration with a comprehensive software suite that includes ThorCam — Thorlabs' Windows GUI — as well as support for third-party applications such as ImageJ/Micromanager, LabVIEW, MatLab and the company's developer-friendly SDK.

The compact housing of the camera is feature rich, enabling seamless integration into a multitude of set-ups. An adjustable C-Mount adapter is factory installed into the SM1-threaded optical aperture of the camera for out-of-the-box compatibility with industry-standard microscopes and camera lenses. Various mounting taps are also provided for optical post and 30 mm cage system compatibility.

Suitable applications include fluorescence microscopy, VIS/NIR imaging, multispectral imaging and low-light inspection.

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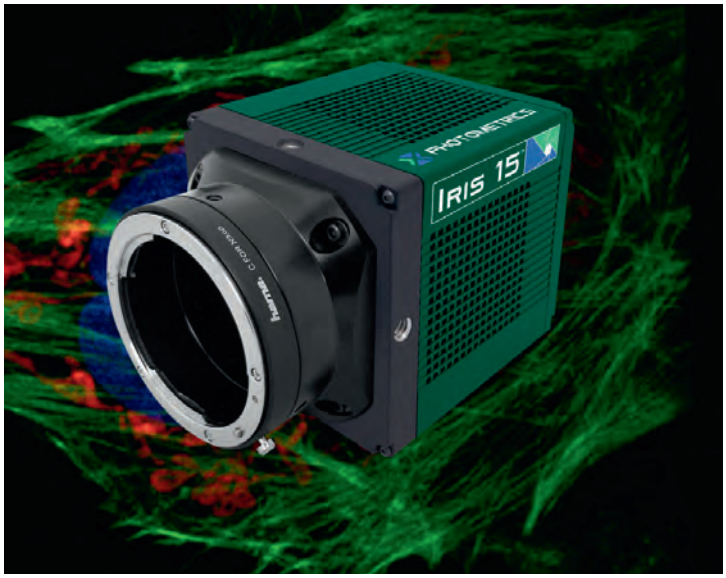

Large field of view sCMOS 15 MP camera

The Iris 15 Scientific CMOS camera from Photometrics is designed with a large field of view for live cell microscopy applications, light sheet microscopy, multicolour fluorescence, genomic analysis/sequencing, high-content and high-throughput cell screening, tissue and cellular imaging as well as tiling applications.

The 15 MP sensor and 25 mm field of view provide high-resolution images over a large imaging area. The camera provides high resolution with video-rate acquisition speeds, ensuring dynamic cellular events are properly captured and documented.

High-resolution images are captured at over 30 frames per second (fps). The camera offers a 4.25 x 4.25 μm pixel area, which meets the requirements for Nyquist spatial sampling at 40 times magnification.

The camera has a high 73% quantum efficiency and low noise levels to maximise dim signal detection and allow for the use of shorter exposure times to minimise cellular photodamage. It is a suitable camera for leveraging the larger fields of view of newer microscopes and is available in colour or monochrome.

SciTech Pty Ltd
www.scitech.com.au

ICONN 2018 — International Conference on Nanoscience and Nanotechnology January 29–February 2, Wollongong

The ICONN 2018 — International Conference on Nanoscience and Nanotechnology aims to bring together Australian and International communities working in the field of nanoscale science and technology to discuss new and exciting developments in the field. The conference will cover nanostructure growth, synthesis, fabrication, characterisation, device design, theory, modelling, testing, applications, commercialisation, and health and safety aspects of nanotechnology.

42nd Condensed Matter and Materials Meeting
January 30–February 2, Wagga Wagga
http://wagga2018.com/

23rd Lorne Proteomics Symposium 2018
February 1–4, Lorne
www.australasianproteomics.org.au

43rd Lorne Conference on Protein Structure and Function
February 4–8, Lorne
www.lorneproteins.org

AMOS-ICSHMO 2018
February 5–9, Sydney
https://www.amos-icshmo2018.com.au/

30th Lorne Cancer Conference
February 8–10, Lorne
www.lornecancer.org

39th Lorne Genome Conference 2018
February 11–13, Lorne
www.lornegenome.org

Science meets Parliament 2018
February 13–14, Canberra
https://scienceandtechnologyaustralia.org.au/event/science-meets-parliament-2018/

Lorne Infection and Immunity Conference 2018
February 14–16, Lorne
www.lorneinfectionimmunity.org

5th Asian and Oceanic Congress on Radiation Protection
May 20–23, Melbourne
http://www.aocrp-5.org

64th Annual Scientific Meeting for the Australian Mammal Society
July 1–5, Brisbane
http://australianmammals.org.au/events/20_64th_annual_scientific_meeting

Australian Society for Microbiology 2018 Meeting
July 1–5, Brisbane
http://asmmeeting.theasm.org.au/

MACRO2018
July 1–5, Cairns
http:// www.macro18.org/

1st World Congress on Nutrition & Food Sciences
July 09–10, Sydney
http://www.nutritionalconference.com/

8th World Congress on Plant Science & Genomics
July 09–10, Sydney
http://plantgenomics.plantscienceconferences.com/

International Conference on Chemistry Education 2018
July 10–14, Sydney
http://www.icce2018.org/

15th Asia-Pacific Pharma Congress
July 16–18, Sydney
http://asiapacificpharmaconference.blogspot.com.au/

International Symposium on Relations between Homogeneous and Heterogeneous Catalysis
July 22–25, Sydney
http://www.ishhc18.com/

9th Vacuum and Surface Science Conference of Asia and Australia
August 13–16, Sydney
http://www.ansto.gov.au/Events/9thVacuumandSurfaceScienceConferenceofAsiaandAustralia/index.htm

International Society for Clinical Biostatistics and Australian Statistical Conference 2018
August 26–30, Melbourne
http://iscbasc2018.com/

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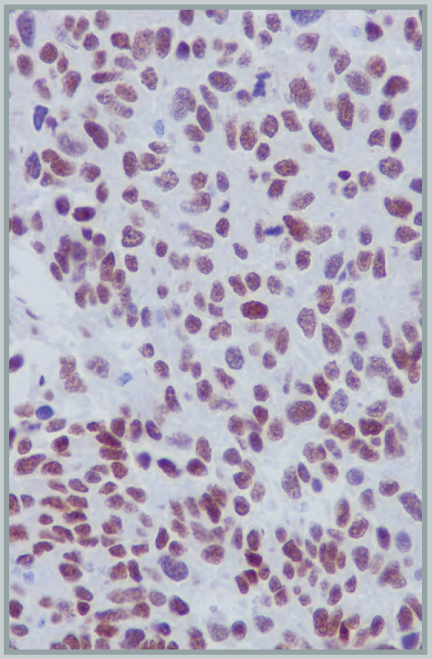
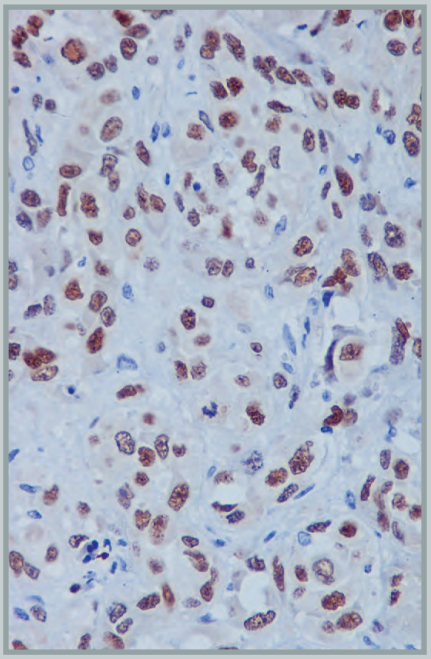
We use our unique recombinant RabMAb® platform and AxioMx's phage display technology to bring you over 9,000 recombinant monoclonal antibodies. These eliminate batch-to-batch variability and give you reliable data, every time.

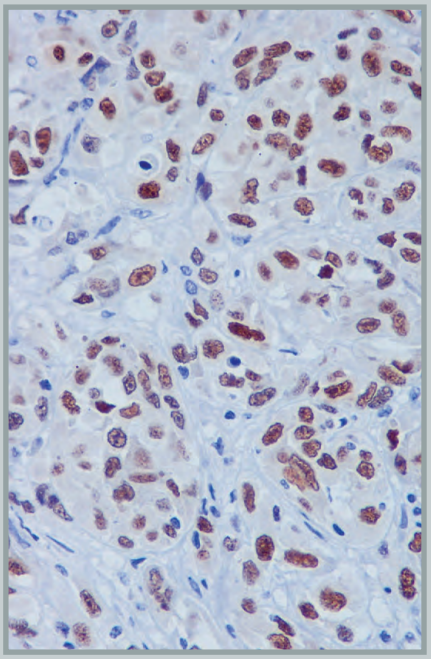
Batch A



Batch B



Batch C



Immunohistochemical analysis of paraffin-embedded human melanoma tissue with Sox10 recombinant RabMAb antibody (ab180862). Data shows a consistent specific Sox10 detection in all three different batches of Sox10 recombinant RabMAb antibody.

www.abcam.com/recombinant