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July/August 2018

The 1918 pandemic: flu research 100 years on

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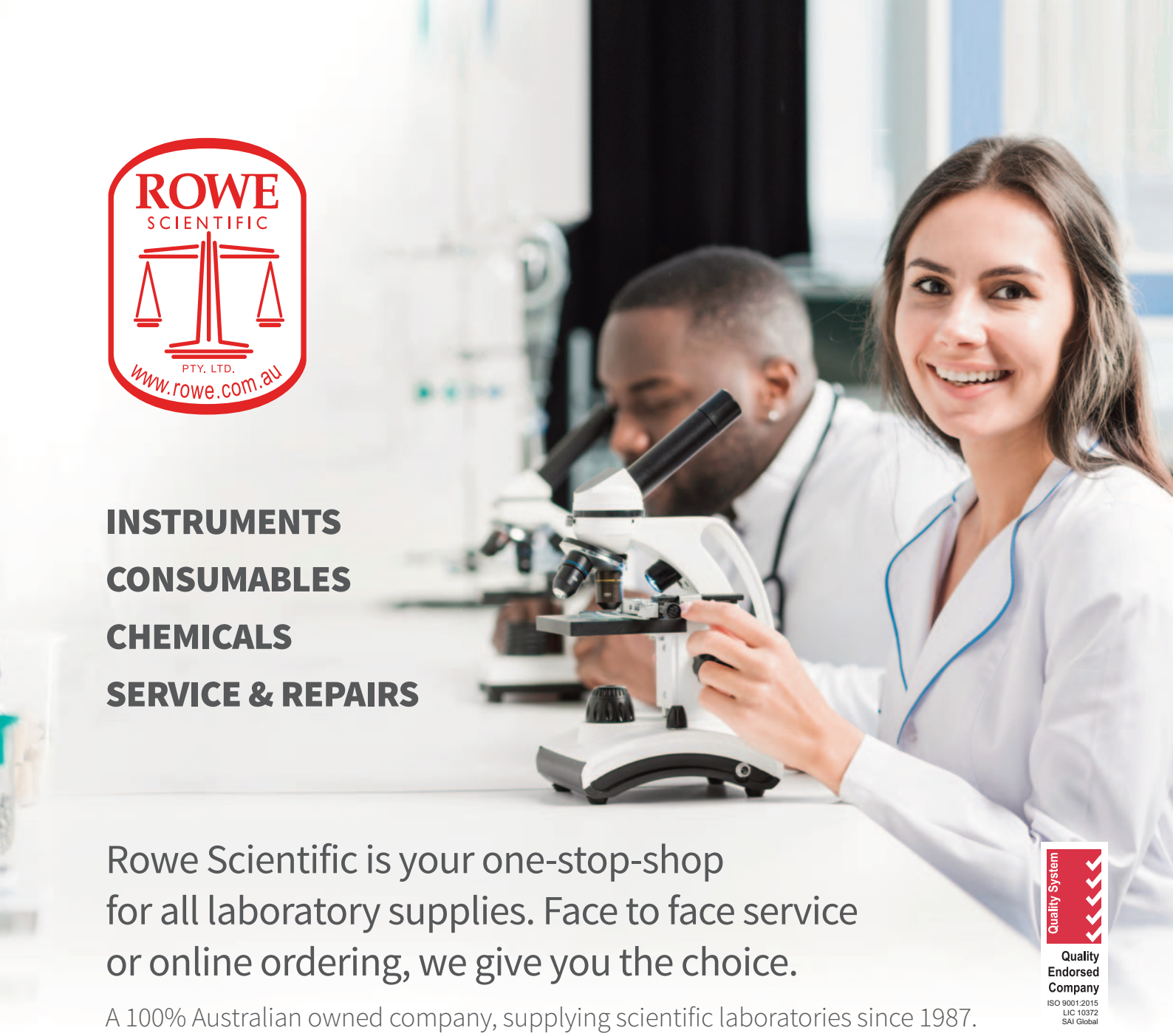

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chemistry in Australia

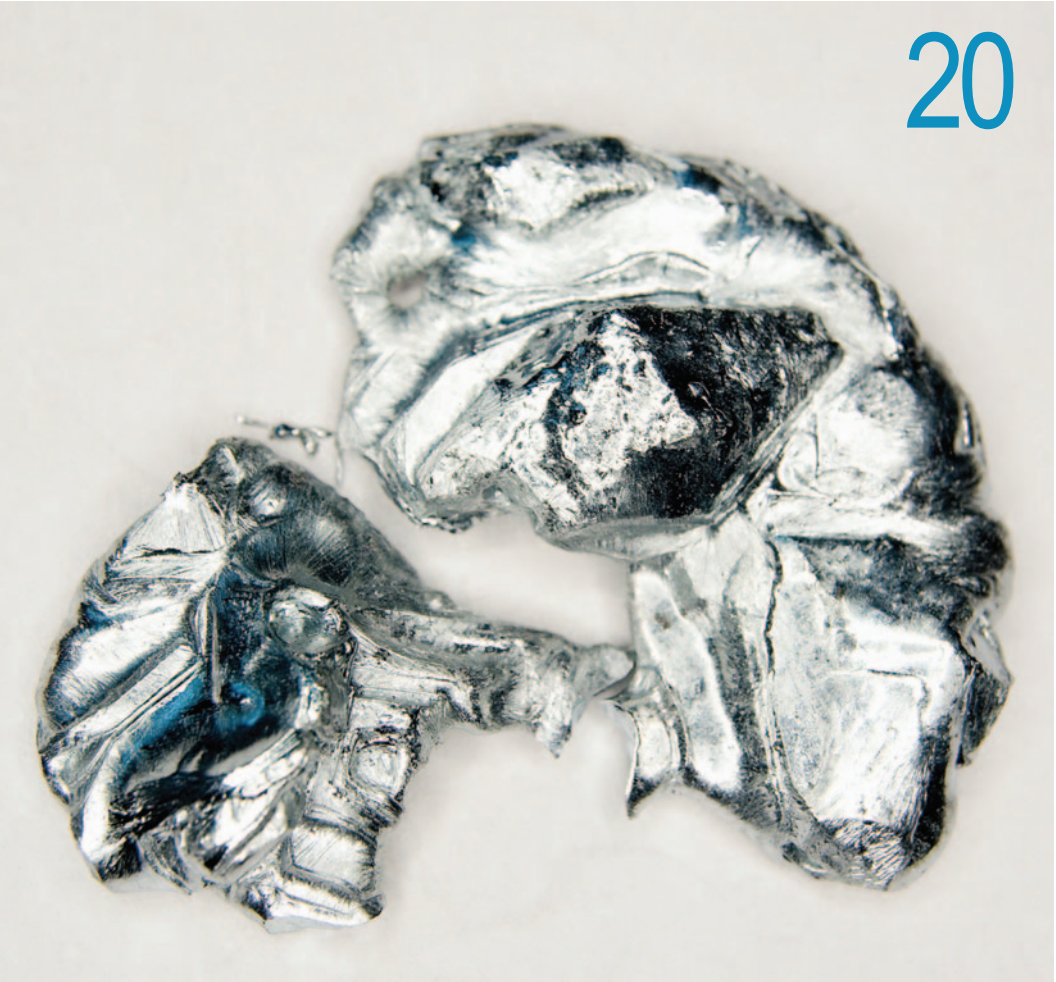
July/August 2018

cover story

Drugs for influenza

A key scientist in one of the earliest examples of structure-based drug design, Peter Colman reflects on work to describe the influenza virus protein neuraminidase and discusses the challenges facing ongoing efforts to expand the portfolio of anti-influenza drugs.

16



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From the President

Recently I received an email from a member about an article that appeared in a local newspaper with a heading 'When chemists go bad: wave of drug store dealers caught pill pushing'. The member was concerned about the indiscriminate interchange of the words *chemist* and *pharmacist* in the article, which could perhaps affect the role and standing of the two professions.

The use of the word *chemist* for *pharmacist* in Australia and several other countries (UK included) has always bothered me. Perhaps from a historical perspective, one can understand where the interplay between the two arose. In the past, a pharmacist was generally adjacent to a general practitioner and would prepare drug treatments, emulsions, ointments and the like in-house. In older times, pharmacies were called apothecaries; over time they became pharmacies, and then, with the use of chemicals, chemists. These days, there is little synthetic work or preparation of samples performed in the store, and it could be argued that this terminology should be dropped. On a semantic level, pharmacy, as a trade, activity or discipline, is a branch of chemistry. And it is the only branch of chemistry with which most people have contact. Hence, a pharmacist is also the only kind of chemist that most people know personally, and this could lead to the continued usage.

In other countries, there is *farmacia* in Spain, Portugal and Italy, *pharmacie* in France, *apotheke* in Germany, аптека in Russia, φαρμακειο in Greece and *pharmacy* or *drugstore* in the US. It is obvious that most other countries discriminate between the professions of pharmacist and chemist, so perhaps this is where we should head in Australia. Although many stores are called pharmacies across our nation, the 'chemist' terminology persists.

I surveyed pharmacy students at James Cook University and they claimed that the profession is moving towards describing the stores as pharmacies and away from being called chemists. There are many 'pharmacies' about, but we still see trade names of pharmacies, such as Chemist Warehouse and Discount Chemist.

In the chemistry profession, I believe most would argue that we are chemists and pharmacists are pharmacists, and we don't want these terms intermingled. The pharmacy students I surveyed certainly didn't want to be known as chemists. Perhaps it's time we did something about it? Or is it just semantics that we should not concern ourselves with? How do members feel about this?

Perhaps if this issue was sorted out, the media would have a better understanding of the two professions and would not interchange them with attempts to link pharmacies with *Breaking Bad* just to embellish a story.

Peter Junk FRACI CChem (president@raci.org.au) is RACI President.

As your RACI member magazine, Chemistry in Australia is the perfect place to voice your ideas and opinions, and to discuss chemistry issues and recently published articles.

Send your contributions (approx. 400 words) to the Editor at wools@westnet.com.au.

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ISSN 0314-4240 e-ISSN 1839-2539

raci

The march for science

Peter Junk in the President's column (May issue, p. 4) urged his readers to take part in the 'March for Science', though unfortunately this information was available to chemists after the march had taken place. In Melbourne the event took place at Birrarung Marr, close to Federation Square. The organisers hoped that 'thousands of Australians [will] join us on Saturday 14 April'. In Melbourne, I would estimate that a small group of about 50 people braved the weather. Speeches went on for over an hour in the rain, with the weather only changing to bright sunshine when the speeches were completed. The names of the speakers and their scientific interests may be found at https://marchforscienceaustralia.org/melbourne.

Marching 'The march for science' in Melbourne actually consisted of a walk of about 300 metres to Flinders Street, where marchers separated. None of the above is intended to be critical of the organisers, but for the march to be effective, it needs more support from the major scientific organisations and their members. I observed only a little information about the event in the weeks before the march. I saw no one on the march who I could identify as being from the RACI; nor was there any RACI banner. I hope that the RACI will provide better support in the future to 'The March for Science' as presumably the small numbers on the march signal to politicians that the scientific community is unimportant. RACI should show that it cares!

William Palmer FRACI CChem

Soil pH measurement

While I'm not an expert in the field of soil pH measurement, I found the article 'Is soil more acidic than we thought?' (June, pp. 38–39) to be odd. It stated that soil pH is measured by the 'traditional laboratory method' of drying, crushing and adding deionised water before measuring pH. I have two problems with this. First, surely this treatment is going to substantially alter the soil pH; for example, through loss of volatile organic acids and altering hydration states of minerals (affecting H^+ adsorption). Second, I always thought that soil pH was measured by equilibrating soil with aqueous $CaCl_2$ to displace exchangeable acidic cations and then measuring the pH. A quick Google search seemed to verify that was the ASTM International method (see ASTM Method D4972).

So, is there really a discrepancy between the field measurement and what the authors described as the traditional method?

Also, how about a bit of simple analytical chemistry method validation to determine changes from volatile organics loss and mineral surface chemistry changes?

On the surface, this seems like a study of questionable authority.

Stephen Grocott FRACI CChem

A crucial component of the Gender Gap in Mathematical, Computing, and Natural Sciences project is the compilation of self-reported data from scientists via a global, multilingual, and multidisciplinary survey. The goal is to study social dynamics in the fields of physics, chemistry, astronomy, biology, computer science and mathematics by asking a large number of scientists and practitioners about their experiences, challenges and interests, as well as focused information about women in these fields.

The analysis of the compiled data will allow comparisons across regions, countries, disciplines, level of development of the country, sector of employment, and age. The insights obtained from this survey will help inform interventions by the International Council for Science (ICSU) and member unions to increase participation in STEM fields, especially for women.

The survey is now open to respondents from all over the world. The survey is available in English, French, Chinese, Japanese, Russian, Spanish and Arabic. If you have studied or worked in mathematical, computing or natural sciences, or in the history and philosophy of science and technology, visit the link to complete the survey and to share this information with your colleagues: https://icsugendergapinscience.org.

Participation will be open until 31 October 2018.

IUPAC (ICSU project partner)

What makes someone believe or reject science? Quality of recordings

Separating fact from fiction in the age of alternative facts is becoming increasingly difficult, and now a new study has helped reveal why. Research by Dr Eryn Newman (Australian National University) and Professor Norbert Schwarz, (University of Southern California, USA) has found that when people listen to recordings of a scientist presenting their work, the quality of audio has a significant effect on whether people believe what they are hearing, regardless of who the researcher is or what they are talking about.

Newman said the results showed that when it comes to communicating science, style can triumph over substance.

'When people are assessing the credibility of information, most of the time people are making a judgement based on how something feels', Newman said. 'Our results showed that when the sound quality was poor, the participants thought the researcher wasn't as intelligent, they didn't like them as much and found their research less important.'

In the study, people viewed video clips of scientists speaking at conferences. One group of participants heard the recordings in clear high-quality audio, while the other group heard the same recordings with poor-quality audio.

Participants were then asked to evaluate the researchers and their work. Those who listened to the poorer quality audio consistently evaluated the scientists as less intelligent and their research as less important.

Researchers then upped the ante and conducted the same experiment with renowned scientists discussing their work on the well-known US Science Friday radio program. This time the recordings included audio of the scientists being introduced with their qualifications and institutional affiliations. 'It made no difference', Newman said. 'As soon as we reduced the audio quality, all of a sudden the scientists and their research lost credibility.'

As with the first experiments, participants thought the research was worse, the scientists less competent and the work less interesting.

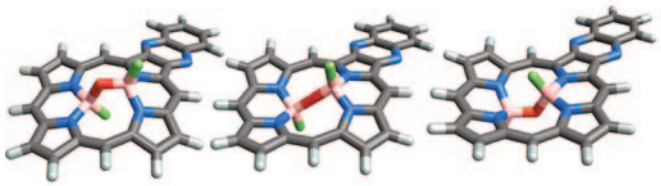
Newman said in a time when genuine science is struggling to be heard above fake news and alternative facts, researchers need to consider not only the content of their messages but features of the delivery.

'Another recent study showed false information travels six times faster than real information on Twitter', she said. 'Our results show that it's not just about who you are and what you are saying, it's about how your work is presented.'

The study has been published in *Science Communication* (doi: 10.1177/1075547018759345).

Australian National University

Discovery for grouping atoms invokes Pasteur



The researchers' molecules change shape by the central oxygen atom (shown in red) bending like a hinge. The left and right images show the shapes of these molecules when stable. If heated up, they transform into each other via the central shape.

Chemists have found a new way of joining groups of atoms together into shape-changing molecules – opening up the possibility of a new area of chemistry and the development of countless new drugs, microelectronics and materials with novel characteristics.

Discoveries of new ways to make isomers were last reported in 1961 and before then in 1914. The discovery of another form of isomerism means that a new range of materials could be prepared either with similar properties or with properties currently out of reach.

As well as new types of drugs, other applications include new materials that can be manipulated to be 'switched on or off', polymers with special performance characteristics and possibly new molecular information storage devices.

The research, which is published in *Nature Chemistry* (doi: 10.1038/s41557-018-0043-6), was led by PhD student Peter Canfield (University of Sydney), working closely with his supervisors Professor Maxwell Crossley (University of Sydney) and Professor Jeffrey Reimers (University of Technology Sydney and Shanghai University, China).

Canfield said he was excited by the possibilities of what might stem from the findings and the team was pursuing commercial applications.

Reimers said: 'Our team's advance sits at the same level of understanding as Louis Pasteur's discovery of chirality – a central feature of most modern molecular science.'

Reimers said the mathematics of geometry describes the fundamental ways in which atoms could be combined and hence all possible types of isomers.

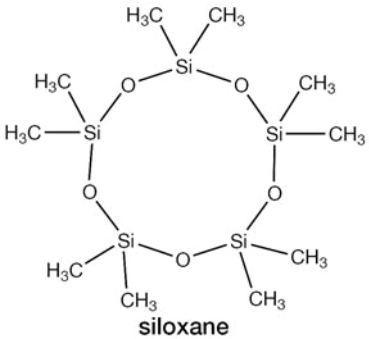
The team used nanoscale porphyrin scaffolds developed by Crossley to 'host' boron 'guest' molecules, resulting in isolable compounds.

Crossley explained: 'Porphyrins are very widely used by nature and by designers to grab and transport molecules and energy – we demonstrate new ways of binding guests to make this happen.'

Reimers concluded: 'Now that it is known that isolable isomers can be made in this way, the possibilities of what chemists could make are endless.'

University of Sydney

Personal care products contribute to pollution 'rush hour'



siloxane

When people are out and about, they leave plumes of chemicals behind them. Emissions of siloxane, a common ingredient in shampoos, lotions and deodorants, are comparable in magnitude to the emissions of major components of vehicle exhaust, such as benzene.

This work, published in *Environmental Science and Technology* (doi: 10.1021/acs.est.8b00506), is in line with other recent findings that chemical emissions from personal care products can contribute significantly to urban air pollution.

'We detected a pattern of emissions that coincides with human activity: people apply these products in the morning, leave their homes, and drive to work or school. So emissions spike during commuting hours', said lead author Matthew Coggon, University of Colorado Boulder, USA.

D5 siloxane (decamethylcyclopentasiloxane) is added to shampoos and lotions to give them a smooth, silky feeling. Siloxane is a volatile organic compound (VOC); once applied, it evaporates quickly. In the air, sunlight can trigger VOCs to react with nitrogen oxides and other compounds to form ozone and particulate matter – two types of pollution that are regulated because of their effects on air quality and human health.

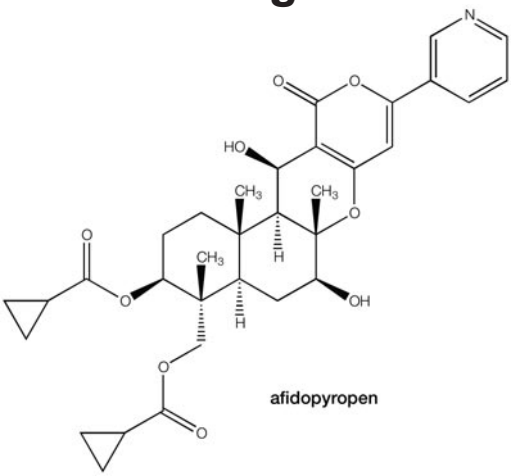
Coggon and his colleagues measured VOCs around Boulder. From about 150 chemicals, one compound caught their attention, which turned out to be siloxane. Although the siloxane emissions correlated with the benzene emissions from traffic, siloxane and benzene weren't coming from the same source. The two chemicals were linked to a particular human behaviour: commuting.

Siloxane emissions peaked in the morning, when people put on personal care products and went outside into their cars or buses. That's when benzene emissions went up too. Emissions of both chemicals decreased during the day, then peaked again during the evening commute. The evening peak of siloxane emissions was lower than in the morning, since the personal care products had largely evaporated throughout the day.

This study is part of an emerging body of research that finds emissions from consumer and industrial products are important sources of urban air pollution. The study also demonstrates that siloxane is a good indicator of the presence of emissions from personal care products. The research team is looking at other chemicals in personal care products that correlate with siloxane – one likely candidate is fragrance compounds. Coggon predicts they may also spike in the morning, as people commute.

University of Colorado at Boulder

Australian farmers get world-first access to latest agvet chemicals



Australian farmers are the first in the world to access new agricultural and veterinary (agvet) chemical technologies following approval from the Australian Pesticides and Veterinary Medicines Authority (APVMA) for afidopyropen and the fungus *Duddingtonia flagrans*.

APVMA Chief Executive Officer, Dr Chris Parker, said the registrations provide Australia's agricultural industries with enhanced access to safe and effective pest management tools for use in vegetable, cotton and livestock production.

Bubba73 (Jud McCranie)/CC BY-SA 4.0

'Australia is the first nation to register afidopyropen, which is an insecticide to aid in the control of aphids and silverleaf whitefly in cotton and vegetables', Parker said.

'The APVMA is also the first regulator to approve *Duddingtonia flagrans*, a biological present as a palatable feed supplement used to treat parasitic gastrointestinal nematodes of grazing animals.'

Details of the active constituent afidopyropen in Versys Insecticide and Duddingtonia flagrans in BioWorma and Livamol with BioWorma products can be found on the APVMA's public database of registered chemicals at portal.apvma.gov.au/pubcris.

APVMA

Breakthrough in battle against rice blast

Scientists have found a way to stop the spread of rice blast, a fungus that destroys up to 30% of the world's rice crop each year.

An international team led by the University of Exeter showed that chemical genetic inhibition of a single protein in the fungus stops it spreading inside a rice leaf – leaving it trapped within a single plant cell.

Rice blast is a hugely important disease in terms of global food security. However, the scientists caution that this is a 'fundamental' discovery – not a cure that can yet be applied outside the laboratory.

The research revealed how the fungus can manipulate and then squeeze through plasmodesmata – natural channels that exist between plant cells.

Senior author Professor Nick Talbot (University of Exeter) said the fungus 'is clearly able to suppress immune responses at pit fields (groups of plasmodesmata), and also regulate its own severe constriction to squeeze itself through such a narrow space.

'And all this is achieved by a single regulatory protein. It's a remarkable feat.'

Rice blast threatens global food security, destroying enough rice each year to feed 60 million people. It spreads within rice plants by invasive hyphae (branching filaments), which break through from cell to cell.

In their bid to understand this process, the researchers used chemical genetics to mutate a signalling protein, PMK1, to make it susceptible to a specific drug.

PMK1 is responsible for suppressing the rice's immunity and allowing the fungus to squeeze through pit fields – so, by inhibiting it, the researchers were able to trap the fungus within a cell.

This level of precision led the team to discover that just one enzyme, an MAP kinase, was responsible for regulating the invasive growth of rice blast.

The research team hopes this discovery will enable them to identify targets of this enzyme and thereby determine the molecular basis of this devastating disease.

The research was led by Dr Wasin Sakulkoo and is published in *Science* (doi: 10.1126/science.aaq0892).

University of Exeter

Corals control their own chemistry to stay healthy


Brocken Inaglory/CC BY-SA 4.0

Scientists from the ARC Centre of Excellence for Coral Reef Studies at the University of Western Australia have found that some corals can combat the effects of ocean acidification by controlling their own chemistry.

Coral reefs play an important role in protecting coastlines from damage by waves and storms, but also provide a habitat and shelter for many marine organisms. Major environmental challenges such as climate change threaten the survival of coral reefs worldwide.

The scientists have identified marine species that are resilient to ocean changes, which will help better understand how to protect coral reefs in the future.

Lead author Dr Thomas DeCarlo said rising CO_2 levels in the atmosphere were reflected in the ocean, which leads to ocean acidification.

'Acidification hampers the ability of the coral to form skeletons and shells, which are the building blocks of reefs', DeCarlo said.

'In the past few decades, hundreds of experiments have shown that corals have a highly diverse response to ocean acidification depending on the species. However, the reasons why some are more tolerant than others are not clearly understood.'

'Our testing showed corals with the most resistance are tolerant because of the way they are able to regulate their calcium levels', DeCarlo said. 'This technique means we can identify species that are relatively resistant to ocean acidification.'

'However, we are also looking at the costs associated with resisting acidification, which may make acidification-resistant corals more vulnerable to other stressors.'

Co-author Professor Malcolm McCulloch said previous studies found that even the more hardy coral species lose their ability to adapt to ocean acidification when they bleach under extreme heat events as experienced in 2016.

'When a coral bleaches, it expels its "powerhouse" – zooxanthellae symbionts – and loses the energy needed to keep its internal mechanisms running', he said. 'The longer corals stay bleached, the less likely they are to recover.'

The paper is published in *Proceedings of the Royal Society B* (https://dx.doi.org/10.6084/m9.figshare.c.4068788).

University of Western Australia

Nanotweezers open doors in medicine and mobile tech

It's difficult to conceptualise a world where humans could casually manipulate nanoscale objects at will or even control their own biological matter at a cellular level with light. But that is precisely what Yuebing Zheng is working towards with his 'nanotweezers' – a new tool for handling nanoparticles using light that could create opportunities for innovations in nanotechnology and individual health monitoring.

Building upon several years of research, Zheng and his team from the Cockrell School of Engineering, University of Texas at Austin, have developed opto-thermoelectric nanotweezers that will help lead to a greater understanding of matter and biological systems and open a range of possibilities for fundamental and technical innovation in nanophotonics – the study of light–matter interactions on the nanometre scale. They explain their new work in *Nature Photonics* (doi: 10.1038/s41566-018-0134-3).

Cooperation between nanophotonics, nanochemistry and nanophysics research has provided the tools to manipulate and analyse nanoparticles in ways that have, until now, been beyond our reach. The research team has demonstrated how, using their nanotweezers, light can be used at the nanoscale in the same way mechanical tweezers are used to handle larger samples.

As a general technique, the nanotweezers are applicable to a wide range of metal, semiconductor, polymer and dielectric nanostructures with charged or hydrophobic surfaces. Thus far, researchers have successfully 'trapped' silicon nanospheres, silica beads, polystyrene beads, silicon nanowires, germanium nanowires and metal nanostructures. The further arrangement of these nanomaterials in a rationally designed manner can lead to a better understanding of how matter organises and the potential discovery of new functional materials.

In a biological setting, Zheng believes that live cell manipulation and cell-to-cell communication will probably be a primary research focus for engineers wishing to exploit the capabilities afforded by the nanotweezers.

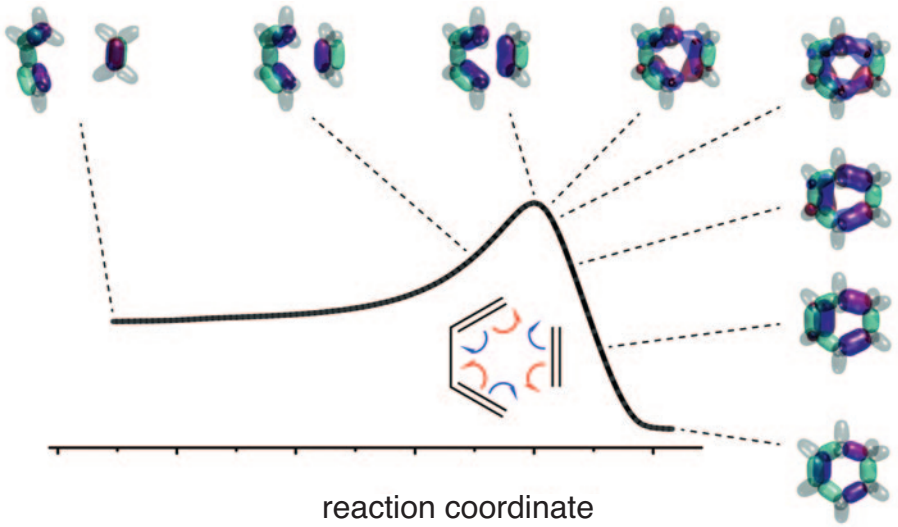
'Optimisation of the current system to make it bio-compatible is the next step of our project', Zheng said. 'We expect to use our tweezers to manipulate biological cells and molecules at single-molecule resolution, to control drug release and to study the cell–cell interaction. The manipulation and analysis of biological objects will open a new door to early disease diagnosis and the discovery of nanomedicine.'

Zheng is confident the technology will be commercialised, even to the point where nanotweezers could be adapted for use in a smartphone app, almost like a modern-day Swiss army knife.

University of Texas at Austin

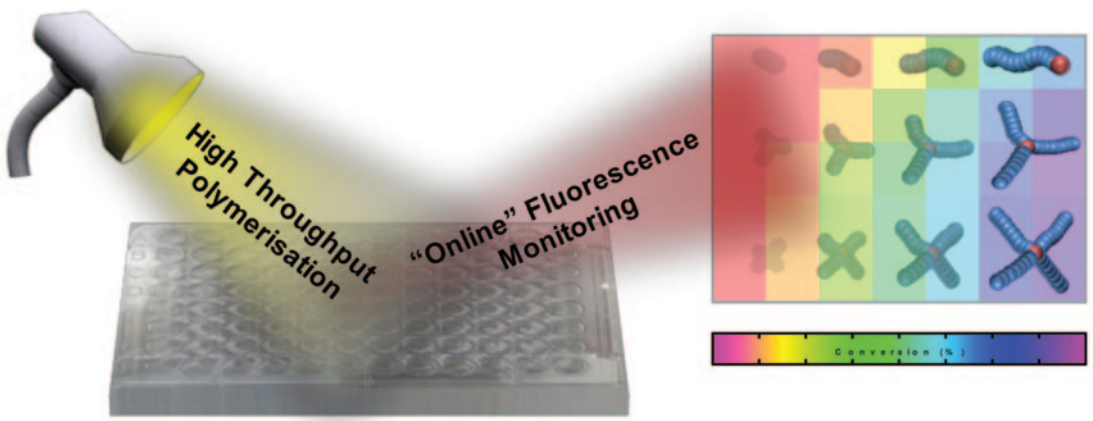
Connecting curly arrows and quantum chemistry

Curly arrows allow us to picture electron movements during an organic reaction mechanism, accounting for bond making and breaking. But, although curly arrows dovetail with our chemical intuition, they require Lewis structures, in which electrons are localised in bonds and lone pairs. How can this be reconciled with the delocalised electrons of molecular orbital theory? Yu Liu, Terry Frankcombe and Tim Schmidt from the University of New South Wales (UNSW) Sydney and UNSW Canberra have made the link by looking at the whole antisymmetrised wavefunction in a new way. When two electrons of the same spin exchange, the wavefunction changes sign but not magnitude, and this means that there are repeating regions in the wavefunction. These wavefunction 'tiles' yield structural elements such as lone pairs and banana bonds. With Phil Kilby from Data 61, the UNSW team showed that by analysing wavefunction tiles along a reaction coordinate, one can follow electron movements, yielding the paths depicted by curly arrow notation (Liu Y., Kilby P., Frankcombe T.J., Schmidt T.W. *Nat. Commun*. 2018, **9**, 1436). Understanding the [4+2] Diels–Alder reaction is a triumph of molecular orbital theory, and some textbooks decline to offer a curly arrow mechanism. Liu and co-workers found that one of each pair of banana bonds of the alkene and diene split, with each electron heading a different way.



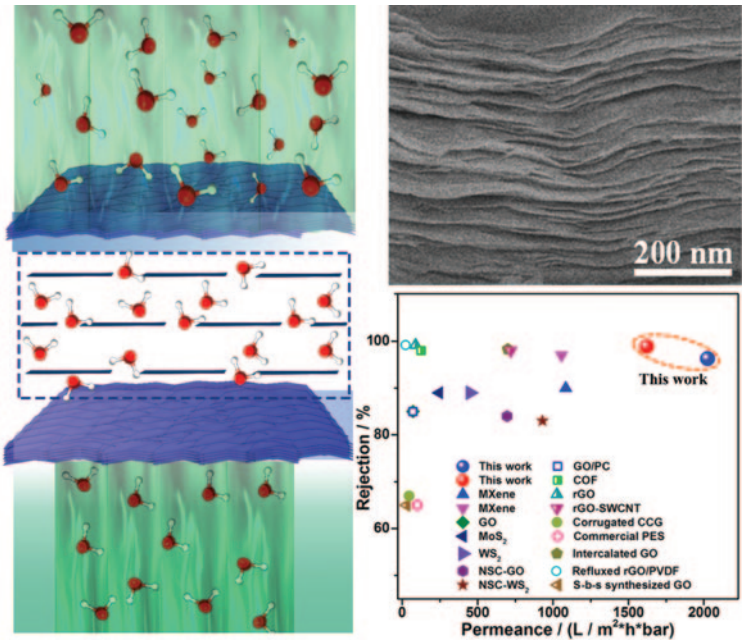
Photocatalyst for mediating and monitoring polymerisation

To improve the rate of materials discovery, oxygen-tolerant radical polymerisation techniques have been developed that can synthesise polymers with controllable molecular weights at ultralow volumes and with high throughput. But current techniques to monitor polymerisation are not ideal for high-throughput synthesis and typically require discrete sampling, which is limited by the sample quantity available. Recently, Cyrille Boyer and co-workers at UNSW have reported the discovery that a single photocatalyst can not only control a living radical polymerisation process in a low-volume high-throughput manner, but can also report on the polymerisation process via its fluorescence (Yeow J., Joshi S., Chapman R., Boyer C. *Angew. Chem. Int. Ed*. 2018, https://doi.org/10.1002/anie.201802992). During polymerisation, the photocatalyst's fluorescence emission shifts to longer wavelengths, allowing a ratiometric approach to quantify monomer conversion non-destructively and without the use of conventional techniques such as NMR spectroscopy. When polymerisation occurs in high-throughput 384-well plates, a fluorescence microplate reader can simultaneously measure monomer conversion across wells in an 'online' manner. This overcomes the issues of performing multiple single-sample measurements and has great potential to be translated into a feedback-controlled automated synthetic process for accelerating the discovery of novel polymer materials.

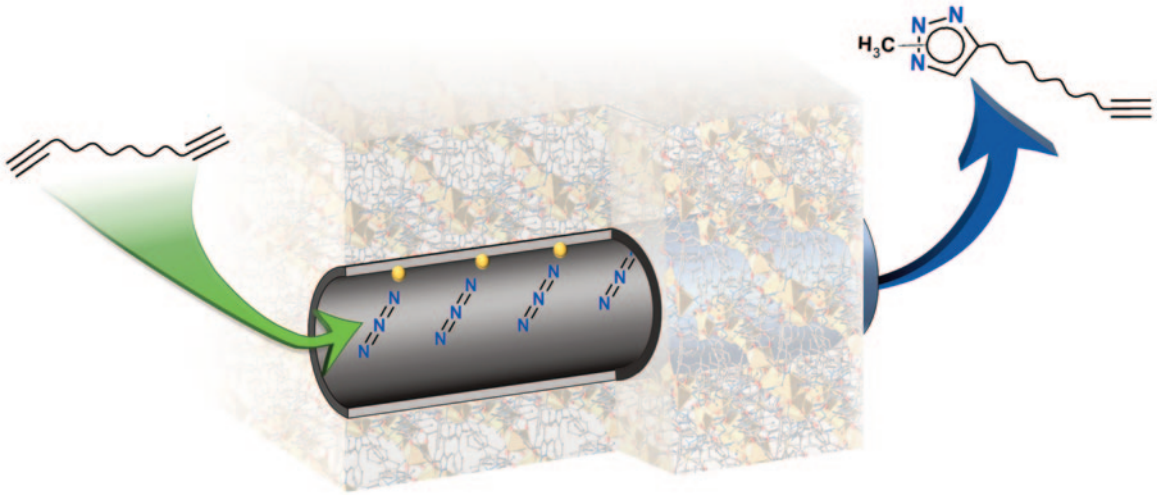


Regular nanochannels for ultrafast molecular transport

Researchers from the University of Adelaide, Zhengzhou University and Nankai University (China), and Kent State University (USA) have fabricated a lamellar membrane possessing ordered pores of uniform size with exceptional molecular permeation properties (Wang J., Chen P., Shi B., Guo W., Jaroniec M., Qiao S. *Angew. Chem. Int. Ed.* 2018, **57**, 6814–8). Double-layered $Ti_3C_2T_x$ MXenes were prepared by a soft-etching method. The rigidity of $Ti_3C_2T_x$ permitted a unique construction of ordered and stable 2 nm channels through a direct self-stacking procedure. This novel membrane exhibited precise molecular rejection of molecules larger than about 2 nm and, importantly, unparalleled molecular permeation. The permeance of the membrane to water and organics reached 2300 and 5000 L m^{-2} h^{-1} bar^{-1}, respectively, outperforming almost all existing lamellar membranes. A model equation was also established to describe the rate of molecular transfer in the confined nanoscale environment. This work paves the way for the nanoscale design of highly efficient fluid-transporting membranes with immense potential for separations, drug release and catalysis.

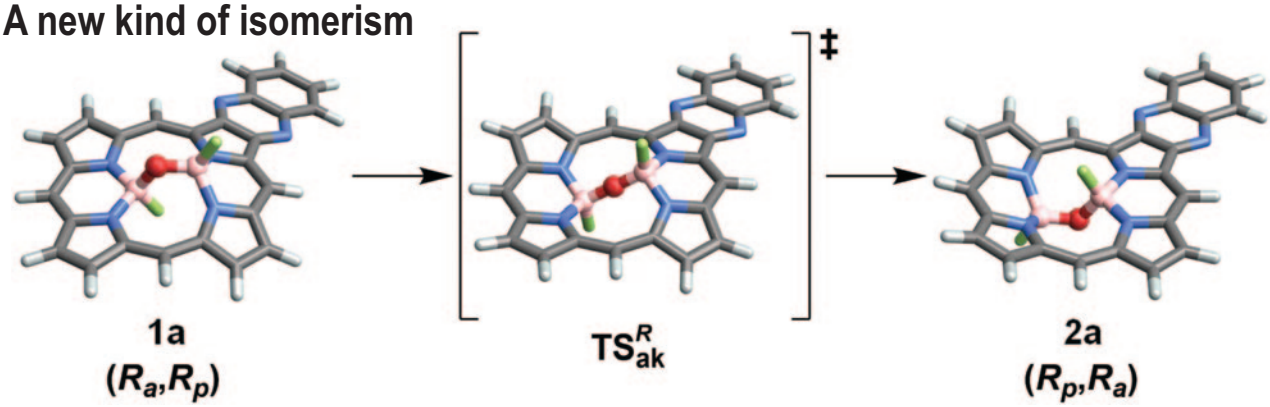


MOF nano-reactor for site-selective synthesis



University of Adelaide researchers, collaborating with colleagues at the University of Nottingham (UK), have employed a metal–organic framework (MOF) as a bespoke nano-reactor for site-selective chemical transformations (Huxley M.T., Burgun A., Ghodrati H., Coghlan C.J., Lemieux A., Champness N.R., Huang D.M., Doonan C.J., Sumby C.J. *J. Am. Chem. Soc.* 2018, **140**, 6416–25). The team prepared a MOF post-synthetically decorated with Mn^{I} tricarbonyl azide complexes that were regularly spaced (separated by 13 Å) along its one-dimensional pores. When exposed to a dialkyne with an alkyne separation less than the azide spacing, an alkyne-functionalised triazolate is selectively furnished by a Huisingen azide–alkyne cycloaddition. The *N*-methyl triazole can then be released by alkylation with methyl bromide, which regenerates the nano-reactor for further cycles. When the alkyne separation of the dialkyne exceeds the azide spacing, the selectivity is lost, resulting in a mixture of bis- and mono-triazole products. The authors showed that, once the short dialkyne has reacted, the pendant alkyne substituent cannot reach the adjacent azide and is subsequently prevented from undergoing the unwanted secondary cycloaddition reaction. This concept of site-selective chemistry, facilitated by the angstrom-scale control of reactive-site positioning that is possible inside MOF nano-reactors, could be tremendously advantageous for organic synthesis.

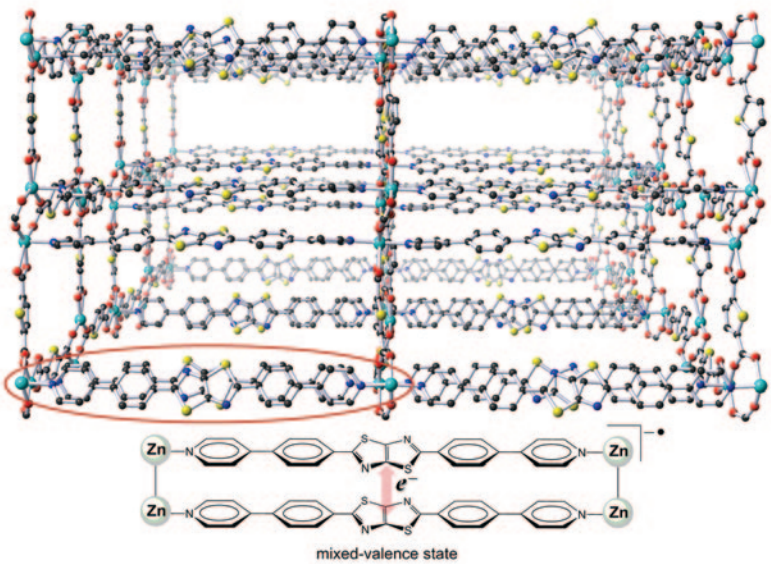
A new kind of isomerism



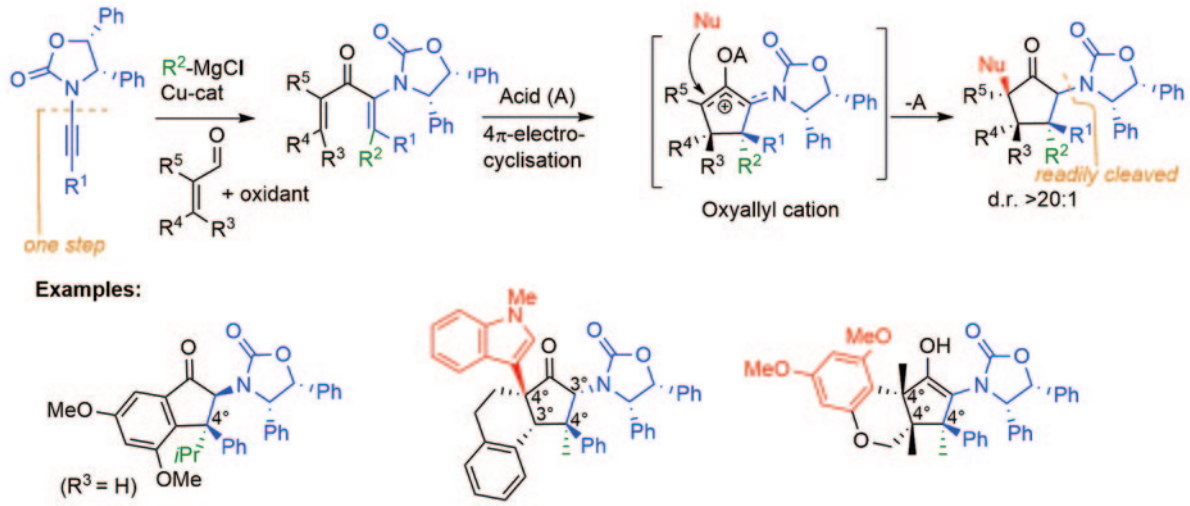
The final possible simple form of conformational isomerism has been revealed by Peter Canfield, his supervisors Maxwell Crossley (University of Sydney) and Jeffrey Reimers (University of Technology Sydney and Shanghai University, China), their teams, and collaborators Elmars Krausz and Rika Kobayashi (ANU) (Canfield P.J., Blake I.M., Cai Z.-L., Luck I.J., Krausz E., Kobayashi R., Reimers J.R., Crossley M.J. *Nat. Chem.* 2018, **10**, 615–24). Careful analysis of stereochemical interconversions led the team to consider that there was *one* unrecognised fundamental type of conformational isomerism remaining that, for example, could be produced by bond-angle inversion about centres of the form L–M–L linked only by single bonds. Calculations suggested that the bond-angle inversion reaction would occur in a constrained system in which the central atom would show an sp^3 to sp to sp^3 rehybridisation in the inversion sequence. This sequence was observed and studied in detail in a quinoxalino–porphyrin system with internal coordinated boron atoms in a 1,3-difluoro-1λ^4,3λ^4-diboroxan-1,1,3,3-tetrayl group ((BF)O(BF)), in which each boron is bonded in a *transoid* fashion to two adjacent pyrrolic nitrogen atoms. Four enantiomerically pure compounds were synthesised and their interconversions studied, each interconverting with complete stereoselectivity with an enantiomerically pure diasteromer (e.g. **1a** and **2a**) with $\Delta G^{\ddagger} = 104 \pm 2$ kJ mol^{-1}, ruling out all mechanisms but bond-angle inversion. The team has named the process *akamptisomerisation* and has introduced a new nomenclature to encompass such compounds.

Charge transfer in 3D framework materials

Mixed valency is ubiquitous in chemical, physical and biological systems – from gemstones such as sapphire to photosynthetic organisms such as purple bacteria that derive their colour and function from this phenomenon. Research led by Deanna D'Alessandro from the University of Sydney has revealed a new through-space mixed-valence mechanism for electron transfer in metal–organic frameworks (MOFs) (Hua C., Doheny P.W., Ding B., Chan B., Yu M., Kepert C.J., D'Alessandro D.M. *J. Am. Chem. Soc.* 2018, **140**, 6622–30). Using a highly complementary experimental and computational approach, the team demonstrated that MOFs containing a cofacial alignment of ligands exist in a mixed-valence state upon solid-state electrochemical, spectroelectrochemical and chemical reduction. Intervalence charge transfer bands provided a definitive optical signature for mixed valency and were analysed by Marcus–Hush theory. The theoretically predicted distance dependence for this electron transfer – well known in simple molecular systems – was also experimentally elucidated for the first time in framework materials. Understanding electron transfer mechanisms in these systems is critical to realising next-generation technologies based on MOFs for applications in energy storage and conversion, electrochromic devices, electrocatalysis and battery materials, among others.



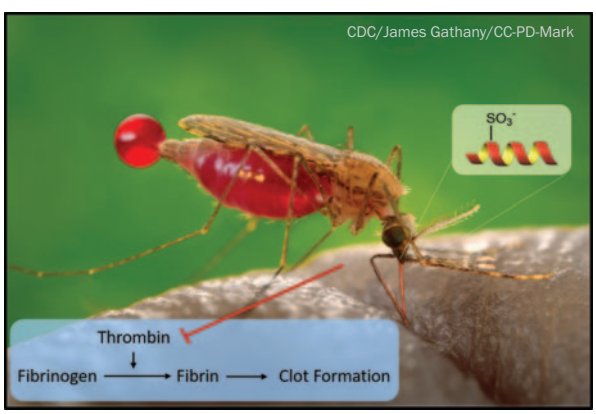
Quaternary stereocentres made easy



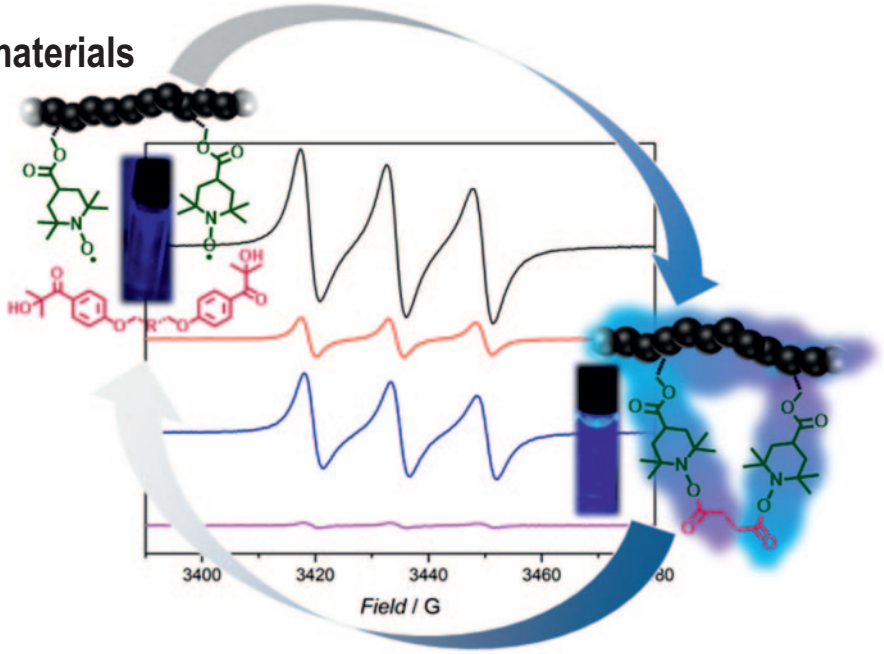
Enantioselective formation of all-carbon quaternary (4°) stereocentres is an enduring challenge in organic synthesis. A strategy for rapid enantioselective assembly of cyclopentanones containing up to three contiguous all-carbon 4° stereocentres has been developed by researchers from Monash University and the University of Queensland (Volpe R., Lepage R.J., White J.M., Krenske E.H., Flynn B.L. *Chem. Sci.* 2018, **9**, 4644–9). Carbometallation of oxazolidinone-substituted alkynes gives ready access to highly substituted divinyl and arylvinyl ketones. The oxazolidinone serves as a powerful chiral promoter of a subsequent acid-catalysed 4π-electrocyclisation (Nazarov cyclisation), enabling the stereoselective cyclisations of these sterically congested substrates to be achieved under remarkably mild conditions. The oxazolidinone stabilises the resultant oxyallyl cation intermediate, enabling the formation of an additional 4° centre through nucleophilic (Nu) trapping. Theoretical studies revealed how the auxiliary accelerates and directs the cyclisation through a combination of covalent and non-covalent interactions, including a key CH–π interaction. The new method converts simple alkynes into a diverse array of sp^3-rich cyclopentanoids in just a few steps, removing 'synthetic tractability' as a deterrent to their use in drug discovery.

Malaria mosquito saliva yields promising anticoagulants

Many blood-feeding organisms, including the malaria mosquito vector *Anopheles*, possess a suite of anticoagulant proteins in their saliva to enable access to their blood meal. Many of these proteins target the central blood-clotting enzyme thrombin, with this interaction modulated by post-translational modifications of the salivary proteins. Post-translational sulfation of tyrosine residues has been predicted to be important for activity, but such modifications are notoriously difficult to detect owing to the extremely labile nature of the aryl sulfate ester modification. The Payne laboratory at the University of Sydney has led a multidisciplinary effort to determine the functional role of this modification in salivary proteins from the *Anopheles* mosquito called the anophelins and demonstrates the potential application of this family of proteins as therapeutic anticoagulants (Watson E.E., Liu X., Thompson R.E., Ripoll-Rozada J., Wu M., Alwis I., Gori A., Loh C.-T., Parker B.L., Otting G., Jackson S., Pereira P.J.B., Payne R.J. *ACS Cent. Sci.* 2018, **4**, 468–76). Using cutting-edge peptide ligation methods, the team synthesised a library of differentially sulfated anophelin proteins in homogeneous form. In vitro biochemical screening of these sulfoproteins demonstrated the importance of modification at these key residues, with sulfation yielding up to two orders of magnitude increase in inhibition of thrombin. Most excitingly, these sulfoproteins were shown to prevent clot formation in an in vivo model of thrombosis, suggesting that they may have clinical significance for diseases such as stroke.

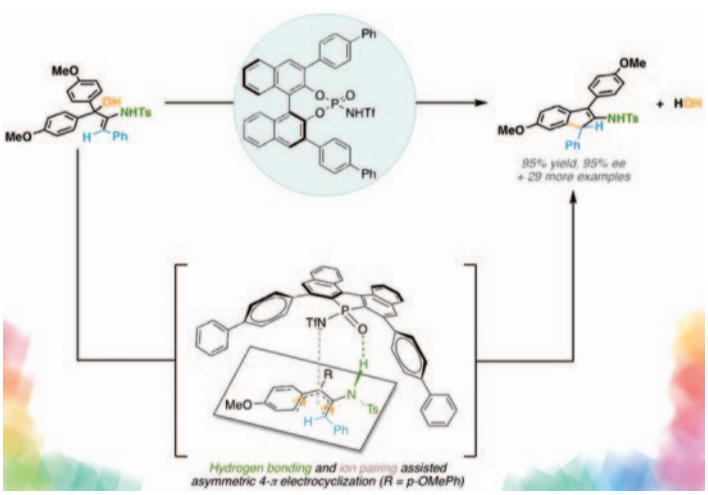


Self-reporting functional materials



A transnational team from the Queensland University of Technology and the Karlsruhe Institute of Technology, Germany, has pioneered a method to track the morphological state of polymer chains by the emissions of photons (Fischer T.S., Spann S., An Q., Luy B., Tsotsalas M., Blinco J.P., Mutlu H., Barner-Kowollik C. *Chem. Sci*. 2018, **9**, 4696–702). The method exploits polymer chains that can self-report via fluorescence emission when they fold into single-chain nanoparticles. Well-defined copolymers featuring nitroxide radicals along the chain were prepared by reversible deactivation radical polymerisation. Subsequent formation of single-chain nanoparticles was achieved in highly dilute solution by exploiting the UV-light-triggered reaction of these nitroxides with a bifunctional crosslinker acting as a photolabile radical source. The reversible and dynamic nature of the covalent crosslinks was exploited to unfold the particles under oxidative conditions. The unambiguous verification of the re-formation of the nitroxide radicals was demonstrated by electron paramagnetic resonance spectroscopy. Most importantly, however, the prepared single-chain nanoparticles self-report via an inherent strong fluorescence, whereas the open unfolded polymer does not fluoresce because of fluorescence quenching by the nitroxide radicals. The work paves the way for reading out the structure of polymer chains by a simple optical signal.

Ion pair assists enantioselective electrocyclisation



A continuing challenge in organic synthesis is the creation of a well-defined stereochemical environment for functional group transformations to occur in an asymmetric manner. An example of this is the dehydrative Nazarov-type electrocyclisation (DNE) reaction of divinyl and hetero(aryl) vinyl alcohols to 1,3-cyclopentadiene derivatives. Recently, studies by Jianwen Jin, Yichao Zhao and Philip Chan at Monash University have led to the development of the first enantioselective variant of the DNE reaction using chiral Brønsted acid catalysis (Jin J., Zhao Y., Gouranourimi A., Ariafard A., Chan P.W.H. *J. Am. Chem. Soc.* 2018, **140**, 5834–41). The asymmetric 4π electrocyclisation reaction provided a convenient and efficient synthetic route to enantio-enriched 1*H*-indenes and 4*H*-cyclopenta[*b*]thiophenes from readily accessible aryl and 2-thienyl vinyl alcohols. The product enantiomeric excess (ee) values of up to 99% obtained in this study were achieved by the assembly of an intimate contact ion-pair species that was further assisted by hydrogen-bonding interactions. The role of this species in the induction of chirality was also supported by computational studies by Ali Gouranourimi and Alireza Ariafard at the University of Tasmania.

Compiled by **David Huang** MRACI CChem (david.huang@adelaide.edu.au). This section showcases the very best research carried out primarily in Australia. RACI members whose recent work has been published in high impact journals (e.g. *Nature*, *J. Am. Chem. Soc.*, *Angew. Chem. Int. Ed.*) are encouraged to contribute general summaries, of no more than 200 words, and an image to David.

Drugs for influenza

A key scientist in one of the earliest examples of structure-based drug design, Peter Colman reflects on work to describe the influenza virus protein neuraminidase and discusses the challenges facing ongoing efforts to expand the portfolio of anti-influenza drugs.

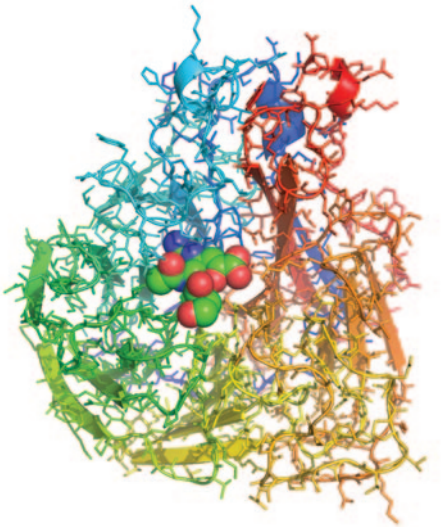
The cover of *Nature* on 5 May 1983 announced the description of the three-dimensional structure of the influenza virus protein neuraminidase. Jose Varghese, Graeme Laver and I used X-ray crystallography to pinpoint the position of more than 3000 non-hydrogen atoms in the structure, showing that the protein chain was folded up in a novel way, resembling a propeller. In the preceding months, others, including our CSIRO colleague Colin Ward, had worked out the sequence of the 400 or so amino acids within the protein, building up a linear picture of how one strain of the virus varied from another. These results, when laid out in three dimensions on the crystal structure, showed that amino acids subject to strain variation were distributed around the surface of the protein but those that were conserved between strains were concentrated in a pocket-shaped feature that we identified as the 'active site' of neuraminidase.

The role of the neuraminidase protein in the viral life cycle is to allow the release of progeny virions from an infected cell. Without a neuraminidase function, the newly made viruses remain tethered to the infected cell by an interaction between another viral protein – the haemagglutinin – and a receptor molecule on the infected cell surface. By clipping off this receptor, the neuraminidase liberates the viral progeny to go and infect other cells. The particular 3D arrangement of amino acids within the active site, recruited there from linearly distant positions in the sequence by the folding of the protein chain, provides the energy required to cut the chemical bond between the receptor molecule and the infected cell. Thus, it is unsurprising that those amino acids in the active site are preserved in all strains of virus; changes to them destroy the neuraminidase's cutting action, without which the virus is not viable.

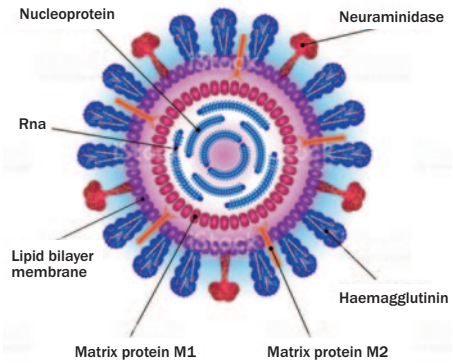
Between 1985 and 1990, supported by a start-up company (Biota Holdings Ltd), Varghese and I worked closely with a team of chemists, including Wen-Yang Wu and Mark von Itzstein, recruited for the purpose of designing and synthesising molecules that might disable the neuraminidase. The idea was that a compound that snugly fitted the neuraminidase active site and inhibited the protein's activity would interrupt the viral life cycle and be effective against all strains of virus. In 1990, Biota licensed our discovery, zanamivir, to Glaxo (now GSK) to see if it could be developed into a drug. In 1993, *Nature* reported the results of our work, including a demonstration by Glaxo that the compound was effective in a ferret model of influenza if delivered intranasally. Three years later, competitors emerged with a close analogue of zanamivir, oseltamivir, that (unlike zanamivir) is membrane-permeable and enters the bloodstream if administered orally. This discovery was driven by the expectation that patients (and physicians) would prefer a drug in tablet form. (That has proven to be the case, even though a topically delivered drug that is unable to cross a membrane is effective because the neuraminidase is located on the outside of the virus and exerts its function when the virus is outside host cells.)

The first study of the efficacy of zanamivir in humans was performed by Fred Hayden at the University of Virginia, USA, and reported in 1996. Hayden's result clearly showed that zanamivir was effective in reducing the viral burden in infected volunteers, but the effect would be marginal if the delay between infection and drug intervention exceeded two days. This result has much to do with the normal cycle of influenza infection, which typically resolves naturally after a week or so, having reached its peak 2–3 days after infection.

Clinical trials over the following years led to registration of both compounds in 1999, zanamivir formulated as Relenza and taken by oral inhalation and oseltamivir formulated as Tamiflu and taken orally. Recently (2014), both of the companies involved, GSK and Roche, have come under fire from the Cochrane Collaboration for selectively publishing results of these trials, some of which showed only marginal benefit in the median time to recovery for trial subjects. (The so-called 'end-point' of these trials is reached when a trial subject declares themselves well again.) It is arguable whether median time to recovery is the best end-point for these difficult clinical trials, which can only be performed when influenza is circulating in the community. Nevertheless, nothing less than full disclosure of clinical trial results should be required for drug registration. Cochrane, a group that monitors and reviews healthcare measures, argued that the benefits of the drugs did not justify expenditure by governments in stockpiling them for use in the event of an influenza pandemic.

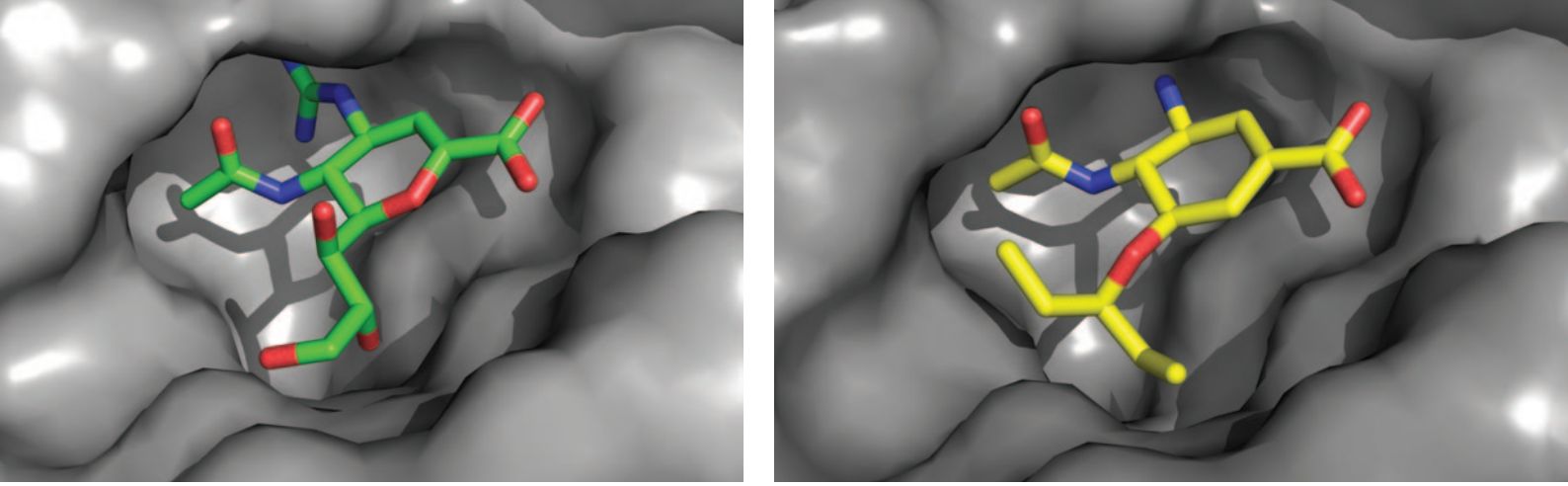


The atomic structure of the influenza virus neuraminidase. Colouring is rainbow, blue at the start of the polypeptide chain and red at the end. The drug molecule zanamivir is represented as spheres (carbon green, oxygen red, nitrogen blue, hydrogen not shown). It binds in a pocket-shaped feature on the surface of the protein where the amino acid sequences of all different strains of influenza virus are invariant. In contrast, amino acid sequence differences between strains litter the remainder of the surface of the molecule.



The structure of the influenza virus.
iStockphoto/moonnoon

The role of the neuraminidase protein in the viral life cycle is to allow the release of progeny virions from an infected cell.



Zanamivir (left: carbon green, oxygen red, nitrogen blue, hydrogen not shown) and oseltamivir carboxylate (right: carbon yellow, oxygen red, nitrogen blue, hydrogen not shown) in the active site pocket of neuraminidase (shown as a grey surface). Two modifications to sialic acid were introduced to generate zanamivir; one was to make the sugar planar at the C2 carbon atom where the carboxylate is attached and the other was to introduce a guanidinium group for the hydroxyl at C4. Oseltamivir carboxylate is further modified with respect to sialic acid, including by the introduction of a pentyl ether for the glycerol side chain.

Immediately following the Cochrane report came the PRIDE Study (University of Nottingham, UK) on the use of the neuraminidase inhibitors on some 30 000 patients hospitalised during the 2009 influenza pandemic. This study did not measure time to recovery but measured recovery itself. For this patient cohort, the odds of dying were halved if they received the drug within two days of the onset of symptoms compared to those whose treatment was delayed to five or more days. The estimated death toll from the 2009 pandemic is in excess of 200 000 and the study suggests that halving that number would have been achievable. Governments continue stockpiling neuraminidase inhibitors, though a debate with Cochrane continues over the PPRIDE study, now centred on methods of statistical analysis of data.

But, how has the claim of drug efficacy against all strains of virus played out? The devil really is in the detail.

Our crystallographic experiments on neuraminidase were performed both with the protein alone and with the protein bound to the influenza receptor sialic acid. This showed that no changes occurred to the neuraminidase structure when it engaged the receptor for its cleavage. Zanamivir is very similar in structure to sialic acid. Only minor, though critical, changes were made to sialic acid to enhance the affinity for the protein and to generate the drug. The crystallography of zanamivir bound to the protein showed that it engaged only conserved amino acids in the active site and, like sialic acid, required no change to the protein structure for its binding.

Oseltamivir carboxylate has many of the features of zanamivir, but critically important changes were made, not to enhance its affinity but to improve its pharmacological properties to allow oral administration. These changes come with some cost because now the neuraminidase structure needs to change very slightly (of the order of an atomic diameter or so) in order to bind the drug. In 2000, we observed that this structural change introduced a 'resistance window' that could compromise Tamiflu's capacity to work against all virus strains. Resistant viruses are readily selected in the laboratory simply by culturing the virus in the presence of the drugs. Later, a circulating influenza virus was discovered containing such a mutation (the substitution of amino acid histidine 275 with tyrosine, H275Y) that impeded the structural change required for oseltamivir carboxylate (but not zanamivir) to bind, and which was, as a result, resistant to Tamiflu.

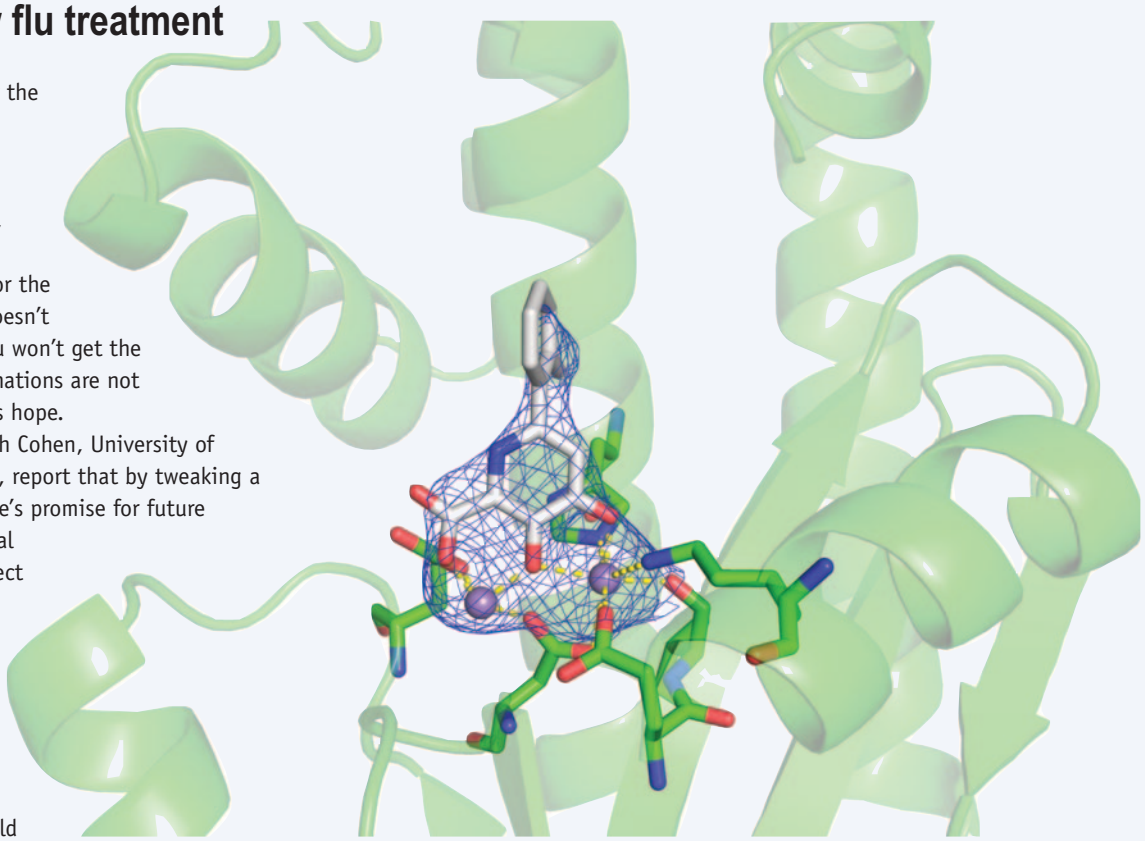
Usually, influenza is an acute infection and drug treatment regimens are for only five days. Under these circumstances, the virus has little time to acquire resistance in a patient undergoing drug treatment. For Tamiflu, five years of monitoring such acquired resistance in patients infected with influenza A viruses resulted in a reported 5% incidence of resistance in viruses of the 2009 H1N1 pandemic strain ('swine flu') and a 2% incidence in H3N2 viruses. All of the N1 resistance was identified as H275Y, and all of the N2 resistance was R292K. For Relenza, which is far less-widely used, no comparable data is available.

Antiviral and antibacterial medicines all face limited utility depending on how quickly the virus or bacterium acquires resistance. One way to tip the odds in favour of the drug is to have it resemble the natural ligands of the target as closely as possible. Other ways include using cocktails of drugs that require multiple mutations before resistance emerges.

Other drug targets in the influenza virus are being actively pursued, including the proteins that copy the viral genes. Typically, these research endeavours are headlined with the promise of drugs that will be effective against all influenza strains. Lessons learned from the neuraminidase inhibitors should inform considerations about the likely emergence of drug-resistant viruses and aid clinical trial design to improve the likelihood of establishing bone fide clinical efficacy.

Peter Colman trained in physics (University of Adelaide) before commencing his research career in structural biology. He was at CSIRO for two decades during the period of the discovery of zanamivir. Since 2001, he has been at the Walter and Eliza Hall Institute investigating the structural biology of cell death and its translation into new medicines for certain cancers.

Hope for a new flu treatment



A new antiviral drug inhibits replication of influenza's genome by binding to manganese ions (purple spheres).
Christine Morrison

Each year, people all over the world die from the flu. To protect against influenza epidemics and their potentially mortal results, medical professionals encourage vaccination. For the healthy, getting a shot doesn't necessarily mean that you won't get the flu because current vaccinations are not foolproof. But now there's hope.

Researchers led by Seth Cohen, University of California San Diego, USA, report that by tweaking a small-molecule drug, there's promise for future production of new antiviral therapies that could protect patients from the flu – regardless of the strain they contract.

'This is a medicinal intervention that will slow down the virus, if not completely stop it', Cohen said. 'The drug could potentially eliminate the virus on its own or just sufficiently slow its reproduction so that the body can ultimately clear it. It's like taking an antibiotic for a viral infection.'

Since the start of the US 2017–18 flu season in October 2017, the Centers for Disease Control and Prevention (CDC) has reported nearly 66 000 positive tests for the virus in the US, resulting in hundreds of deaths. The CDC attributes such an active season to the presence of influenza A H3N2. Flu vaccines are less effective against these 'H3' type viruses because these pathogens are more likely than other strains to mutate after the vaccine has been produced. Although in most years the vaccine is highly effective at keeping people from contracting the flu, this 'H3 flaw' is motivating scientists to seek more reliable treatments.

In order to develop an antiviral drug for influenza, scientists had to find an area within its structure that would prove vulnerable. The influenza virus is a lipid-enveloped, negative-sense, single-strand RNA virus, meaning the genetic information it uses for replication is contained in RNA strands held inside a protein shell that is coated by a fatty layer. Instead of relying on a host's straightforward DNA replication process as some other viruses do, influenza depends on its own enzyme called RNA-dependent RNA polymerase. So, scientists have consistently focused research efforts on developing a drug that would affect this viral process.

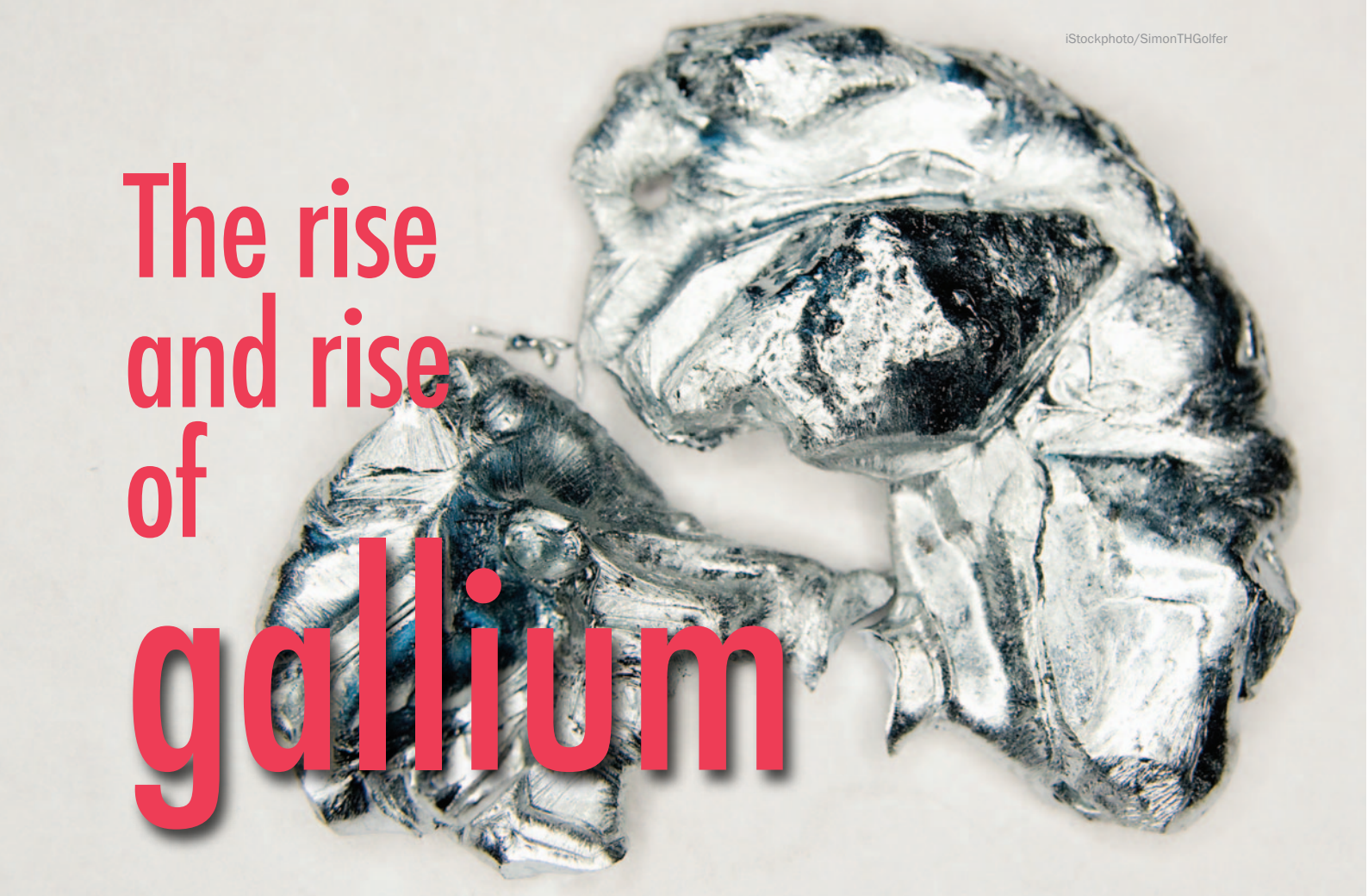
Cohen notes that the RNA polymerase complex remains constant across many different versions and mutations of the influenza virus. Therefore, any therapies that target it are not likely to suffer from the issue the vaccine faces; namely, the H3 flaw. The RNA polymerase itself is divided into three subunits. Cohen has homed in on a metal-centred domain within one of the subunits.

The subunit relies on two manganese ions to initiate the replication of the genetic information. Scientists have reasoned that a drug that could bind to the manganese ions would shut down the protein's ability to work, leaving the virus unable to reproduce and spread through the body. This could weaken or perhaps completely stop the virus, thereby treating the flu.

Cohen has spent the past two years developing a better drug that would serve as a wrench in the virus' replication works. 'We modified our small-molecule drug so that it would bind to both manganese ions simultaneously', he said.

He then tested the molecule on the RNA polymerase protein. 'The modification dramatically improved the potency of the compound over previous drugs we created', he said. 'The team is hopeful that in the coming months, it will be just as effective when they challenge the whole influenza virus with the molecule.'

UC San Diego



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The rise and rise of gallium

Dave Sammut and **Chantelle Craig** report on the history and emerging applications of an element with a controversial past and strategic future.

Early on the morning of 7 September 2010, the Chinese fishing vessel *Minjinyu 5179* was detected in disputed Japanese territory near the Senkaku Islands. During the subsequent chase, the Chinese vessel reportedly twice rammed Coast Guard vessels. Its captain and crew were arrested and detained. Within three weeks, the Japanese controversially capitulated to escalating Chinese diplomatic pressure to release the captive fishermen.

Regardless of its diplomatic victory, China took direct retaliatory action that precipitated a global metals crisis. With more than 95% of global capacity for the production of purified rare earth metals and oxides, the Chinese were in a position to strangle international supply. Prices skyrocketed until two successive World Trade Organization judgements declared China's actions illegal. In 2015 the country was forced to remove trade restrictions.

The West was delivered a lesson in how incredibly vulnerable its supplies of key strategic metals had become. By December 2017, under Presidential order, the US Geological Survey (USGS) had issued a list of more than 30 critical minerals 'essential to the economic and national security of the United States'.

This is not another story about the (somewhat misleadingly named) 'rare earth' metals. It's about an element that hasn't been in the news, an element with a storied history and an increasingly strategic future: gallium.

Gallium came to the scientific community in fascinating, if somewhat controversial, circumstances. When Dmitri Mendeleev first laid down his version of the periodic table in the 1869 German publication *Zeitschrift für Chemie*, he left several spaces for elements yet to be discovered. Most importantly, he used the periodicity of his approach to *predict* the elements of these as-yet unknown elements.

One of these Mendeleev named 'eka-Aluminium', borrowing a Sanskrit word for the prefix, most usually translated as 'beyond'. He predicted that the missing element would have an 'atomic weight' (more accurately, a relative atomic mass) of approximately 68 grams, a density of about 6 g/cm^3, valence of 3 and a low melting point, and that it would be discovered by spectroscopy.

When French chemist Paul-Émile Lecoq de Boisbaudran discovered this

element six years later with spectroscopic studies, Mendeleev was quick to claim a portion of the credit. This didn't go down well, and the two soon began to argue in the scientific journals. It was an early version of a 'flame war', at a time when the Bunsen burner had only recently been invented.

Lecoq de Boisbaudran claimed that he had never seen Mendeleev's table, and later that Mendeleev had stolen his idea from an obscure French researcher. Conversely, observers have argued that Lecoq de Boisbaudran specifically looked for gallium in zinc-bearing sphalerite ores on the basis of its proximity and anticipated similarity to zinc. His first pure sample of 0.65 grams of gallium was painstakingly extracted from 430 kilograms of ore, which is a lot of trouble to go to if Lecoq de Boisbaudran wasn't fully expecting the new element to be present.

Lecoq de Boisbaudran's troubles didn't end there. He was accused of naming gallium after himself (Lecoq, 'the rooster', is *gallus* in Latin), while he insisted that the name was a patriotic reference to *Gallia*, the Latin for France.

Escalating the feud, Mendeleev declared that Lecoq de Boisbaudran's initial published characterisation of the properties of this new element were incorrect, because they didn't match his predicted values. After more thorough testing, Mendeleev was proved correct, and Lecoq de Boisbaudran was forced to retract his initial data. It was a major vindication for Mendeleev's still-contentious periodic table, and for theoretical science over empirical science in general. In the words of Albert Einstein, 'It is the theory that decides what can be observed'.

As it turns out, gallium's actual values are atomic mass 69.72 grams, density 5.9 g/cm^3, valence 3, and melting point just 29.7°C. It is one of only four metals that melt at low temperature (the others being mercury, caesium and francium). This curious property was the basis for a famous 19th-century practical joke. The jokester would cast a lustrous grey metal spoon (somewhat like aluminium) in gallium, which would rapidly melt when used to stir the unwitting victim's tea. Sam Kean used this for the title of his entertaining science history book *The disappearing spoon*.

As Mendeleev predicted, gallium is reactive with both acids and alkalis. Unlike even aluminium, its elemental form is never found in nature, and it is most commonly found as a substitute for elements with similar atomic size and charge, particularly in bauxite, sphalerite and (by mechanisms still unknown) coal. Even in these materials, it is relatively scarce (around 50 g/t).

With such low abundance, there are no economic primary sources of gallium. It is recovered only as a

On the critical list

Under the US Executive Order, the following commodities qualify as 'critical minerals' because each has been identified as a non-fuel mineral or mineral material that is essential to the economic and national security of the USA, that has a supply chain vulnerable to disruption, and that serves an essential function in the manufacturing of a product, the absence of which would have significant consequences for the economy or national security.

Critical mineral	Uses
Aluminium (bauxite)	Almost all sectors of the economy
Antimony	Batteries and flame retardants
Arsenic	Lumber preservatives, pesticides and semiconductors
Barite	Cement and petroleum industries
Beryllium	Alloying agent in aerospace and defence industries
Bismuth	Medical and atomic research
Caesium	Research and development
Chromium	Stainless steel and other alloys
Cobalt	Rechargeable batteries and superalloys
Fluorspar	Manufacture of aluminium, petrol and uranium fuel
Gallium	Integrated circuits and optical devices such as LEDs
Germanium	Fibre optics and night vision applications
Graphite (natural)	Lubricants, batteries and fuel cells
Hafnium	Nuclear control rods, alloys and high-temperature ceramics
Helium	MRIs, lifting agent and research
Indium	LCD screens
Lithium	Batteries
Magnesium	Furnace linings for manufacturing steel and ceramics
Manganese	Steelmaking
Niobium	Steel alloys
Platinum group metals	Catalytic agents
Potash	Fertiliser
Rare earth elements group	Batteries and electronics
Rhenium	Lead-free petrol and superalloys
Rubidium	Research and development in electronics
Scandium	Alloys and fuel cells
Strontium	Pyrotechnics and ceramic magnets
Tantalum	Electronic components, mostly capacitors
Tellurium	Steelmaking and solar cells
Tin	Protective coatings and alloys for steel
Titanium	White pigment or metal alloys
Tungsten	To make wear-resistant metals
Uranium	Nuclear fuel
Vanadium	Titanium alloys
Zirconium	High-temperature ceramics industries

Source: https://on.doi.gov/2xdWWdw

... blue LEDs (and their ability to combine with red and green to give white light LEDs) now form the basis for a substantial and growing portion of global gallium demand.

by-product, with about 90% of primary global supply coming from the Bayer process for bauxite processing to alumina. Under the highly caustic Bayer conditions, both the aluminium and gallium dissolve:

$$Al(OH)_3 + NaOH \rightarrow Na[Al(OH)_4]$$
$$AlOOH + NaOH + H_2O \rightarrow Na[Al(OH)_4]$$
$$Ga_2O_3 + 2NaOH + 3H_2O \rightarrow 2Na[Ga(OH)_4]$$

Upon cooling and seeding, the aluminium is precipitated from the Bayer liquor:

$$Na[Al(OH)_4] \rightarrow Al(OH)_3 + NaOH$$

but with its higher solubility, the gallium stays in solution. Over multiple cycles, the gallium accumulates in solution, up to about 300 mg/L. Up until the 1990s, this was then recovered by a multistep process of carbonation/acidification, redissolution and reprecipitation, but modern processes are more likely to employ solvent extraction to recover the gallium.

Like many elements, gallium remained in relative obscurity up until the 1950s, towards the dawn of the modern electrical age. It is stable in dry air, but reacts slowly in the presence of moisture to form a protective Ga_2O_3 layer, much like aluminium. It does not react with water below 100°C, but reacts with mineral acids to form 3+ cations. Being amphoteric, it reacts with alkalis to form gallates $Ga(OH)_4^-$.

It readily forms alloys with other metals that have lower melting points than each of the other components (eutectic properties). More importantly, its position on the periodic table means that it forms stable compounds with group 15 elements (nitrogen, phosphorus, arsenic and antimony) and group 13 elements (aluminium and indium). Its most

Gallex neutrino study

Deep underground in the Baksan valley of the Northern Caucasus, Russia, lies a truly interesting facility – the Baksan Neutrino Observatory. Staffed by scientists and engineers from the local village of Neutrino, the laboratory uses the thick layers of soil and rock to shield the observatory from muons produced by cosmic radiation in the atmosphere.

About 50 tonnes of liquid gallium are used as a target for an experiment to detect low-energy solar neutrinos, to confirm cosmological theories about the solar flux. In 1965, Vadim Kuzmin proposed that solar neutrinos generated by proton–proton fusion reactions at about 0.4 MeV could be measured using the reaction:

$$^{71}Ga + \upsilon_e \rightarrow {}^{71}Ge + e^-$$

An undisclosed chemical technology is used to extract about 15 germanium atoms from the 50 tonnes of liquid gallium each month. The decay of the germanium-71, with a half-life of 11.43 days, is detected by counters. Each detected decay corresponds to one detected neutrino.

Operating since 1986, the Soviet–American Gallium Experiment (SAGE) has measured the solar pp neutrino flux to be $6.0 \pm 0.8 \times 10^{10}\,cm^{-2}\,s^{-1}$, compared to the predicted $5.98 \pm 0.04 \times 10^{10}\,cm^{-2}\,s^{-1}$ from the 'standard solar model'.

Ongoing experiments at this and other facilities around the world continue to probe the neutrino frontier, with gallium playing an essential role in being able to selectively detect low-energy neutrinos down to a limit of 233 keV.

commercially useful compounds are nitride (GaN), arsenide (GaAs) and more complex compounds such as copper–indium–gallium selenide ('CIGS').

Chemists would remember that the 2014 Nobel Prize in Physics was awarded to Japanese researchers Professors Isamu Akasaki, Hiroshi Amano and Shuji Nakamura for their revolutionary use of GaN in the development of blue LEDs. Developed in the 1990s, these blue LEDs (and their ability to combine with red and green to give white light LEDs) now form the basis for a substantial and growing portion of global gallium demand. Beyond just electrical devices such as TVs and mobile phones, white light LEDs offer much better electrical efficiency than most alternatives.

Gallium utility in LEDs (as both GaN and GaAs) stems from its semiconductor properties. When current is applied to crystals of sufficient size (a major aspect of the Nobel Prize), the energy is directly converted to a photon of light, without the heat wastage associated with incandescent or fluorescent lighting.

More recently, GaN is emerging as a critical transistor material in developing radar systems for the detection of stealth aircraft. Conventional radar primarily operates in the 'X band' of 8–12 GHz, the beams of which stealth aircraft are designed to deflect, so that the signal does not return to the radar. Emergent platforms (particularly those being developed by the Russians and Chinese) reportedly use different frequencies, particularly the 'L band'. The L band transceivers require more power and cooling, where GaN can offer very high power, while generating little heat.

Moreover, gallium nitride transistors can achieve much faster switching, which is useful for both modern active electronically scanned array (AESA) radar and computing in general. Where silicon devices can work in gigahertz switching, GaN is reported to achieve terahertz. Combined with its low heat generation and better energy efficiency, this could be transformative technology.

Another substantive and growing market for gallium is photovoltaics, particularly in the use of CIGS, and as a minor component in NdFeB magnets. With the much larger mass of magnets, even this small usage is expected to significantly influence demand in coming years.

As noted earlier, most of the current primary gallium supply comes as a by-product of base metal production (particularly Al). There is also production from secondary sources, but importantly this recycled gallium only comes from the wastage in the production processes using gallium materials. At the moment, there is no satisfactory recycling technology for post-use gallium materials.

While market data is thin for most minor metals, available data suggests that the 2016 market for gallium was about 300–375 tonnes. This is estimated to grow at least 20-fold by 2030. According to the USGS, approximately 80% of primary production capacity was located in China as at the end of 2015. While the West does have a greater proportion of the small secondary production capacity, it is little wonder that gallium featured on the USGS's critical minerals list.

Gallium is an essential component of the digital world, and its range of uses is only set to grow in both civilian and military applications. For an element that emerged into the world in contentious circumstances, it would seem that its period of contention is not yet over. We'll be hearing a lot more about this element over coming years.

Dave Sammut FRACI CChem and **Chantelle Craig** are principals of DCS Technical, a boutique scientific consultancy, providing services to the Australian and international minerals, waste recycling and general scientific industries.

2018 Medicinal Chemistry and Chemical Biology Division award winners

The Medicinal Chemistry and Chemical Biology Division of the RACI recently decided the winners of the Division's three main annual awards: the Adrien Albert Award, Peter Andrews Award and Graham Johnston Award. The Adrien Albert Award is the Division's premier award for sustained outstanding research in the field of medicinal chemistry or chemical biology; the Peter Andrews Award is a mid-career award for innovative research on the design, synthesis and development of bioactive agents; and the Graham Johnston Award is for the best PhD thesis in medicinal chemistry or chemical biology submitted in the last two years.

Adrien Albert Award

Professor Jonathan Baell FRACI CChem is a principal research fellow of the National Health and Medical Research Council, and a Larkins Fellow at Monash University, where since 2012 he has been a research-only Professor in Medicinal Chemistry. He is also co-director of the Australian Translational Medicinal Chemistry Facility.

He graduated with a BSc(Hons) in 1986 from the University of Tasmania, and his PhD was undertaken at the then Victorian College of Pharmacy and confirmed in 1992 by the University of Melbourne. He then took up a position within CSIRO (Division of Animal Health, Sydney then Parkville) from 1991 to July 1996 and then the Biomolecular Research Institute at the Chemistry Clayton Laboratories until December 2000. For the next decade he was Head of Medicinal Chemistry at the Walter and Eliza Hall Institute of Medical Research, based mainly at the Biotechnology Facility on the La Trobe University campus, which he helped design and where he was the principal architect for Australia's 370 000 small-molecule HTS (high-throughput screening) library, housed at Compounds Australia in Queensland.

For his patents disclosing small molecule blockers of the Kv1.3 channel as potential multiple sclerosis treatments, he won in 2004 the RACI Peter Andrews Award (then called the Biota Award). His current research interests include HTS library design, H2L medicinal chemistry, infectious and neglected diseases, epigenetic modifiers, and peptidomimetic design and synthesis.

He has more than 120 publications (100 peer-reviewed primary research) in *Nature*, *Nature Communications* and *Nature Chemical Biology* and frequently publishes (16 publications) in top specialist journal *Journal of Medicinal Chemistry*. His 2010 'PAINS' publication in the *Journal of Medicinal Chemistry* describing nuisance screening compounds has already been cited more than 1200 times. He consults widely for the biotech industry, is on many company and journal scientific and ethical advisory boards, and is senior editor of *Future Medicinal Chemistry*.

Perhaps more importantly as a medicinal chemist, Baell has made a battery of pharmaceutical discoveries disclosed in several dozen granted patents and successfully licensed to a variety of third parties.

Peter Andrews Award

Associate Professor Lenka Munoz MRACI CChem received her Doctor of Pharmacy (PharmD) from Comenius University, Slovakia, in 2001 and her PhD in medicinal chemistry from the University of Bonn, Germany, in 2005. She undertook postdoctoral studies in molecular pharmacology was at the Northwestern University, USA (2006–2007). After a career break, she started at the University of Sydney in 2011. Munoz currently holds a Career Development Fellowship (2016–2018) from the Cancer Institute NSW and is head of the Cell Signalling Laboratory at the Charles Perkins Centre at the University of Sydney.

Menoz's research focuses on understanding the molecular mechanism of action of kinase inhibitors in cancer models and developing effective therapies for glioblastoma. Recent work includes publications in *Nature Reviews Drug Discovery*, *Cancer Cell*, *Journal of Medicinal Chemistry*, *Biochemical Pharmacology*, *Oncogene* and *Cell Death Discovery*. She also has a substantial intellectual property and out-licencing portfolio around neuro-oncology therapeutics that she has developed.

Graham Johnston Award

As an undergraduate student, **Dr Angie Jarrad** MRACI CChem was drawn to medicinal chemistry because of its interdisciplinary nature between chemistry and biology and its fundamental goal – to improve health. At the University of Adelaide, she completed a BSc(Hons) in molecular biology with majors in chemistry and biochemistry.

Jarrad's honours project, undertaken in the Booker and Abell groups, was the design, synthesis and biological evaluation of inhibitors of biotin protein ligase, a new drug target in staphylococci. That year, the theme of World Health Day was 'Antibiotic resistance: no action today, no cure tomorrow'. Unlike other classes of medicines, antimicrobials become redundant over time because of bacterial resistance, and new drugs must constantly be developed. This motivated Jarrad to continue research with a PhD in the development of new anti-infective agents.

Jarrad then moved to the Institute for Molecular Bioscience, University of Queensland, with a Queensland Smart Futures Scholarship to undertake a PhD in the Cooper group. Her PhD research focused on the development of new derivatives of existing metronidazole and vancomycin therapies targeting the gut pathogens *Clostridium difficile*, *Giardia lamblia* and *Entamoeba histolytica*. She was the winner of the 2015 Women in Technology PhD Career Start Award.

Jarrad is dedicated to engaging the public with science. She has been a science ambassador for the Wonder of Science Program (Australian Academy of Technological Sciences and Engineering) and a speaker on antimicrobial resistance for Pint of Science. She also contributed to the local chemistry community in Brisbane as event coordinator for the RACI Queensland Young Chemists Group.

She recently moved to Germany to work with Professor Mark Brönstrup at the Department of Chemical Biology, Helmholtz Centre of Infection Research. She is working to solve a difficult problem – improving antibiotic uptake by Gram-negative bacteria. Jarrad is currently a recipient of the Alexander von Humboldt Postdoctoral Research Fellowship.

New Fellow

Currently based in Japan, as Department Learning Leader of Science at Nagoya International School, **Gary Horner** has contributed widely to the International Baccalaureate (IB) community since 2000. He is an experienced workshop leader and a team leader and examiner of Chemistry for Paper 2 and the Individual Investigation IA. He has led annual IB Chemistry summer workshops in Tokyo since 2013, training administrators and teachers of chemistry as part of a Japanese Ministry of Education-funded, IB joint project. His commitment to internationalism and the importance of the global IB education community has seen him both lead (since 2006) and attend IB workshops in Australia, Spain, France, Canada, India, Hong Kong, Singapore, Portugal and Japan. In the area of curriculum design and assessment development, Horner was invited in 2010 to become a member of the Curriculum Review Committee for Group IV, which worked over a number of years, meeting in Cardiff and The Hague. He was also a member of a small team developing the Nature of Science Standard Level Science pilot course.

Prior to his current position, Horner taught for 10 years at King George V School in Hong Kong and before that in Switzerland at the International Schools of Geneva and Lausanne. His extensive curriculum experience includes IB Diploma and middle years program IB Chemistry, Advanced Placement (AP) Chemistry and International General Certificate of Secondary Education (IGCSE). He has held a number of leadership roles, including head of science, head of chemistry, assistant head of studies, Creativity, Activity, Service (CAS) coordinator at ISG and physics coordinator. Prior to teaching internationally, Horner was on staff at All Saints Anglican School, Queensland, and taught for Education Queensland.

Australian by birth, Horner has taught at the secondary level for over 32 years and was involved with the teacher training program at Griffith University. He holds a BSc, GradDipEd and Master of Educational Studies from the University of Queensland, and in 2010 was awarded a professional diploma in Mid-Level Leadership in International Schools from the Faculty of Education, Chinese University of Hong Kong.

Another significant dimension to Horner's professional life and contribution to the teaching of chemistry is his writing for Oxford University Press. He has written *MYP Chemistry: a concept-based approach* (May 2018) and co-authored the *IB Diploma Programme Chemistry Course Companion* (May 2014).

Queen's Birthday Honours 2018

The following scientists in chemistry and chemical engineering were recognised in the Queen's Birthday 2018 Honours List.

- Professor Rose Amal (Companion (AC) in the General Division)

For eminent service to chemical engineering, particularly in the field of particle technology, through seminal contributions to photocatalysis, to education as a researcher and academic, and to women in science as a role model and mentor.

- Professor San Hoa Thang FRACI CChem (Companion (AC) in the General Division)

For eminent service to science, and to higher education, particularly in the fields of polymer chemistry and materials science, through seminal contributions as a research innovator, as a mentor, and to the community.

- Professor Sever Sternhell FRACI CChem (Officer (AO) in the General Division)

For distinguished service to education in the field of organic chemistry, specifically to nuclear magnetic resonance, as an academic and researcher, and to scientific institutions.

- Emeritus Professor David Brynn Hibbert FRACI CChem (Member (AM) in the General Division)

For significant service to science in the discipline of chemistry, to professional societies, and to sport through illicit drug profiling.

New Fellows of Australian Academy of Science

Three Australian chemists were among 21 scientists who were elected as Fellows of the Australian Academy of Science in May.

- Professor Kliti Grice FRACI CChem, Curtin University
- Professor Colin Raston FRACI CChem, Flinders University
- Professor Martina Stenzel FRACI CChem, UNSW Sydney

Australian Academy of Science President, Professor Andrew Holmes, congratulated the new Fellows for making significant and lasting impacts in their scientific disciplines.

'These scientists were elected by their Academy peers, following a rigorous evaluation process', Holmes said.

'From 23 Founding Fellows in 1954, the election this year of our new Fellows brings our total number of living Fellows to 568. They join a prestigious group – six Nobel Prize winners and luminaries, including Sir Mark Oliphant, Professor Nancy Millis, Sir Douglas Mawson, Professor Frank Fenner and Sir David Attenborough.'

With Australian Academy of Science

RACI fellows elected as Fellows of Royal Society

Two RACI fellows are among the 50 scientists elected in May as Fellows of the Royal Society.

- Margaret Brimble CNZM FRS, Distinguished Professor, Chair of Organic Chemistry and Director of Medicinal Chemistry, School of Chemical Sciences and School of Biological Sciences, University of Auckland
- Frank Caruso FRS, Melbourne Laureate Professor and NHMRC Senior Principal Research Fellow, Department of Chemical Engineering, University of Melbourne

Venki Ramakrishnan, President of the Royal Society, said:

Our Fellows are key to the Royal Society's fundamental purpose of using science for the benefit of humanity. From Norwich to Melbourne to Ethiopia, this year's newly elected Fellows and Foreign Members of the Royal Society are testament that science is a global endeavour and excellent ideas transcend borders. We also recognise the cutting edge innovation taking place across industry, with many of this year's Fellows coming from the thriving tech industry. For their outstanding contributions to research and innovation, both now and in the future, it gives me great pleasure to welcome the world's best scientists into the ranks of the Royal Society.

The Member Advantage benefits program can save you thousands each year, as a RACI member.

Your family and friends can also access the benefits program and enjoy a large range of lifestyle and financial services and products.

Access accommodation, tours, airline lounges and more with your travel benefits.

Treat everyone with savings on dining and special meal offers.

From new car purchases to rentals and petrol gift cards, discover the range of automotive benefits.

Protect what's important with discounted premiums on insurance policies.

Enjoy more of life with savings on movie tickets and popular attractions.

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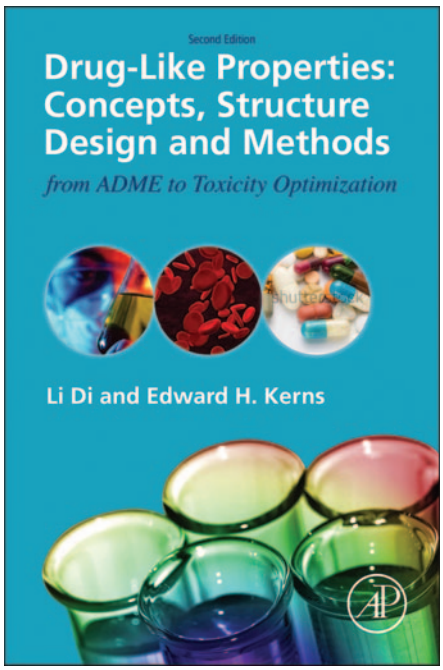
Drug-like properties: concepts, structure design and methods from ADME to toxicity optimization

Di L., Kerns E., Academic Press, 2016, 2nd edition, hardback, ISBN 9780128010761, pp. 580, $215 (approx.)



There are many people who believe that if you get incredibly talented and good individuals, provide them with every resource they need and ample budgets, then anything can be achieved. If you are one of those people, then this book is for you. Unless of course you don't enjoy getting illusions shattered.

The authors are exemplary, and to understand the value of the book, it is important to appreciate the authors and the context.

This book is the second edition, the first being published in 2008 when both authors were employed at Wyeth Research in Groton, Connecticut, USA (Edward Kerns was associate director and Li Di was principal research scientist at the time). Wyeth was a pharmaceutical company purchased by Pfizer in 2009. In 2008, Pfizer invested $US7.9 billion in pharmaceutical R&D while Wyeth spent $US3.4 billion, for a total of $US11.3 billion.

Kerns (BA(Biochem), MS(Chem)) retired in 2014 after an illustrious career, and remains active as a volunteer at a number of organisations, including the Smithsonian National Air and Space Museum. His career highlights include his 178 publications and 4748 citations. Di (BS, MS and PhD in Chemistry, postdoc in Biophysics) is currently an associate research fellow, Pfizer Global Research and Development, USA. The recipient of the Thomas Alva Edison Patent Award, the New Jersey Association for Biomedical Research Outstanding Woman in Science Award, the Wyeth President's Award, Peer Award for Excellence and Publication Award, she has more than 100 publications, including two books, and has presented more than 70 invited lectures.

This book centres on optimisation and commercial development for prospective drugs to maximise the number of selected candidates likely to exit the 'pipeline' and make it through the critical phase I/II human clinical trials (TRL6 (technology readiness level 6)) and thus be viable commercial product candidates. It is an excellent reference in terms of the process and techniques used to select and consequently move candidate molecules through the pipeline from TRL 1–2 to TRL 8 (see February issue, p. 16).

When the first edition came out in 2008, I thought the book was outstanding. It had a few areas that could have been improved upon and some general weaknesses, but was an excellent book nevertheless. This review of the second edition is aimed at both new readers and those familiar with the first edition. The changes introduced in this second edition are not, despite the marketing claims, particularly major between the editions. Where cost is a consideration, acquiring the first edition is a good option.

It is a great book that I highly commend but perhaps not for the reasons readers may assume at first. It is well referenced and presents executive-summary level explanations of various terms, concepts and techniques in logical progression through the process. It is not a 'how-to' manual in the sense that it does not include examples of actual recipes, specific procedural protocols or analytical or synthetic methodology; nor are the guidelines sufficient in their own right for those not already familiar with the subject matter.

The book's major weakness is that it tries to be a textbook but is not. It fails as a textbook candidate primarily because it lacks sufficient detail to be able to apply any described method (it is an excellent summary and very useful reminder to those who already understand and know these matters). It is also not textbook material because of its cost (relative to its practical value to educate students) and perhaps most critically because the questions it provides are often loaded and used to guide to give a 'cultural' response favourable to commercial mindsets, and not necessarily ones that lead to producing blockbuster successful drugs – a fact reflected in the success stories (or more precisely, the frequent lack thereof) within industry.

The book makes very good reading for academics, those in public policy areas, students and postgrads (assuming availability at libraries) and anyone interested in real-world commercial medicinal chemistry areas. As such, I commend the book to librarians at universities with medical, chemistry and chemical engineering faculties, especially those that have medicinal chemistry students, also to industry technical libraries and the larger public libraries (for the benefit of the general public).

In addition to summarising the prevailing and logical technical steps in the process, the book offers a fascinating insight into the mindset of big pharma, of how and why they make their choices, how they decide which external projects to fund and which of their internal candidate molecules to proceed with.

I highly commend it as a study in how not to achieve your stated goals because, frankly, if the criteria described within this book were to be applied to existing and historical blockbuster drugs, then some of the best known, highest selling and most useful ones probably wouldn't be around today.

The book's real strength, ironically, lies in its greatest weakness. It highlights the mindset of stakeholder-focused

efforts, a weakness that applies to most large organisations, be they private enterprise, government or academia. In this case, it highlights the central ideology of big pharma of maximising dollars and the probability that candidate molecules make it all the way through the development pipeline into commercial sales while seeking to minimise risk and future production costs.

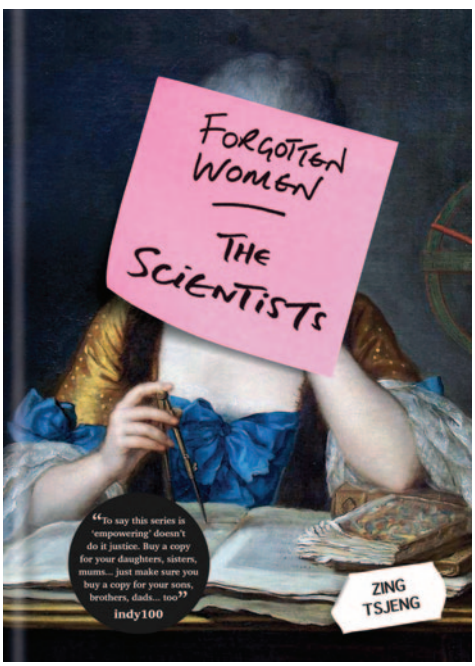
Ideally, the goal is simple, safe and convenient solid oral dosing – good for patients and excellent for sales and profitability. The trouble lies when stock value takes higher precedence then bedside value. The irony is that in commercial mindsets, the need for ROI (return on investment) ultimately creates an internal environment that is least effective to producing it. The industry has an incredibly lacklustre track record of performance in terms of producing blockbusters despite the exceedingly ample fiscal, technical and personnel resources available to them. It is not for lack of cash, facilities, the best equipment money can buy, nor talent of the highest calibre.

The book shines a bright light on the reality of risk-averse-stakeholder-focused-and-checklist-based-faulty-closed-loop-mentality and culture (dare I say 'a cult of mediocrity' expressed as 'better to pursue mediocre candidate molecules that meet more checklist criteria and are thus more likely to exit the pipeline than the riskier pursuit of potential blockbusters') and for this alone it's well worth the read.

Motty Sobol FRACI CChem

Forgotten women: the scientists

Tsjeng Z., Hachette Australia, 2018, hardback, ISBN 9781844039838, $27.99



Forgotten women: the scientists is a product of the New Historia initiative directed by Gina Luria Walker, Professor of Women's studies at 'The New School' in New York City. New Historia aims to promote the scientific achievements of women who have previously gone unrecognised.

The 48 profiles contained in the book are those of women whose accomplishments have largely been forgotten or omitted by history. Some of the women featured are from long ago, such as Tapputi-Belatekallim from Babylon and Greek physician Aspasia, but many others are modern women whose achievements were overshadowed by their colleagues. In author Zing Tsjeng's words, 'This book is an attempt to wrestle the spotlight back onto these unknown heroes'.

Tsjeng is an accomplished journalist and editor of *Broadly*, VICE's female-focused digital channel in the UK. She has also authored other *Forgotten women* books, including *Forgotten women: the leaders*.

The book has a unique format in that it does not use photographs, but offers a collection of illustrations and stylised images to augment each profile's specific details. Some of these illustrations, while a little vague, do offer a sense of the limitations of records available. What is more obvious though is the sheer determination of each of the featured women to pursue their passion for learning and for science (today what we would call STEM). All pursued study, travel and adventure for a chance at personal scientific discovery, regardless of the obstacles.

Only two or three pages are devoted to each accomplished woman, and a few pages of endnotes and bibliographies hint at options for further research. Certainly the 'forgotten' part of these women's pasts means that there is often little information recorded. In many cases, women were not officially enrolled in a university, their colleagues took credit for scientific discoveries, or they were not considered for grants or awards they were entitled to.

The lone Australian woman included in this book is Ruby Payne-Scott, a physicist who worked with ASIO during World War 2 before moving on to the CSIRO. Her story is typical of a modern 'forgotten woman', fighting for equal pay and the right to work for the CSIRO after she was married. Ultimately, she was not successful and eventually recast her career as a science teacher.

Forgotten women: the scientists tells the stories of women who pursued their dreams regardless of the challenges they faced. In the modern era, they fought for the right to enter university, to gain employment, and to be paid the same as their colleagues, although in many cases they did not succeed. *Forgotten women* offers us the chance to learn of their unique and valuable contributions to science in all its forms. While the New Historia website is still in its infancy as the project gathers momentum, it is certainly worth a visit (www.thenewhistoria.com).

Samantha Profke MRACI

I was a student of Stephen Hawking's – here's what he taught me

As for many students of my generation, Stephen Hawking had already had enormous influence on me long before we ever met. When I was hesitating about my A-level choices, it was his book *A brief history of time* that convinced me to continue with physical sciences. In 1994, Hawking and mathematical physicist Roger Penrose gave a series of inspiring lectures about cosmology in Cambridge. As a direct result, I chose courses on black holes and relativity for my fourth year of study at the University of Cambridge.

I first saw Hawking when I was an undergraduate. At that time he was living in an apartment building just behind my student house. He was already so famous that friends would come to my room just to watch him leaving and entering his apartment. But as an undergraduate I never tried to talk with him, feeling much too junior and intimidated.

After I finished my fourth year, I was invited in to talk to Hawking, who was already using a speech synthesiser, about options for my PhD. I was quite nervous when I first met him, but he jumped straight into physics and soon we were discussing black holes. I became a student at the time of the 'Second String Theory Revolution' in theoretical physics. Hawking had not worked actively in string theory, but he was very keen to understand the new ideas.

Following that meeting, he sent me off to read all the papers that Edward Witten, a famous string theorist, had written that year. My task was to come back and summarise them for him – the student teaching the master. It's difficult to describe how hard this task actually was: Hawking expected me to jump straight to the frontier of string theory as a starting graduate student. He also chose the title for my PhD thesis: 'Problems in M-theory', which I worked on from 1995 to 1998.

I can only hope that my explanations of string theory were helpful. Hawking went back and forth on his views on M-theory, but eventually ended up thinking that it may be our best bet for a theory of everything.

No hand-holding

PhD students were enormously important to Hawking. In the early phase of his illness, his students helped take care of him. By the time I became his student he needed round-the-clock nursing. At this point, his students were no longer involved in his physical care, but remained essential to his research. Theoretical physics begins with ideas and concepts, but these then evolve into explicit detailed calculations. Hawking had a remarkable ability to do complex calculations in his head, but he still relied on collaborators to develop and complete his research projects.

Theoretical physicists typically give early PhD students 'safe' research projects, and guide them through the calculations required. As the students develop, the projects become more ambitious and risky and students are expected to work independently. However, PhD students working with Hawking did not have the luxury of this gentle introduction – he needed us to work on his own high-risk, high-gain projects.

Hawking's communication via his speech synthesiser was necessarily concise and he simply could not provide detailed guidance about calculations, making it extremely challenging to work with him. But it was also stimulating, forcing students to be creative and independent. He did give praise when he thought it was due. He once sent me away with a very hard problem – finding exact rotating black hole solutions of Einstein's equations with a cosmological constant – and was stunned when I came back a few days later with the solution. I can't even remember exactly what he said but I will never forget his enormous smile.

Hawking was a determined and stubborn person. On many occasions he got through serious medical issues with sheer determination. This same determination could make him very difficult to work with. But it could also push research projects forward: Hawking would refuse to give up on seemingly unsolvable problems.

In fact, never giving up is the main thing Hawking has taught me – to keep attacking problems from different directions, to reach for the hardest problems and find a way to solve them. It's immensely important as a scientist, but also in other aspects of life.

Pithy one-liners

Hawking was devoted to his family. His eyes would light up when one of his children came to visit or when he proudly showed us pictures of his first grandchild. In many respects, Hawking treated his PhD students and collaborators as a second family. However busy he was, he always made time for us, often making dignitaries wait outside his office while he talked physics with a student. He would eat lunch with us several times per week, and funded a weekly lunch for the wider group to bring everyone together.

There were many occasions when physics discussions merged seamlessly into social activities: going to the pub, eating dinner at one of his favourite Cambridge restaurants, and so on. Hawking had a wonderful sense of humour. He turned his communication difficulties into an advantage, composing pithy one-liners. For instance when changing his mind about what happens to information in a black hole, he announced it in the pub by turning the volume up on his synthesiser, saying simply: 'I'm coming out'. He would discuss anything and everything in a

... never giving up is the main thing Hawking has taught me, to reach for the hardest problems and find a way to solve them.

Stephen Hawking delivering a speech entitled 'Why we should go into space' during a lecture series honouring NASA's 50th anniversary at George Washington University's Morton Auditorium in Washington, 2008. NASA/Paul Alers

social setting: politics, movies, other branches of science, music.

As we worked in closely related fields, we saw each other regularly even after I finished my PhD. In 2017, I attended a conference in Cambridge celebrating his 75th birthday. The list of participants illustrates Hawking's influence on academia and beyond. Many of his former students and collaborators have gone on to become leaders in research in cosmology, gravitational waves, black holes and string theory. Others have had huge impact outside academia, such as Nathan Myhrvold at Microsoft.

There is currently pressure on academics to demonstrate the immediate impact of their research on society. It is perhaps worth reflecting that impact is not easily measurable on short time scales. Hawking's was truly blue-sky research – and yet it has fascinated millions, attracting many into scientific careers. His academic legacy is not just the remarkable science he produced, but the generations of minds he shaped.

There's no doubt Hawking's death is a huge loss to physics. But personally, what I will miss most is his humour and the general feeling of inspiration I got from being around him.

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This article was first published at theconversation.com.

Stephen Hawking had pinned his hopes on 'M-theory' to fully explain the universe – here's what it is

Rumour has it that Albert Einstein spent his last few hours on Earth scribbling something on a piece of paper in a last attempt to formulate a theory of everything. Some 60 years later, another legendary figure in theoretical physics, Stephen Hawking, may have passed away with similar thoughts. We know Hawking thought something called 'M-theory' is our best bet for a complete theory of the universe. But what is it?

Since the formulation of Einstein's theory of general relativity in 1915, every theoretical physicist has been dreaming of reconciling our understanding of the infinitely small world of atoms and particles with that of the infinitely large scale of the cosmos. While the latter is effectively described by Einstein's equations, the former is predicted with extraordinary accuracy by the so-called Standard Model of fundamental interactions.

Our current understanding is that the interaction between physical objects is described by four fundamental forces. Two of them – gravity and electromagnetism – are relevant for us on a macroscopic level; we deal with them in our everyday life. The other two, dubbed strong and weak interactions, act on a very small scale and become relevant only when dealing with subatomic processes.

... in 1995, physicists proposed that the five consistent string theories are actually only different faces of a unique theory which lives in 11 spacetime dimensions and is known as M-theory.

The standard model of fundamental interactions provides a unified framework for three of these forces, but gravity cannot be consistently included in this picture. Despite its accurate description of large-scale phenomena such as a planet's orbit or galaxy dynamics, general relativity breaks down at very short distances. According to the standard model, all forces are mediated by specific particles. For gravity, a particle called the graviton does the job. But when trying to calculate how these gravitons interact, nonsensical infinities appear.

A consistent theory of gravity should be valid at any scale and should take into account the quantum nature of fundamental particles. This would accommodate gravity in a unified framework with the other three fundamental interactions, thus providing the celebrated theory of everything. Of course, since Einstein's death in 1955, a lot of progress has been made and nowadays our best candidate goes under the name of M-theory.

String revolution

To understand the basic idea of M-theory, one has to go back to the 1970s when scientists realised that, rather than describing the universe based on point-like particles, you could describe it in terms of tiny oscillating strings (tubes of energy). This new way of thinking about the fundamental constituents of nature turned out to solve many theoretical problems. Above all, a particular oscillation of the string could be interpreted as a graviton. And unlike the standard theory of gravity, string theory can describe its interactions mathematically without getting strange infinities. Thus, gravity was finally included in a unified framework.

After this exciting discovery, theoretical physicists devoted a lot of effort to understanding the consequences of this seminal idea. However, as often happens with scientific research, the history of string theory is characterised by ups and downs. At first, people were puzzled because it predicted the existence of a particle that travels faster than the speed of light, dubbed a 'tachyon'. This prediction was in contrast with all the experimental observations and cast serious doubt on string theory.

Nevertheless, this issue was solved in the early 1980s by the introduction of something called 'supersymmetry' in string theory. This predicts that every particle has a superpartner and, by an extraordinary coincidence, the same condition actually eliminates the tachyon. This first success is commonly known as 'the first string revolution'.

Another striking feature is that string theory requires the existence of ten spacetime dimensions. Currently, we only know of four: depth, height, width and time. Although this might seem a major obstacle, several solutions have been proposed and nowadays it is considered as a notable feature, rather than a problem.

For example, we could somehow be forced to live in a four-dimensional world without any access to the extra dimensions. Or the extra dimensions could be 'compactified' on such a small scale we wouldn't notice them. However, different compactifications would lead to different values of the physical constants and, therefore, different physics laws. A possible solution is that our universe is just one of many in an infinite 'multiverse', governed by different physics laws.

This may seem odd, but a lot of theoretical physicists are coming around to this idea. If you are not convinced you may try to read the novel *Flatland: a romance of many dimensions* by Edwin Abbott, in which the characters are forced to live in two space dimensions and are unable to realise there is a third one.

M-theory

But there was one remaining pressing issue that was bothering string theorists at the time. A thorough classification showed the existence of five different consistent string theories, and it was unclear why nature would pick one out of five.

This is when M-theory entered the game. During the second string revolution, in 1995, physicists proposed that the five consistent string theories are actually only different faces of a unique theory which lives in 11 spacetime dimensions and is known as M-theory. It includes each of the string theories in different physical contexts, but is still valid for all of them. This extremely fascinating picture has led most theoretical physicists to believe in M-theory as the theory of everything – it is also more mathematically consistent than other candidate theories.

Nevertheless, so far M-theory has struggled in producing predictions that can be tested by experiments. Supersymmetry is currently being tested at the Large Hadron Collider. If scientists do find evidence of superpartners, that would ultimately strengthen M-theory. But it still remains a challenge for current theoretical physicists to produce testable predictions and for experimental physicists to set up experiments to test them.

Most great physicists and cosmologists are driven by a passion to find that beautiful, simple description of the world that can explain everything. And although we are not quite there yet, we wouldn't have a chance without the sharp, creative minds of people like Hawking.

Lorenzo Bianchi is a Marie Curie Fellow in Theoretical Physics, Queen Mary University of London. This article was first published at theconversation.com.

Could your company benefit from the R&D tax incentive or EMDG programs?

Kate Mahady, Director, FB Rice R&D Tax Consulting

The R&D Tax Incentive program is designed to help Australian companies offset the cost of undertaking research and development (R&D) activities and provide much-needed cash flow.

The incentive is a broad, industry-based program applied as a tax offset, which can help decrease your tax liability and can be refundable. It's available to companies incorporated in Australia and is well applied across Australia's chemical science industry sector.

Currently, applicants to the program are facing increased compliance scrutiny from both AusIndustry and the ATO, highlighting the need for companies undertaking R&D to develop strong tax compliance processes.

What is the benefit?

The current rates are:

- 43.5% refundable tax offset for eligible entities with an aggregated turnover of less than $20 million
- 38.5% non-refundable tax offset for eligible entities with an aggregated turnover of more than $20 million
- eligible companies with R&D expenditure in excess of $100 million are limited to a benefit of 30% for any R&D expenditure in excess of the $100 million cap (cap increased to $150 million effective 1 July 2018).

Proposed changes to the R&D Tax Incentive recently announced in the 2018 Budget, which, if passed, will be effective 1 July 2018, include:

- $4 million annual cap on cash refunds for claimants with aggregated turnover of less than $20 million
- claimants with aggregated turnover of more than $20 million will be subjected to an intensity-based rate.

Are my activities eligible?

R&D activities are defined as being experimental in nature and the outcomes of the activities can not be known in advance. R&D activities follow a systematic progression of work, from hypothesis to experimentation to conclusion.

The activities must also result in the creation of new knowledge in the form of new or improved materials, products, devices, processes or services.

What documentation do I need to be compliant?

The program is a self-assessed program; however, as with any claim for a tax benefit, the onus to establish the entitlement to the claim rests with the taxpayer. That means that all expenditure and technical activities must be substantiated with documentary proof that they took place as described in the registration document.

Recently, a number of claimants for the R&D tax incentive have failed in their claims when audited because they could not adequately provide evidence of their activities or the associated costs, highlighting the importance of maintaining documentation.

How do I register the R&D activities?

All R&D activities must be registered with AusIndustry within 10 months of the end of the financial year in which they were undertaken. It is important for companies to describe the activities accurately and concisely in these registration forms and understand the eligibility definitions.

Are you expanding to overseas markets?

The Export Market Development Grant (EMDG) is aimed at assisting small and medium-sized Australian businesses to promote the export of goods or services. It provides a reimbursement of up to 50% of eligible expenditure (minimum expenses of $15 000).

Costs that could be claimed include overseas Intellectual Property registration and related insurance, overseas representatives, marketing consultants, marketing visits, free samples, trade fairs, advertising and bringing overseas buyers to Australia.

Each application is audited and all of the claimed expenses have to be substantiated.

For expenses incurred from 1 July 2017 to 30 June 2018, applications must be submitted between 1 July and 30 November 2018. However, first time claimants can include expenses from 1 July 2016 to 30 June 2017 as well.

For assistance or more information on the R&D Tax Incentive or EMDG please contact our experienced team at FB Rice (Kate Mahady, kmahady@fbrice.com.au, or Reuben Wu, rwu@fbrice.com.au).

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IP The IP Navigators

Reducing landfill

Compared to most of the developed world, when it comes to rubbish, Australia is a lucky country, because our rubbish can be disposed of at relatively low cost. Rubbish is taken away from homes and industry and dumped in landfill. Some, but not much, is sent for recycling, but full recycling rates are relatively low. Excess recyclable rubbish is shipped off-shore for recycling or even dumped in other countries. And for intractable waste and excess recyclable material, the cost of storage in large warehouses is minimal – out of sight, out of mind.

Unfortunately, this happy situation has been disrupted by a recent Chinese decision to stop importing other countries' rubbish. This decision has caused consternation among rubbish disposal contractors and local authorities, who now have to consider alternatives.

In many other wealthy countries, local authorities are legally obliged to minimise landfill by maximising recycling and using incineration to reduce the volume of the waste going to landfill. Thirty years ago when I came to Australia, domestic incineration was widespread – most houses on quarter-acre blocks had a small domestic incinerator in the back yard. Since then, local environmental regulations, considerably reduced block sizes and the growth of apartment living have rendered a return to that practice difficult if not impossible.

Australia has not embraced industrial incineration of waste to any significant extent, but the inability to export waste may soon force state and local authorities to evaluate the technology in order to minimise and dispose the waste stream going to landfill or storage.

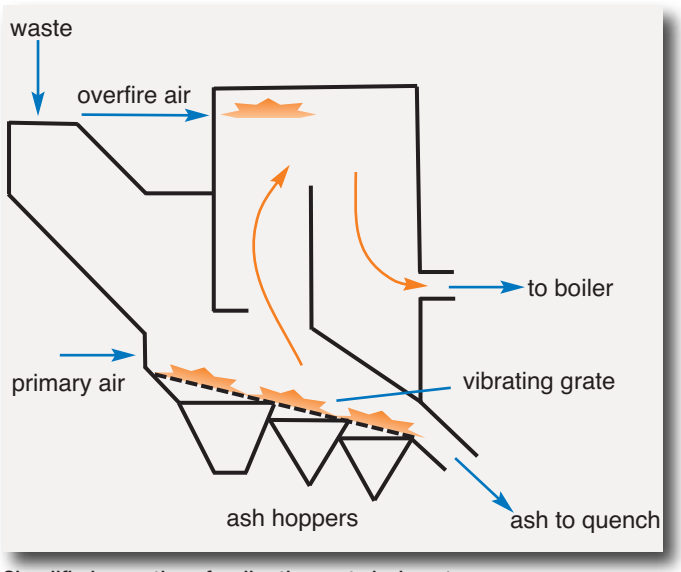
Other than recycling, there are three approaches to reducing the volume of municipal waste going to landfill: pyrolysis, incineration and gasification. For all three methods, the municipal waste stream is sorted as much as possible. The objective is to separate out material that leads to the optimum operation of the plant from non-combustible materials that could be recycled, such as steel, aluminium, concrete/bricks and glass.

The separated waste stream, which now contains food waste, plastics, paper and other carbon-containing products, is sent to the facility. Industrial waste can also be merged with this stream. Often, industrial waste streams are relatively 'clean' in that the stream contains only one type of material – waste oil, for example – which requires little, if any, sorting or pre-treatment.

In pyrolysis, the sorted waste stream is heated to about 600°C in the absence of air; the materials thermally decompose to generate combustible gases, liquids and a carbon-rich solid ash. The gases and liquids can be used to operate the pyrolysis unit. The ash occupies considerably less volume than the entering waste stream and so achieves the objective of reducing the volume of material going to landfill.

This type of technology has been developed in the past for upgrading poor-quality coal. The products were a combustible solid of higher calorific value than the coal and a liquid that had the potential of a crude oil substitute; the gaseous products were used to fuel the process. Large demonstration plants were built but the technology never took off. Another variation of pyrolysis is in the production of shale oil from shale rock, which was demonstrated in large facilities near Gladstone.

The pyrolysis route for handling municipal waste has fallen out of favour compared to incineration, which is generally the most widely used process. A common method is shown in the following diagram, which illustrates the operation of a vibrating grate incinerator.



Simplified operation of a vibrating grate incinerator.

iStockphoto/PN_Photo

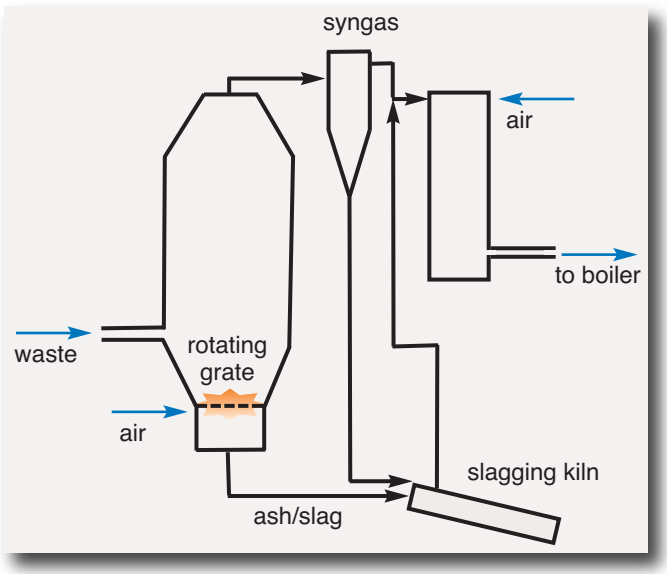
Australia has not embraced industrial incineration of waste to any significant extent but the inability to export waste may soon force state and local authorities to evaluate the technology ...

In a vibrating grate incinerator, the sorted waste stream falls onto a vibrating grate, where the waste burns to release combustion gases and ash. The ash falls through the grate and is collected in hoppers. The hot combustible gases are further burned higher in the incinerator and the hot flue gas goes to a waste-heat boiler to generate steam.

The ash contains a significant portion of metals and is often sent to a metals extraction facility before final disposal to landfill.

The third method is gasification, where the waste is burned in a restricted quantity of air to form carbon monoxide and hydrogen; this is subsequently burned, generating steam. Although more complex and costly than an incinerator, the process operates at a higher thermal efficiency, generating more steam and power (see diagram below).

There are several variants on the design of gasifiers for municipal waste. The waste feed is finely shredded and fed by a screw conveyer or in a stream of inert gas to the gasifier, where partial combustion occurs to form a synthesis gas (syngas), which ascends up the gasifier. Ash falls to the base through a rotating grate, which prevents clogging. Ideally, the temperature is high enough for the ash to form a molten slag. The syngas, which contains a lot of particulate matter, is passed through a cyclone, where the solids are separated and mixed with the slag from the gasifier and further heated into a slag in a slagging kiln. The slag is drawn from the kiln (not shown) for disposal. The syngas is then burned in a combustion chamber and the hot gases are passed to a waste heat boiler to generate steam.



A gasifier for municipal waste.

In variations of incinerators and gasifiers, the waste heat boiler produces steam for central district heating or, more commonly, for generating power that is fed into the local electricity grid.

Municipal waste varies in calorific value, which can be exacerbated by seasonal issues. These variations affect the performance of the incinerator or gasifier. To mitigate this, a high calorific fuel, such as waste oil or natural gas, can be added. Furthermore, combustion is improved if enriched air is used. For gasifiers, this boosts the operating temperature, ensuring a molten slag product.

One of the main concerns with incinerators and gasifiers is the emission of highly toxic materials, such as dioxins and mercury, in the flue gas. A significant amount of flue gas treatment is required to ensure emissions are within legislated emission standards.

The destruction of municipal waste in incinerators and gasifiers is capital intensive. Costs increase further if gas or oxygen is used to optimise efficiency. Many jurisdictions regard generated electricity supplied to the grid as renewable power and this attracts appropriate credits. However, the electricity benefit and sale of any recyclable material does not cover the operational costs, and the main income stream is upfront charges to the municipality (rate payers) for use of the incinerator or gasifier.

Despite there being no current examples in Australia, there is some experience. During the early 2000s, a municipal gasifier operated for a while at Whytes Gully near Wollongong. Furthermore, blast furnaces have been used as a waste plastic/waste oil incinerator where the plastic or waste oil offsets gas and coke used in the smelting of ore.

Duncan Seddon FRACI CChem is a consultant to coal, oil, gas and chemicals industries specialising in adding value to natural resources.

It's all right to be wrong in science

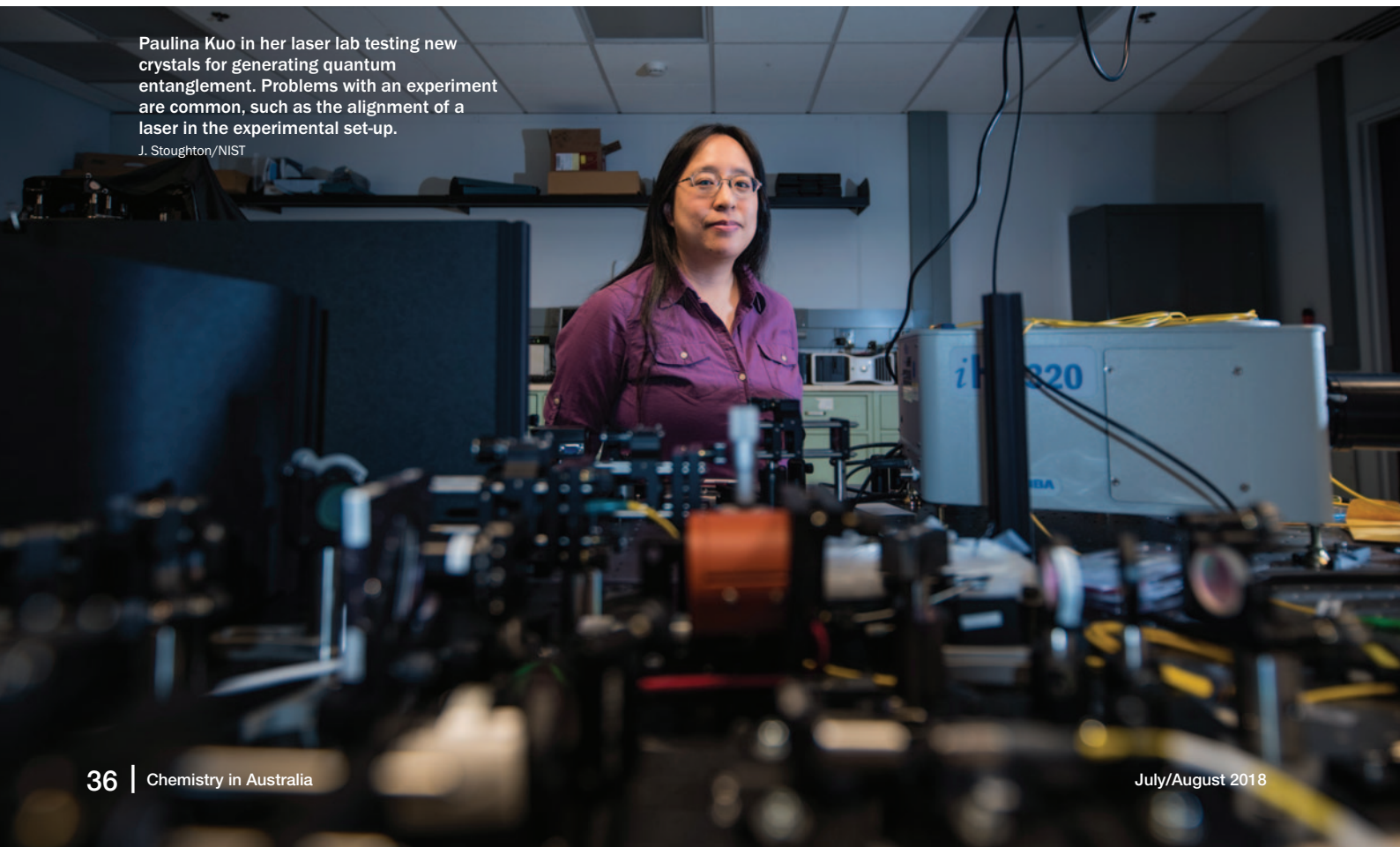
I am a scientist. I am often wrong, and that's okay.

You may have heard about major errors in science and engineering that made the news headlines, like the collapse of the Tacoma Narrows Bridge, aka 'Galloping Gertie', or the 1999 crash of the Mars Climate Orbiter. Or maybe you've seen the recent video from SpaceX, 'How Not to Land an Orbital Rocket Booster.' You may not realise how often scientists are wrong, but being wrong is actually part of the process of doing science. The trick is to catch errors before they leave the lab, and certainly before they make the front-page news, though, obviously, that doesn't always happen.

Thomas Edison famously said, 'Genius is one per cent inspiration and 99 per cent perspiration'. Why so much perspiration? Because of all the effort you put into testing your inspirations, having them be wrong and not work, and then trying again. This is brilliantly illustrated by something Edison supposedly also said about making light bulbs: 'I have not failed 700 times. I've succeeded in proving 700 ways how not to build a light bulb'.

I have had many moments of being wrong in my scientific career. One of my most memorable moments was during a hands-on exam in school when I was given equipment to observe and measure the radioactive decay of a certain isotope. I remember thinking that I needed to repeat the measurement several times to find the average decay rate. I diligently recorded the number of clicks read by the Geiger counter during a fixed time interval and then I averaged the results. In the process of doing this averaging, I completely overlooked the fact that the rate of radioactive decay decreases over time. I had incorrectly assumed that this experiment would have the same property as most science experiments: that the results (in this case, the decay rate) wouldn't change over time. After hearing the chatter of the other students after the exam, I immediately realised my mistake, but it was too late. My answers to the exam were completely wrong. I was mortified.

... the experience taught me that it's okay to be wrong if you are willing to accept that possibility and make corrections.



Paulina Kuo in her laser lab testing new crystals for generating quantum entanglement. Problems with an experiment are common, such as the alignment of a laser in the experimental set-up.
J. Stoughton/NIST

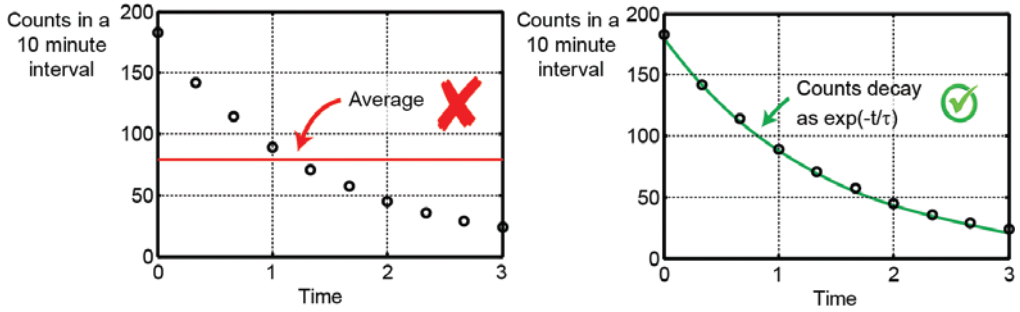
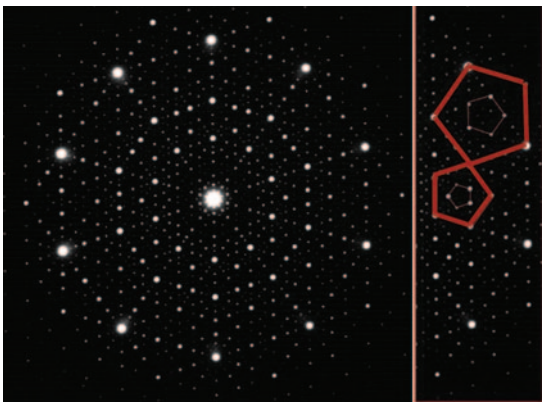


Illustration of incorrect and correct answers for my radioactive decay experiment. P. Kuo/NIST

Looking back, this experience taught me several lessons. First, I learned that science can be humbling. I shouldn't be overly confident in my conclusions because there's always a chance I might be wrong, something that Mother Nature will no doubt reveal to me (or my colleagues) at some point. More importantly, though, the experience taught me that it's okay to be wrong if you are willing to accept that possibility and make corrections. In this case, I had followed the scientific method, but I ran out of time before I could correct myself. In other words, I hypothesised that the rate of radioactive decay did not change over time. I tested the hypothesis by observing and recording the rates. I analysed the data, but I failed to notice that there was a downward trend. With more time, I probably would have caught my error and revised my hypothesis and data analysis, accordingly.

In my current work, I often follow the same basic framework. I have a hypothesis that I want to test. I do experiments and analyse the data to look for evidence that will confirm or disprove that hypothesis. Many times, the trend I find does not match my expectations, so I go back and re-examine my hypothesis and/or check whether I'm doing the experiment correctly. Problems with an experiment are common because it's easy to overlook factors like the temperature stability or uniformity inside an oven, or the alignment of a laser in the experimental set-up. A lot of effort in the laboratory is spent troubleshooting and repeating experiments before arriving at a conclusion.

This vigilance against errors is the key ingredient to making advances in science. One of the greatest discoveries made at NIST was of quasicrystals by Dan Shechtman, who earned the Nobel Prize in Chemistry in 2011 for this work. While studying the electron diffraction patterns from a rapidly solidified aluminium alloy in 1982, Dan saw symmetries that – according to the existing theory of crystal structure – were impossible. His observations and hypothesis were opposed by both the prevailing theory and two-time Nobel Prize-winner Linus Pauling, one of the world's most famous scientists. Shechtman spent more than two years gathering data and debating with colleagues before he was able to publish his work. To do this, Dan had to painstakingly eliminate all the other possible explanations for his measurements, including experimental



Electron diffraction patterns from crystals with five- (right) and ten-fold (left) symmetry, both once considered impossible. D. Shechtman/NIST

errors. Dan's determination – his perspiration – proved the conventional wisdom about crystal symmetry – and a double-Nobel-Prize-winner – wrong.

See? Even world-renowned experts can be wrong sometimes! (Pauling, however, never conceded.)

As this example shows, being wrong is not the same as being incompetent. Whereas incompetence involves being both wrong and lacking the conceptual tools to discover that you're wrong, it's okay to be wrong if you are able to realise your error and take steps to both correct and learn from it. Thinking like a scientist involves recognising that you will occasionally (or more than occasionally) be wrong and knowing how to find out why. Science is a journey, and part of that journey is making errors and being empowered to make changes based on lessons learned.

Even the news-making science errors have had lasting, positive impacts. From the Tacoma Narrows bridge collapse, scientists learned the importance of wind and aerodynamics for bridges. After the Mars orbiter crash, NASA made changes that enabled the success of the two Mars rovers, Spirit and Opportunity. Making errors in science is just part of the process and allows scientists to learn and broaden what we know. It's only by being wrong that we ever learn what's right.

So, to all you scientists and non-scientists, go forth and be wrong! You'll probably discover something new on your journey.

Paulina Kuo is a physicist in the Applied and Computational Mathematics Division in NIST's Information Technology Laboratory. First published at www.nist.gov/blogs/taking-measure/its-all-right-be-wrong-science.

Why good claim drafting is essential under Australia's revised *Patents Act*

The recent Patent Office decision in Cytec Industries Inc. v Nalco Company [2018] APO 4 dealt with interpreting the 'Raising the Bar' revised requirements of a subsection of Australia's *Patents Act 1990* in relation to post acceptance claim amendments (see box).

This article will focus on the Patent Office's consideration of whether, as a result of the proposed claim amendments filed by the Patent Applicant, the complete Specification disclosed the claimed invention clearly and completely enough to satisfy the requirement of subsection 40(2)(a) of the *Patents Act 1990*. It will also consider whether a proper understanding of the invention and correct claim drafting could have saved the claim.

Relevant patent law

Subsection 102(2) of the *Patents Act 1990* states that:

An amendment of a complete Specification is not allowable after the relevant time if, as a result of the amendment:

(a) a claim of the Specification would not in substance fall within the scope of the claims of the Specification before amendment; or

(b) the Specification would not comply with subsection 40(2) or (3),

where the 'relevant time' is after the Specification has been accepted.

Subsection 40(2) of the Act states that:

A complete Specification must: (a) disclose the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the relevant art.

Background

Cytec Industries Inc ('Cytec', the Opponent) filed an Opposition against the acceptance of Nalco Company's ('Nalco', the Applicant) Patent Application, which was directed to reducing scale in a Bayer process. During the Opposition Proceedings, Nalco filed a request to amend Claim 1 to recite:

A method for the reduction of aluminosilicate containing scale in a Bayer process comprising the steps of:

adding to the Bayer process stream an aluminosilicate scale inhibiting amount of a composition comprising at least one small molecule,

wherein the small molecule is selected from the group consisting of compounds (I) through (XIII), (XV) through (XXX), (XXXII) through (LVIII) and (LX) through (LXVII): [structures omitted].

Prior to filing the amendment, Claim 1 recited a method for the reduction of aluminosilicate containing scale in a Bayer process comprising adding to the Bayer process stream an aluminosilicate scale-inhibiting amount of a composition comprising at least one small molecule selected from a broad class of small molecules defined in a generic 'Markush' format (a representation of a chemical structure where a group of alternative substitute atoms or functional group is listed; for example, CH_2X_2, where X = F, Cl, Br and I). Since all the small molecules specified in the proposed amended Claim 1 fell within the scope of the broad class defined in the previously accepted Claim 1, Subsection 102(2)(a) was satisfied.

Opposition to the amendment

One of the grounds asserted by Cytec was that the compounds denoted by LXVI and LXVII, which were not specifically claimed previously, are not disclosed in the complete Specification in a clear enough and complete enough manner for the invention to be performed by a person skilled in the relevant art (PSA) as required by Subsection 40(2)(a) of the *Patents Act 1990*.

The Delegate's observations

Did the Specification disclose the subject matter (i.e. the compounds denoted by LXVI and LXVII) now claimed as a result of the amendments, in a clear enough and complete enough manner to be performed by the person skilled in the art?

In answering this question, the Patent Office Delegate followed the same process of reasoning applied in UK and the European Patent Office decisions. In so doing, the Delegate had to determine:

(i) the scope of the invention as claimed
(ii) what the Specification disclosed to the PSA
(iii) whether the Specification provided an enabling disclosure of all the things falling within the scope of the claims.

The Delegate construed Claim 1 as being directed to reducing aluminosilicate scale in a Bayer process stream comprising the step of adding to the process stream an amount of a composition. The use of the term 'comprising' in relation to the step meant that additional steps, which were not explicitly defined in the claim, could be included within the claimed method. The Delegate also considered that the composition to be added may optionally contain more than one of the components specified in the Claim. Accordingly, the composition to be added to the Bayer process could include either of the compounds denoted by LXVI and LXVII, in the presence of or in the absence of any other of the small molecules specified in the Claim.

The Delegate determined that the Specification referred to the small molecule as being a reaction product between an amine molecule and an amine-reactive molecule, or a mixture of such reaction products. Thus, it was considered that mixtures of scale-inhibiting small molecules were clearly envisaged in the Specification.

This decision teaches that being silent about how a single molecule could be made, and yet explicitly claiming 'at least one small molecule', led to the refusal of the amendment request.

The Delegate noted that there were no depictions of structures of compounds LXVI and LXVII; however, he concluded that these compounds were inherently disclosed in the Specification.

Notably, the Specification contained one Example teaching a general method of combining three components, designated A, G and E, to form mixtures of compounds of the invention. Importantly, the Specification only ever referred to isolating the 'product mixture' and there was no disclosure or any worked examples demonstrating how each component of the mixture could be isolated.

Evidence submitted by the Opponent, Cytec, suggested that the product mixture obtained by following the example would in fact be a complex mixture of many compounds, the actual composition of which would vary according to numerous factors. The Delegate considered that it was plausible that the reactions disclosed in the Specification produced mixtures containing compound LXVI or LXVII. However, it was clear that these compounds could only be produced as part of a complex mixture involving at least 15 possible compounds being formed from reagents having several reactive functional moieties.

Accordingly, the Delegate considered that the Specification enabled the production of compound mixtures.

In relation to the question of whether each of these compounds on its own, as claimed, could be produced, the Delegate then considered whether each compound could be produced without undue burden.

The Applicant, Nalco, made submissions to the effect that the PSA would not expect chemical additives for use in the Bayer process to be 100% pure compounds and that it was commonplace to use chemical structures to denote industrial-grade mixtures of chemical compounds. Therefore, their isolation is not necessary.

Despite what the PSA might expect, the Delegate considered that it is the scope of the claims, as defined by the words used, that must be given due consideration.

The Delegate agreed that the Claims and teaching of the Specification do not require the isolation of compounds LXVI and LXVII, but that this in itself did not help in determining whether as a result of the amendment, a real and reasonable clear disclosure of the invention as claimed had been satisfied. The Delegate recognised that the Claims included the possibility of the compounds in question being in their isolated forms, yet the Specification only disclosed use of a complex mixture containing many compounds.

Since the Specification was silent about how a PSA could isolate, identify or quantify the individual components of the mixture in the presence of the other components in the mixture, the Delegate considered that there was insufficient information in the Specification for a PSA to produce the individual compounds absent others and therefore that the PSA would be unable to perform the full scope of the claimed invention without undue burden.

Accordingly, the proposed amendments were rejected.

Take-home message

For applicants seeking patent protection of their invention in Australia, this decision confirms that there is a real need to ensure that the Specification fulfils enablement requirements across the full scope of the claimed invention. As the law currently stands, this does not mean that everything that could fall within the scope of the claim has to be disclosed in the Specification and practically demonstrated to work, but, rather, everything that has been explicitly claimed must be practically demonstrated for enablement purposes. This decision teaches that being silent about how a single molecule could be made, and yet explicitly claiming 'at least one small molecule', led to the refusal of the amendment request.

The authors take a moment to reflect back to their training years many years ago and wonder if the actual inventive concept had been identified by first identifying the problem to be solved by the invention, then perhaps this lack of enablement issue would not exist. A possible representative claim could be drafted as follows:

A method of reducing siliceous scale in a Bayer process stream, the method comprising adding an aluminosilicate scale-inhibiting amount of a composition comprising N-[(hydroxy)alkyloxyalkyl[(trihydroxy)silyl]]-N-alkyldiamine to the process stream.

Such a claim would avoid the need to explicitly claim both single compounds and mixtures by referring to the common structural features of the relevant compounds used for reducing scale in the Bayer process. As a result, it would be unlikely that the Delegate would entertain the question of whether or not production of single compounds had been disclosed, since that subject matter would not have been explicitly claimed.

Dr Jim Y. Onishi and **Dr Elizabeth E. Houlihan** FRACI CChem are Patent & Trade Mark Attorneys of Houlihan[2].

Grape berries and oxygen

iStockphoto/anna1311

A recent media release from the University of Adelaide was entitled 'Discovery shows wine grapes gasping for breath' (bit.ly/2kID9tP). A somewhat eye-catching title perhaps for an article that summarised recent research on hypoxia (deficiency in the amount of oxygen reaching the tissue) in grape berries that in turn may lead to cell death. Cell death in some wine grape varieties can lead to potentially negative impacts on grape composition and consequently affect wine characters.

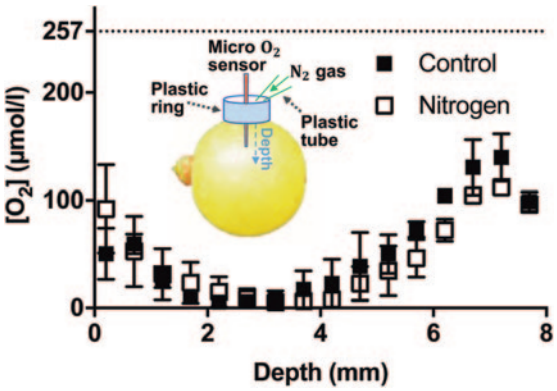
The research was performed by PhD student Zeyu Xiao, from the ARC-funded Training Centre for Innovative Wine Production, together with Professor Steve Tyerman, Chair of Viticulture at the University of Adelaide, Dr Victor Sadras from the South Australian Research and Development Institute and Dr Suzy Rogiers, NSW Department of Primary Industries, Wagga Wagga. This research on oxygen access into the ripening grape berry is a great example of the combination of viticulture science and analytical chemistry and is published in the open access *Journal of Experimental Botany* (2018, vol. 69(8), pp. 2071–83).

Some grape berry anatomy to commence this story. The pericarp of a grape berry is the zone between the skin or epidermis and the seeds. The pericarp itself consists of three layers: external exocarp, inner endocarp and the central bulk known as the mesocarp. Cell death in the mesocarp was the focus of this present study. The berry is connected to the pedicel, which in turn is connected via the peduncle to the vine stem. The presence of lenticels, pore-like structures, are required to allow gas exchange, and oxygen ingress in particular, to the interior tissue. In grape vines, lenticels are present on the skin of the berry and the pedicel, although those on the skin can be blocked by wax (Rogiers et al. *American Journal of Enology and Viticulture*, 2004, vol. 55, pp. 121–7), leaving the pedicel to play the crucial role in oxygen access.

Now to the analytical chemistry side. Direct oxygen measurements within the mesocarp were achieved using a Clark-type microelectrode. The challenges in setting up the electrode were, first, the need for the skin to be punctured and, second, creating a seal to stop air ingress around the electrode during measurements. The electrode was calibrated in sugar-free solutions. The extent to which the high sugar content of the berry affected the accuracy of the electrode response seemed not to be assessed. Measurements were performed on three separate berries to assess the reliability of the measurement strategy.

The object of the measurement was to determine the oxygen profile through the mesocarp. The presence of seeds in the case of Shiraz limited the depth to which the electrode could be inserted. A full depth profile could be achieved with Ruby Seedless, a table grape variety, and also for Chardonnay. The seeds in Chardonnay could be visualised and the direction of electrode insertion adjusted appropriately.

The image shows the oxygen depth profile for Chardonnay at 90 days after anthesis (DAA is the common acronym and anthesis refers to flower opening). There is an obvious drop in the oxygen concentration from the skin to about the centre of the mesocarp. These oxygen concentration measurements were repeated during ripening with a parallel assessment of cell vitality using fluorescein diacetate. A positive correlation was observed between the decrease in oxygen concentration and cell death, as reflected by the loss of cell vitality (see Figure 2 in Xiao et al.).



Oxygen depth profile for Chardonnay at 90 days after anthesis.
Xiao et al. *Journal of Experimental Botany*, 2018, vol. 69(8), pp. 2071–83

The same oxygen concentration/cell death relationship was not observed in Ruby Seedless, suggesting that seeds could contribute to the oxygen concentration/cell death profile in the seeded varieties. Seeds consume oxygen during respiration. However, separate experiments showed that seed respiration declined markedly in the latter stages of ripening, essentially discounting this biochemical process for the lack of oxygen.

The second proposal for reduced oxygen in the mesocarp is a reduction in air ingress. X-ray micro-computed tomography identified air spaces in the berry. A more detailed description of berry anatomy than described above shows that these air spaces are connected to the lenticels in the pedicels and are the source of oxygen to the berry. This was demonstrated in experiments where the lenticels were blocked with silicone or flushed over with nitrogen, resulting in a significant drop in the internal berry oxygen concentration. In essence, the reduction in air ingress leads to hypoxia or 'grapes gasping for breath'.

There are significant outcomes of this research for future grape growing with the increasing temperatures that are linked to global warming. Higher temperatures result in an increased respiratory demand as well as lenticel blockage. As the study authors suggest, the outcome of this study provide a basis for viticulture management in a warming climate.

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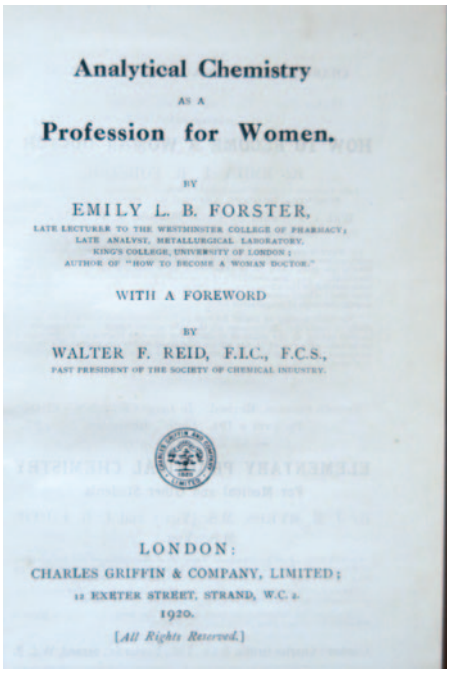
Emily's career advice

I have a special bookshelf for little volumes. This one, *Analytical chemistry as a profession for women*, was published in London in 1920. It has 125 pages of size 10 × 16 cm. The author was Emily L.B. Forster, described on the title page as late lecturer to the Westminster College of Pharmacy; late analyst, metallurgical laboratory, Kings College, University of London; and author of *How to become a woman doctor*. In her preface, Forster says that 'many women engaged in the somewhat monotonous work of school teaching are turning their attention to "practical" scientific work', and the foreword provided by Walter F. Reid, past president of the Society for Chemical Industry, writes of chemical control in the industry and the need for qualified analysts, especially women, in this fascinating profession. Forster, writing so soon after World War I, adds another dimension to analytical chemistry in a chapter on 'Science and Patriotism'. Although they were not in the firing line, women could do their bit for the war effort.


Analytical Chemistry
AS A
Profession for Women.
BY
EMILY L. B. FORSTER,
LATE LECTURER TO THE WESTMINSTER COLLEGE OF PHARMACY;
LATE ANALYST, METALLURGICAL LABORATORY,
KING'S COLLEGE, UNIVERSITY OF LONDON;
AUTHOR OF "HOW TO BECOME A WOMAN DOCTOR."
WITH A FOREWORD
BY
WALTER F. REID, F.I.C., F.C.S.,
PAST PRESIDENT OF THE SOCIETY OF CHEMICAL INDUSTRY.
LONDON:
CHARLES GRIFFIN & COMPANY, LIMITED;
12 EXETER STREET, STRAND, W.C. 2.
1920.
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Successive chapters deal with the cost of training, the nature of work in private and government laboratories, self-employment, and the role of the public analyst. The courses available at 24 British universities are summarised, and there are chapters on the Institute of Chemistry (on which the Australian Chemical Institute was modelled, by the way), scientific societies and their libraries. There is advice that would now seem to be patronising, if not actually provocative, in 'Hints to the Woman Worker'. These are explicitly addressed to the woman analyst as role model in her laboratory, and they cover things like punctuality, tidiness, cleanliness, all apparatus being in its appointed place, and dress that is 'modest and trim' although preferably covered by a good dustcoat or overall.

Marelene and Geoff Rayner-Canham have written quite a bit about British women chemists, and they included Forster in their 2008 *Chemistry was their life: British women chemists 1880–1949*. They have contributed to the extensive literature on gender-typing of science careers, and identified crystallography, radiochemistry and biochemistry as fields where women felt most welcome. Joan Radford, historian of the School of Chemistry at the University of Melbourne, felt that women were most attracted to disciplines where manual skill and attention to detail were important, such as microscopy and analytical chemistry.

Forster was a serial author who began her publishing career in 1917 with *How to become a dispenser: the new profession for women*. *Woman doctor* was published in 1918, before *Analytical chemistry* in 1920. There was a gap until 1926 when *Vegetarian cookery* was published; then in 1942 a revised and enlarged edition appeared, with a special chapter on wartime food. Before *Dispenser* appeared, Forster's article 'The Ideal Neighbourhood for the Woman Pharmacist' was published in the *Pharmaceutical Journal and Pharmacist* in August 1916. A country position would provide broader scope for the work of the pharmacist, ranging from extracting a tooth or poisoning a cat, to attending to a sick cow and gossiping over the counter with the farmer who hoped to save on veterinary fees, Forster observed. However, such a position might not prove congenial for a lady chemist. Seaside towns would provide only seasonal business, and cathedral towns should be avoided because anything new there is looked upon with suspicion. Good choices could be London suburbs where there were clusters of girls' schools. Wherever she practised, the woman pharmacist with 'modern views' might nonetheless need to offer sidelines such as nursery and toilet goods (and possibly, the article seemed to imply, unmentionables) if the business were to survive.

Her books met with mixed reviews. The reviewer of *Dispenser* said that it contained nothing that could not be gleaned from institutional publicity and that, because of the fees involved in taking the necessary examinations, the profession was unlikely to become over-crowded. In the foreword to *Woman doctor*, Dr W.J. Fenton, Dean of the Medical School at Charing Cross Hospital, wrote that 'it contains all the information likely to be required by anyone taking up the study of medicine … is thoroughly up to date … and recommended with every confidence as to its accuracy and merits'. On the other hand, an Irish reviewer said that Forster had overlooked the opportunities for studying medicine in Ireland, and that the book was full of mistakes that needed to be corrected before a second edition were published.

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events

ICCE2018 – International Conference on Chemical Education
10 July 2018, University of Sydney, NSW
ivvy.com.au/event/CED681

ICCCE 2018 – 9th International Conference on Chemistry and Chemical Engineering
11–18 July 2018, University of Liverpool, Liverpool, UK
iccce.org

ICABC 2018 – 5th International Conference on Advances in Biology and Chemistry
6–8 August 2018, National Taipei University of Technology, Chemical Engineering & Biotechnology, Taipei, Taiwan
icabc.org

8th IUPAC International Conference on Green Chemistry
9–14 September 2018, Bangkok, Thailand
greeniupac2018.com

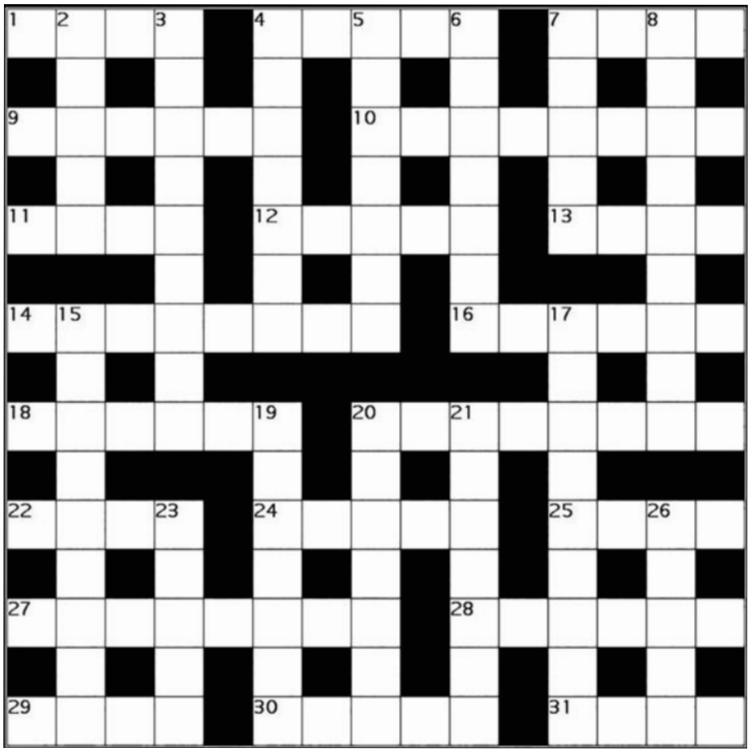
8th International Conference on Environmental Chemistry and Engineering
20–22 September 2018, Berlin, Germany
environmentalchemistry.conferenceseries.com

CBEE 2018 – 10th International Conference on Chemical, Biological and Environmental Engineering
27–29 September 2018, Hotel Berlin, Berlin, Germany
icbee.org

Organic 18 – 24th RACI Organic Chemistry Conference
2–6 December 2018, University of Western Australia, WA
ivvy.com.au/event/OGD780

RACI events are shown in blue.

cryptic chemistry



Across

1 Alone with a new moon. (4)
4 American state: first Pennsylvania then Oregon follows Virginia. (5)
7 See 9 Across.
9 & 7 Across Hormone med taken to a new place. (6,4)
10 Nine if it goes big. (8)
11 Tube taken into testing stage. (4)
12 Practice of uranium guru. (5)
13 Three elements and a legume. (4)
14 Appears as tiny if in unlimited space. (8)
16 Admission of group of candidates. (6)
18 Second fish mephitis. (6)
20 Adverse camber with einsteinium clutches. (8)
22 Call round. (4)
24 Used twice to express sympathy in that place. (5)
25 A cat (a little one). (4)
27 Prised einsteinium mess to scatter. (8)
28 Not outside with 49. (6)
29 Current SPAM treatment. (4)
30 Expired unknown milky liquid. (5)
31 Used more capital. (4)

Down

2 Oxygen sector. Oxygen, oxygen, oxygen! (5)
3 Carmen perhaps moves into procedure. (9)
4 Circumvent urination through a device which causes fluid pressure change. (7)
5 Basic army rip off. (7)
6 Insect ruined Spooner's mirror. (7)
7 Applause for the workers. (5)
8 Element harmlessly ends reaction to form carbine. (9)
15 $[RCNH]^+$ reaction limit. Ruin! (9)
17 Odd person to catch rear action. (9)
19 Earthly demise for indol-1-yl, for example. (7)
20 Einsteinium is one on the table. (7)
21 Business used to make honeycomb. (7)
23 Crack and einsteinium is wide open. (5)
26 NH_4^+ is one μ-ion broken down. (5)

Graham Mulroney FRACI CChem is Emeritus Professor of Industry Education at RMIT University.
Solution available online at Other resources.

December 3 - 6, 2018 / The University of Western Australia

The Organic Division Conference of the Royal Australian Chemical Institute for 2018, will be held at The University of Western Australia on 3 - 6 December 2018.

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Heritage Medical Research Institute Investigator, Caltech

Dave MacMillan
Professor of Organic Chemistry in the Department of Chemistry at Princeton University

Professor Ben Davis
Professor of Chemistry in the Department of Chemistry at the University of Oxford

Veronique Gouverneur
Professor of Chemistry at the University of Oxford

Conference Organisers

Professor Michael Sherburn
Chair, RACI Organic Chemistry Division

~

Dr Matthew Piggott
The University of Western Australia

~

Dr Scott Stewart
The University of Western Australia

Women in Organic Chemistry Pre-Symposium

Hosted by Professor Kate Jolliffe

Invited Speaker

Professor Margaret Brimble
The University of Auckland

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