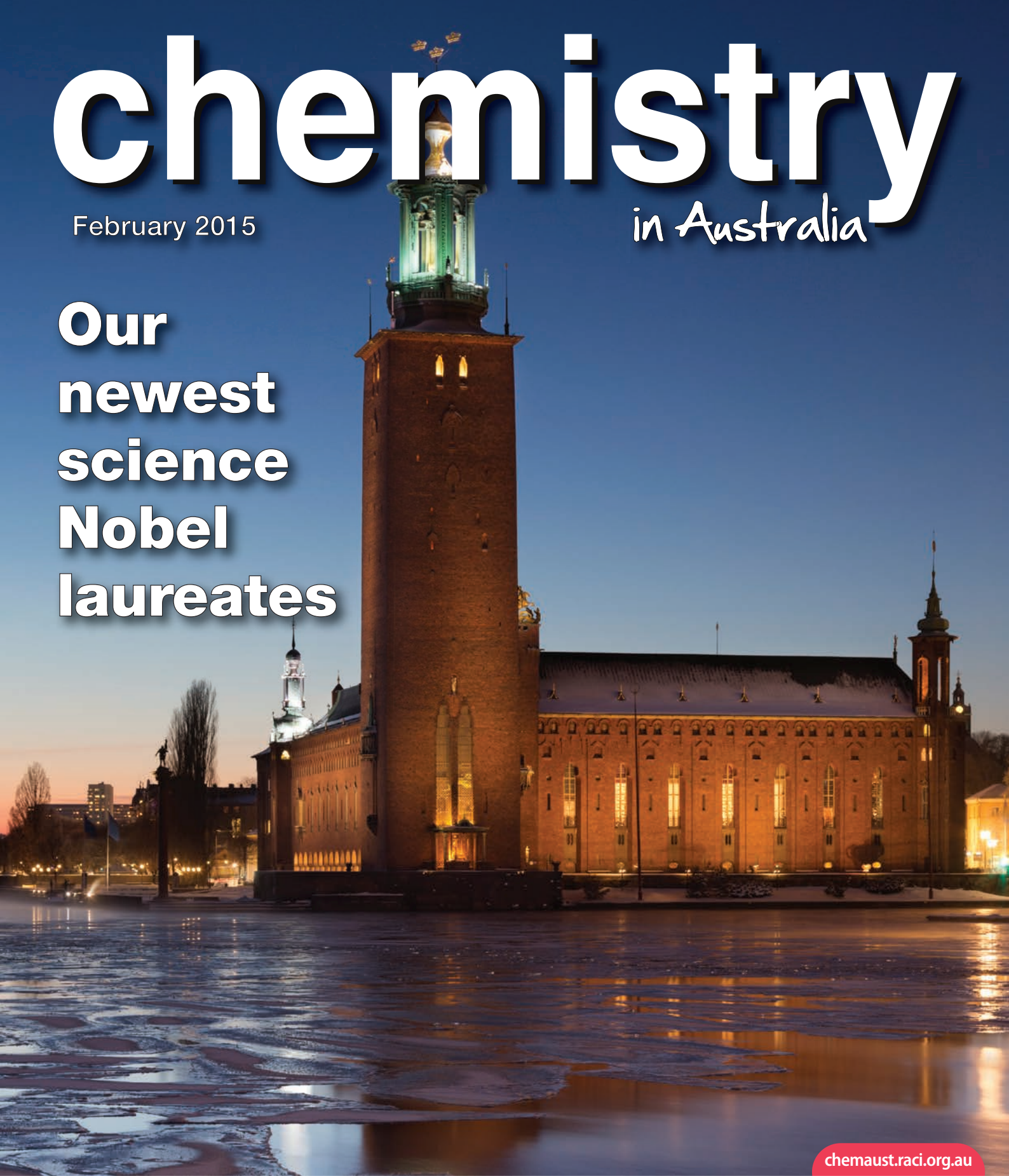


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## cover story

### Super resolution microscopy: it's all about the molecule

Microscopy has been the purview of biology for some 400 years. This year's Nobel Prize in Chemistry marks the crossing of light microscopy to the molecular level, revealing incredible secrets of the nanoworld.

Stockholm City Hall – the venue for the Nobel Prize banquet each year.

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## Science not always a safe bet

Online awards betting took a new turn a few years ago when British company Ladbrokes Betting & Gambling slotted the Nobel Prize in Literature between Aussie Rules and baseball, in the Awards section of its list of punting pleasures.

Last year *The New Yorker* asked a Ladbrokes spokesman why Ladbrokes only takes bets for literature. He replied that it 'seems to be the category above all others to capture bettors' imaginations' (<http://nyr.kr/1vg3dMg>).

Bets for the Nobel Prize in Chemistry might be off at Ladbrokes, but there's still plenty of speculation and prediction from October each year.

On its ScienceWatch website, Thomson Reuters included RACI Fellows Graeme Moad, Ezio Rizzardo and San H. Thang, for their work on RAFT polymerisation, in its citations-based Nobel predictions for 2014.

According to Thomson Reuters, since 2002 their 'analysis has identified more than two dozen eminent scientists who went on to win the Nobel Prize'. You can see the full list of correct predictions, and read a methodological essay about their citation analysis, at [sciencewatch.org/nobel](http://sciencewatch.org/nobel).

The Thomson Reuters analysis missed the mark this time around, with Eric Betzig, Stefan W. Hell and William E. Moerner taking out the chemistry gong for the development of super-resolved fluorescence microscopy. Peter Karuso tells us more on page 14.

As a result of the recent CSIRO cutback program, sadly San Thang was made redundant and he is currently an Honorary Fellow of CSIRO. San told me that what he has done so far in his career is merely a small contribution to the scientific research field and he will continue his RAFT work for wider applications to advancing a better world.

Although he wasn't taking wagers, Paul Bracher at ChemBark blogged odds of 7–1 for Moerner, who was among his official picks: 'I think this [single-molecule spectroscopy/laser] is an inevitable prize, so why the heck shouldn't I keep picking it until it wins?' (<http://bit.ly/11pDi9m>)




Sally Woollett (editor@raci.org.au)

### Other 2014 chemistry Nobel predictions\*

**Mesoporous materials:** Dr Charles T. Kresge, Chief Technology Officer, Saudi Aramco; Ryoo Ryong, Professor of Chemistry, Head of Center for Functional Nanomaterials, Korea Advanced Institute of Science and Technology; Professor Galen D. Stucky, Department of Chemistry and Biochemistry, University of California.

**Organic light-emitting diodes:** Ching W. Tang, Doris Johns Cherry Professor, Chemical Engineering Department, University of Rochester; Steven Van Slyke, Chief Technology Officer, Kateeva Inc.

\* Based on Thomson Reuters citations analysis



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## The cost of solar

Perhaps organic solar would compare better to silicon if it also enjoyed an unbroken half-century of research and manufacturing development cross-subsidies by revolutions in the aerospace and semiconductor industries. Certainly, other technologies have the potential, realised or no, to be cheaper and more efficient. However, because they struggle to compete in risk-averse markets saturated by more mature technology, improvements will only come from researchers and funding bodies prepared to bet on this potential.

Andrew Danos MRACI (Student)

## Gender imbalance

I wish to highlight the gender imbalance in RACI-invited speakers to the annual Regional Organic Chemistry Symposia, typically held in late November/early December.

These regional symposia are run by the local branches but the invited, typically overseas, plenary speakers are chosen at a divisional level, and typically visit several cities where the branches host them. In Brisbane, this conference is called BBOCS (Brisbane Biological and Organic Chemistry Symposium), which evolved from BOCS in 2001 to reflect the increase in biologically focused chemistry being done in the region. BBOCS is typically rotated amongst the three major campuses in Brisbane – University of Queensland, Griffith University and Queensland University of Technology – with these institutions themselves rotating the event between the chemistry departments themselves and various research institutes. The Melbourne event is known as the Melbourne Annual Organic Synthesis Symposium, and the NSW/Canberra event is the One-Day Symposium.

Drawing upon my own collection of local BBOCS programs, and limited publicly available programs for Victoria and New South Wales, it is disturbing that Brisbane has seen only one female speaker in the last 14 years (out of 26 speakers), although one of the 2010 RACI-invited speakers was female but could not make it to Brisbane.

Please note that this is not a complaint directed at the regional organisers who organise the program around the speakers that the RACI provides, and generally perform excellently in providing a balanced program, particularly with regards to student and early career speakers.

I would like to suggest that the Institute consider developing a policy regarding the selection process for invited speakers. This might include, for example, ensuring that the committee selecting speakers is gender-balanced itself.

This letter is a personal letter from me, and does not reflect the views of any employers past or present.

Martin Stoermer MRACI CChem

## November issue

Sally, congratulations to you and the staff on the November 2014 issue. It took a lot of thought to try this and it was very successful to me and a number of my non-scientific friends. My only comment was to my brain as I had no Smarties, I had to think and work out what would happen in each case. It may have been easier to just go out and buy some.

Kevin Wolff MRACI CChem

## 'Your say' guidelines

We will consider letters of up to 350 words in response to material published in *Chemistry in Australia* or about novel or topical issues relevant to chemistry. Letters accepted for publication will be edited for clarity, space or legal reasons and published in print and online. Full name and RACI membership status will be published. Please supply a daytime contact telephone number (not for publication).

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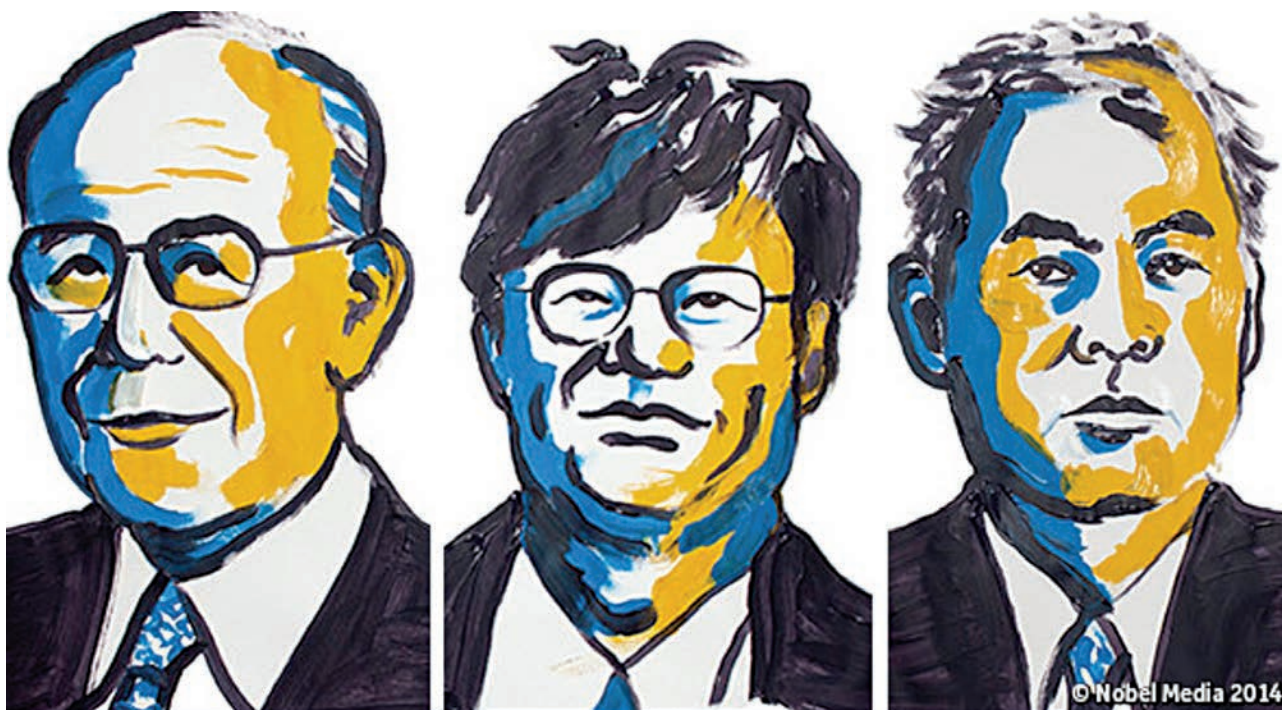
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# 2014 science Nobel Prizes

## Physics: new light to illuminate the world



**Isamu Akasaki** is a Japanese citizen born 1929 in Chiran, Japan. He obtained his PhD in 1964 from Nagoya University, Japan. **Hiroshi Amano** is a Japanese citizen born in 1960 in Hamamatsu, Japan. He obtained his PhD in 1989 from Nagoya University, Japan. **Shuji Nakamura** is an American citizen born in 1954 in Ikata, Japan. He obtained his PhD in 1994 from the University of Tokushima, Japan. © Nobel Media 2014

The Royal Swedish Academy of Sciences awarded the Nobel Prize in Physics for 2014 to Isamu Akasaki (Meijo University, Nagoya, and Nagoya University, Japan), Hiroshi Amano (Nagoya University, Japan) and Shuji Nakamura (University of California, Santa Barbara, California, USA)

for the invention of efficient blue light-emitting diodes which has enabled bright and energy-saving white light sources.

The Nobel Laureates are rewarded for having invented a new energy-efficient and environmentally friendly light source – the blue light-emitting diode (LED). In the spirit of Alfred Nobel, the Prize rewards an invention of greatest benefit to mankind; using blue LEDs, white light can be created in a new way. With the advent of LED lamps, we now have more long-lasting and more efficient alternatives to older light sources.

When Isamu Akasaki, Hiroshi Amano and Shuji Nakamura produced bright blue light beams from their semiconductors in the early 1990s, they triggered a fundamental transformation of lighting technology. Red and green diodes had been around for a long time but without blue light, white lamps could not be created. Despite considerable efforts, both in the scientific community and in industry, the blue LED had remained a challenge for three decades.

They succeeded where everyone else had failed. Akasaki

worked together with Amano at the University of Nagoya, while Nakamura was employed at Nichia Chemicals, a small company in Tokushima. Their inventions were revolutionary. Incandescent light bulbs lit the 20th century; the 21st century will be lit by LED lamps.

White LED lamps emit a bright white light, are long-lasting and are energy-efficient. They are constantly improved, getting more efficient with higher luminous flux (measured in lumen) per unit electrical input power (measured in watts). The most recent record is just over 300 lm/W, which can be compared to 16 for regular light bulbs and close to 70 for fluorescent lamps. As about a quarter of world electricity consumption is used for lighting purposes, the LEDs contribute to saving the Earth's resources. Materials consumption is also diminished as LEDs last up to 100 000 hours, compared to 1000 for incandescent bulbs and 10 000 hours for fluorescent lights.

The LED lamp holds great promise for increasing the quality of life for over 1.5 billion people around the world who lack access to electricity grids: due to low power requirements it can be powered by cheap local solar power.

The invention of the efficient blue LED is just 20 years old, but it has already contributed to create white light in an entirely new manner to the benefit of us all.



## Physiology or Medicine: how the brain maps space



Wiki/Per Henning/NTNU

**John O'Keefe** was born in 1939 in New York City, USA, and holds both American and British citizenships. He received his doctoral degree in physiological psychology from McGill University, Canada, in 1967. After that, he moved to England for postdoctoral training at University College London. He has remained at University College and was appointed Professor of Cognitive Neuroscience in 1987. John O'Keefe is currently Director of the Sainsbury Wellcome Centre in Neural Circuits and Behaviour at University College London.

**Edvard I. Moser** was born in 1962 in Ålesund, Norway, and has Norwegian citizenship. He obtained his PhD in neurophysiology from the University of Oslo in 1995. He was a postdoctoral fellow together with his wife and co-Laureate May-Britt Moser, first at the University of Edinburgh and later a visiting scientist in John O'Keefe's laboratory in London. In 1996, they moved to the Norwegian University of Science and Technology in Trondheim, where Edvard Moser became Professor in 1998. He is currently Director of the Kavli Institute for Systems Neuroscience in Trondheim. **May-Britt Moser** was born in Fosnavåg, Norway, in 1963 and is a Norwegian citizen. She studied psychology at the University of Oslo together with her future husband and co-Laureate Edvard Moser. She received her PhD in neurophysiology in 1995. She was a postdoctoral fellow at the University of Edinburgh and subsequently a visiting scientist at University College London before moving to the Norwegian University of Science and Technology in Trondheim in 1996. May-Britt Moser was appointed Professor of Neuroscience in 2000 and is currently Director of the Centre for Neural Computation in Trondheim.

The Nobel Assembly at Karolinska Institute awarded half of the 2014 Nobel Prize in Physiology or Medicine to John O'Keefe and the other half jointly to May-Britt Moser and Edvard I. Moser.

for their discoveries of cells that constitute a positioning system in the brain.

How do we know where we are? How can we find the way from one place to another? And how can we store this information in such a way that we can immediately find the way the next time we trace the same path? This year's Nobel Laureates have discovered a positioning system, an 'inner GPS' in the brain that makes it possible to orient ourselves in space, demonstrating a cellular basis for higher cognitive function.

In 1971, John O'Keefe discovered the first component of this positioning system. He found that a type of nerve cell in an area of the brain called the hippocampus that was always activated when a rat was at a certain place in a room. Other nerve cells were activated when the rat was at other places. O'Keefe concluded that these 'place cells' formed a map of the room.

More than three decades later, in 2005, May-Britt and Edvard Moser discovered another key component of the brain's positioning system. They identified another type of nerve cell, which they called 'grid cells', that generate a coordinate system and allow for precise positioning and pathfinding. Their subsequent research showed how place and grid cells make it possible to determine position and to navigate.

The discoveries of John O'Keefe, May-Britt Moser and Edvard Moser have solved a problem that has occupied philosophers and scientists for centuries – how does the brain create a map of the space surrounding us and how can we navigate our way through a complex environment?



Geir Mogen/NTNU

## How do we experience our environment?

The sense of place and the ability to navigate are fundamental to our existence. The sense of place gives a perception of position in the environment. During navigation, it is interlinked with a sense of distance that is based on motion and knowledge of previous positions.

Questions about place and navigation have engaged philosophers and scientists for a long time. More than 200 years ago, the German philosopher Immanuel Kant argued that some mental abilities exist as a priori knowledge, independent of experience. He considered the concept of space as an inbuilt principle of the mind, one through which the world is and must be perceived. With the advent of behavioural psychology in the mid-20th century, these questions could be addressed experimentally. When Edward Tolman examined rats moving through labyrinths, he found that they could learn how to navigate, and proposed that a 'cognitive map' formed in the brain allowed them to find their way. But questions still lingered – how would such a map be represented in the brain?

## John O'Keefe and the place in space

O'Keefe was fascinated by the problem of how the brain controls behaviour and decided, in the late 1960s, to attack this question with neurophysiological methods. When recording signals from individual nerve cells in the hippocampus, in rats moving freely in a room, O'Keefe discovered that certain nerve cells were activated when the animal assumed a particular place in the environment. He could demonstrate that these 'place cells' were not merely registering visual input, but were building up an inner map of the environment. O'Keefe concluded that the hippocampus generates numerous maps, represented by the collective activity of place cells that are activated in different environments. Therefore, the memory of an environment can be stored as a specific combination of place cell activities in the hippocampus.

## May-Britt and Edvard Moser find the coordinates

May-Britt and Edvard Moser were mapping the connections to the hippocampus in rats moving in a room when they discovered an astonishing pattern of activity in a nearby part of the brain called the entorhinal cortex. Here, certain cells were activated when the rat passed multiple locations arranged in a hexagonal grid. Each of these cells was activated in a unique spatial pattern and collectively these 'grid cells' constitute a coordinate system that allows for spatial navigation. Together with other cells of the entorhinal cortex that recognise the direction of the head and the border of the room, they form circuits with the place cells in the hippocampus. This circuitry constitutes a comprehensive positioning system, an inner GPS, in the brain.

## A place for maps in the human brain

Recent investigations with brain imaging techniques, as well as studies of patients undergoing neurosurgery, have provided evidence that place and grid cells exist also in humans. In patients with Alzheimer's disease, the hippocampus and entorhinal cortex are frequently affected at an early stage, and these individuals often lose their way and cannot recognise the environment. Knowledge about the brain's positioning system may, therefore, help us understand the mechanism underpinning the devastating spatial memory loss that affects people with this disease.

The discovery of the brain's positioning system represents a paradigm shift in our understanding of how ensembles of specialised cells work together to execute higher cognitive functions. It has opened new avenues for understanding other cognitive processes, such as memory, thinking and planning.

NOBEL MEDIA

## Chemistry: surpassing the limitations of the light microscope

The Nobel Prize in Chemistry 2014 was awarded jointly to Eric Betzig, Stefan W. Hell and William E. Moerner

for the development of super-resolved fluorescence microscopy.

These laureates are featured elsewhere in this issue (p. 14).



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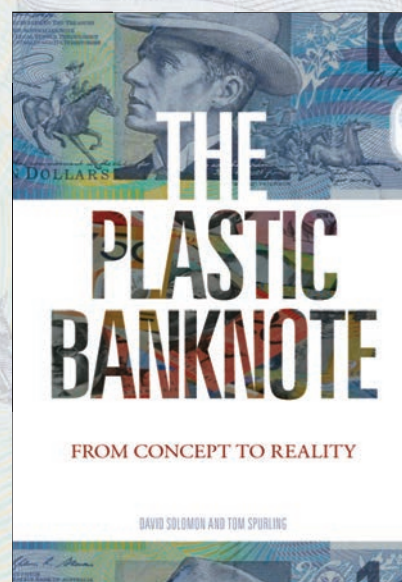
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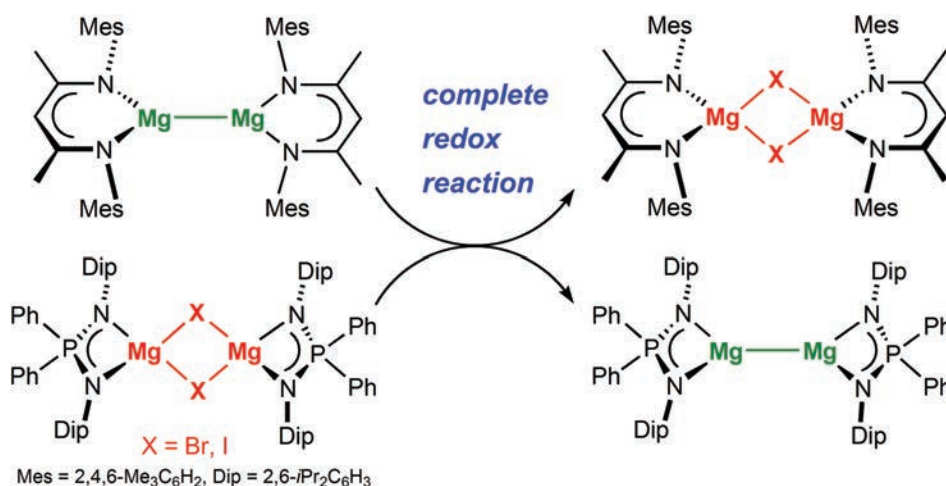
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## Magnesium(I) complex from a $\text{Mg}^{\text{I}}/\text{Mg}^{\text{II}}$ redox reaction

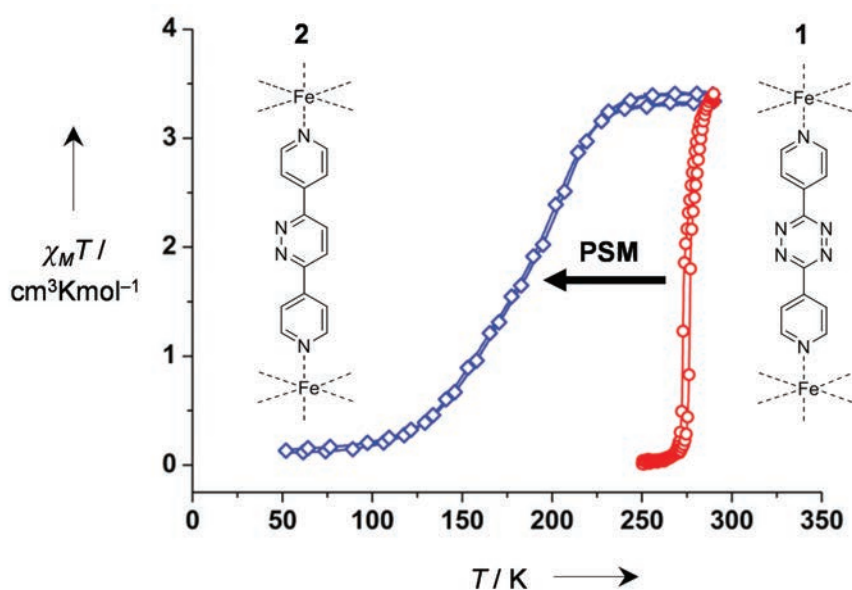
Synthesising novel, stable, low oxidation state magnesium complexes is a challenging but rewarding task, and their many chemical applications have been reported in this column by Professor Cameron Jones and Dr Andreas Stasch from Monash University. All previous examples have been accessed by Na or K reduction of some magnesium(II) precursors featuring CN-based ligands. Now, magnesium(II) halide complexes of a sterically demanding diiminophosphinate ligand have been converted to a novel magnesium(I) dimer, simply by reduction with a known  $\beta$ -diketiminato magnesium(I) dimer at elevated temperatures (Stasch A. *Angew. Chem. Int. Ed.* 2014, **53**, 10200–3). The success of this reaction is believed to stem from the flexible coordination properties of the diiminophosphinate ligand and probably proceeds for kinetic

reasons. The novel magnesium(I) dimer has a similar structure and reactivity to previous examples, as has been demonstrated by a C–C coupling reaction of an organic isocyanate. The complex is, furthermore, quite thermally stable

despite uniting the highly reducing  $\text{Mg}_2^{2+}$  ion and a high oxidation state  $\text{P}^{\text{V}}$  iminophosphorane ligand. The synthetic strategy is promising for other ligand classes and will help expand the family of low oxidation state group 2 complexes.



## Post-synthetic modification of a MOF



The versatile synthetic chemistry and open lattices of metal–organic frameworks lend themselves to the achievement of a range of interesting electronic/magnetic properties. One such

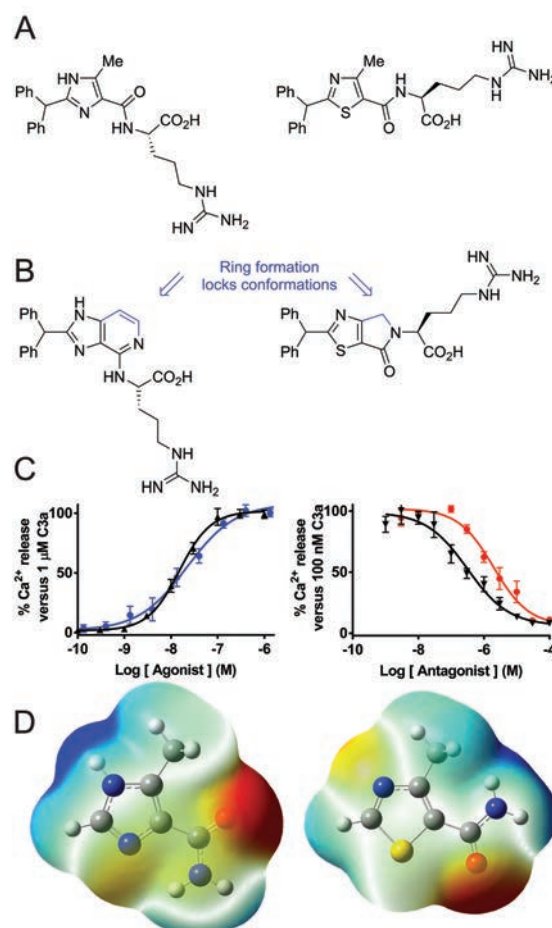
family of functional materials are porous spin crossover (SCO) frameworks, for which the cooperative spin-switching properties of transition metal centres within the host lattices are often highly

sensitive to the exchange of labile guest molecules. With an interest in extending the chemical capabilities of such materials, researchers at the University of Sydney have recently synthesised a chemically reactive SCO framework that undergoes covalent post-synthetic modification (PSM) to form a topotactic crystalline phase in which the overall structure is closely retained (Clements J.E., Price J.R., Neville S.M., Kepert C.J. *Angew. Chem. Int. Ed.* 2014, **53**, 10164–8). Upon the adsorption of Diels–Alder reagents into the pores of this material, framework tetrazine units convert rapidly and quantitatively to diazine, inducing subtle structural perturbations and leading in turn to pronounced changes to the SCO properties. This application of covalent PSM establishes a new method for manipulating SCO behaviour in a controllable fashion. Future extension promises to allow the introduction of increased structural complexity into SCO systems, thereby expanding the scope of this class of materials through the opportunity to incorporate specific functional sites.



## Twinking amide conformation with heterocycles

Researchers from the Institute of Molecular Bioscience, University of Queensland, have shown how different heteroatoms in a five-membered heterocycle can impart opposing functional properties on a small molecule that selectively targets a protein on immune cells (Reid R.C., Yau M.K., Singh R., Lim J., Fairlie D.P. *J. Am. Chem. Soc.* 2014, **136**, 11914–17; recommended by Faculty1000Prime (<http://f1000.com/prime/718522891>)). Heterocycles adjacent to amides can profoundly influence molecular structure due to stereoelectronic effects exerted by the heteroatom. This is shown in the figure for imidazolyl- and thiazolylamides by comparing low-energy conformations (derived from ab initio MP2 and DFT calculations), charge distribution, dipole moments, and known crystal structures, which support a general principle. Switching a heteroatom from nitrogen to sulfur altered amide conformation, producing different three-dimensional electrostatic surfaces, which could be explained by altered dipole and orbital alignments. The subtle change in atomic composition translated spectacularly into opposing agonist vs antagonist activity in modulating a G-protein-coupled receptor for inflammatory protein complement C3a on human macrophages. Influences of the heteroatom were confirmed by locking the amide conformation using fused bicyclic analogues. These findings show that stereoelectronic effects of heterocycles modulate molecular conformation, which can impart strikingly different biological properties.

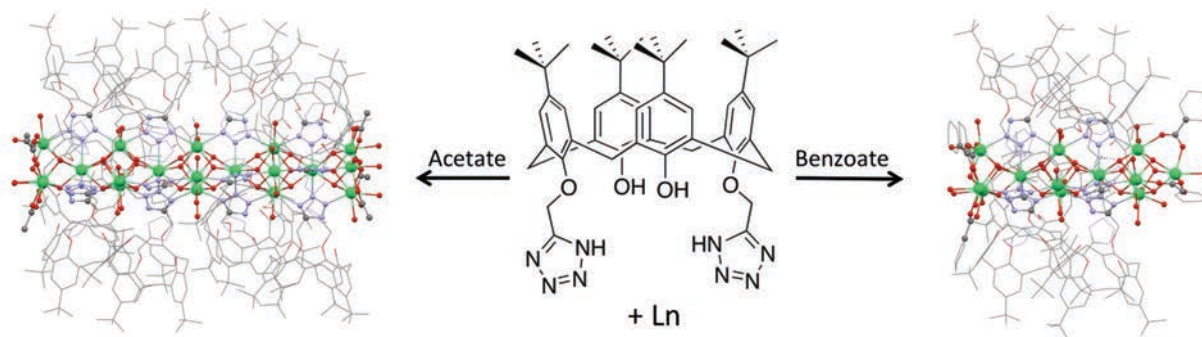


## Bottlebrush clusters

Coordination clusters sit between mononuclear metal complexes and nanoparticulate materials, and provide an opportunity to enter the nanometre size range from the 'bottom up' with a structurally consistent product. Some spectacular structures have been made, including large spheres, capsules and molecular wheels. What have been missing so far from this structural smorgasbord are discrete rod-like structures. This is not surprising, as

intuition suggests that any tendency to form elongated structures will lead to the formation of coordination polymers. Researchers at Curtin University, in collaboration with ANSTO and the University of Western Australia, have now shown that nanometer-long rod-like coordination clusters can be formed (D'Alessio D., Sobolev, A.N., Skelton B.W., Fuller R.O., Woodward R.C., Lengkeek, N.A., Fraser B.H., Massi M., Ogden M.I. *J. Am. Chem. Soc.* 2014, **136**, 15122–5).

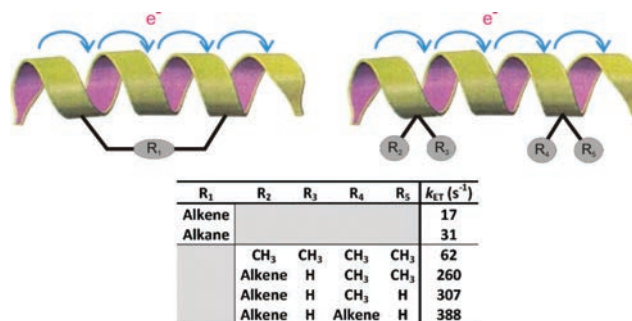
Elongated Ln<sub>10</sub> clusters were isolated, supported by a tetrazole-functionalised calixarene and acetate co-ligands. The cluster core is built from apex-fused trigonal bipyramids, with an aspect ratio of ~7:1. Remarkably, changing the co-ligand from acetate to benzoate gave shortened Ln<sub>12</sub> clusters, but with the same repeat unit. Systematic variation of the cluster size is now being investigated, to enable study of the cluster properties as a function of size and shape.



## Tunable peptide-based molecular wires

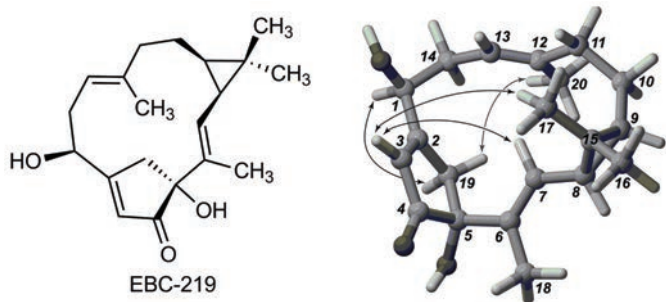
Electron transfer pathways in naturally occurring proteins require a sophisticated framework that is provided by well-defined secondary structures. Researchers at the University of Adelaide and Flinders University recently reported a series of peptides constrained into either a  $3_{10}$ -helix or a  $\beta$ -strand conformation, with a varied number of electron-rich alkene-containing side chains (Horsley J.R., Yu J., Moore K.E., Shapter J.G., Abell A.D. *J. Am. Chem. Soc.*, 2014, **136**, 12479–88; selected for F1000Prime and recommended as being of special significance in its field). Electrochemical and theoretical studies confirmed the ability of the alkene(s) to facilitate electron transfer through the peptides by acting as a ‘stepping stone’. Two of the peptides were further rigidified with a side-chain tether introduced by ring-closing metathesis. A comparison of the resulting unsaturated and saturated tethered peptides revealed, for the first time, an interplay between backbone rigidity and effects arising from the alkene side chains, with

both factors clearly contributing to the efficiency of electron transfer in the constrained peptides. This allows for manipulation of energy barriers and hence conductance in peptides, a crucial step in the design and fabrication of molecular-based electronic devices.



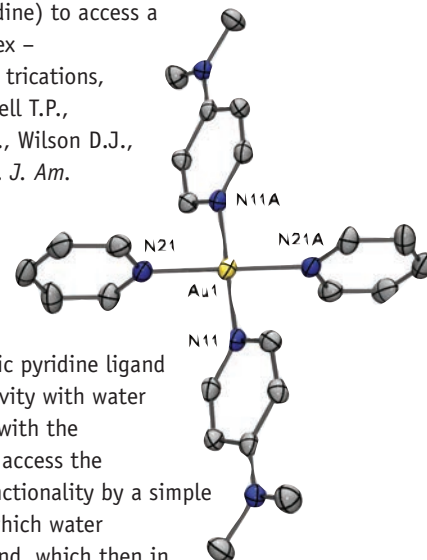
## Anti-Bredt natural product

Professor Craig Williams and co-workers have described the isolation and identification of an unusual natural product, EBC-219, from the Australian rainforest (Maslovskaya L.A., Savchenko A.I., Krensk E.H., Pierce C.J., Gordon V.A., Reddell P.W., Parsons P.G., Williams C.M. *Angew. Chem. Int. Ed.* 2014, **53**, 7006–9). The work is the culmination of a three-way collaboration between EcoBiotics Ltd, QIMR Berghofer Medical Research Institute, and the School of Chemistry and Molecular Biosciences at the University of Queensland. The structure of EBC-219, which defines a new diterpene skeletal class, was elucidated by a combination of spectroscopic methods and DFT circular dichroism predictions. This molecule is particularly interesting because it possesses a bridgehead double bond, which invoked Bredt's rule considerations bicyclo[10.2.1] bridgehead olefin. The application of Bredt's rule to natural products has historically been problematic and a follow up review covering this area suggests that it should not necessarily be applied to natural products, or analogues of naturally occurring anti-Bredt systems (Mak J.Y.W., Pouwer R.H., Williams C.M. *Angew. Chem. Int. Ed.* 2014, **53**, doi: 10.1002/anie.201400932).



## Golden result for hypervalent iodine

Hypervalent iodine(III) compounds such as  $\text{PhICl}_2$  and  $\text{PhI}(\text{OAc})_2$  have recently found major use as highly effective oxidants for late transition metal complexes. In particular, they have been used to access  $\text{Pd}^{\text{IV}}$ ,  $\text{Pt}^{\text{IV}}$  and  $\text{Au}^{\text{III}}$  compounds, with the iodine(III) being used to both oxidise the starting complex (e.g.  $\text{Pd}^{\text{II}}$ ) and deliver stabilising ligands. The team led by Drs Barnard, Hogan, Wilson and Dutton, from La Trobe University, have used the dicationic  $\text{I}^{\text{III}}$  reagent  $[\text{PhI}(\text{pyr})_2]^{2+}$  (pyr = pyridine) to access a new class of  $\text{Au}^{\text{III}}$  complex – homoleptic  $\text{Au}^{\text{III}}$ -centred trications,  $[\text{Au}(\text{pyr})_4]^{3+}$  (Corbo R., Pell T.P., Stringer B.D., Hogan C.F., Wilson D.J., Barnard P.J., Dutton J.L. *J. Am. Chem. Soc.* 2014, **136**, 12415–21). The new compounds were found to have very tunable reduction potentials, depending on the specific pyridine ligand employed. Unique reactivity with water was also demonstrated, with the trications being used to access the challenging  $\text{Au}^{\text{III}}\text{-OH}$  functionality by a simple reaction with water in which water displaces a pyridine ligand, which then in turn acts as a base giving  $\text{Au}^{\text{III}}\text{-OH}$ .



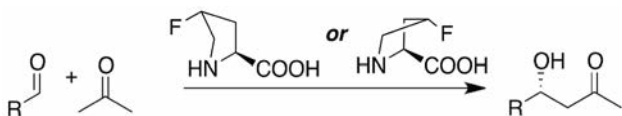
Compiled by **Matthew Piggott** MRACI CChem (matthew.piggott@uwa.edu.au). This section showcases the very best research carried out primarily in Australia. RACI members whose recent work has been published in high impact journals (e.g. *Nature*, *J. Am. Chem. Soc.*, *Angew. Chem. Int. Ed.*) are encouraged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



## Aust J Chem

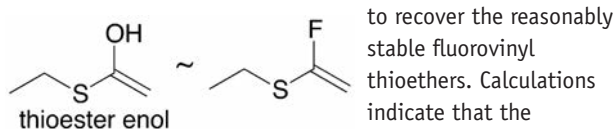
There has been a recent resurgence of interest in organofluorine compounds driven by the discovery of several new, versatile fluorinating reagents, which allow safe and convenient fluorination. Several such reagents are now commercially available. Due to the small size of the fluorine atom, its presence in a molecule does not significantly change the shape, yet its high electronegativity can profoundly alter the electronic and chemical properties and hence factors such as stability, lipophilicity and biological reactivity and action. As a result, a large number of pharmaceuticals contain fluorine atoms. An early and still highly successful example is the effective topical drug for treating skin cancer, 5-fluorouracil.

The January issue contains a series of papers on fluorine chemistry put together by Luke Hunter (University of New South Wales). Hunter and co-workers investigated the application of *cis*- and *trans*-4-fluoroprolines as enantioselective organo-catalysts for, inter alia, the aldol reaction, Michael addition and Robinson annulation and found that the ring puckering is responsible for changes in the relative selectivities, whereby the *trans* compound produces significantly higher enantioselectivity.



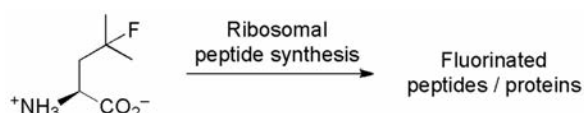
Chebib (Macquarie University), Hunter and co-workers review the mode of neurotransmitter binding to GABA receptors and describe how fluorinated GABA analogues can be used to develop an accurate pharmacophore of neurotransmitter binding to the diverse binding sites of individual GABA receptors. Harper and co-workers report a general rate acceleration of  $S_N2$  reactions in ionic liquids containing bis(trifluoromethanesulfonyl)-imide, dicyanamide, hexafluorophosphate and tetrafluoroborate as anions; and Blanch et al. (University of Queensland) describe the generation of trifluoromethylphenylcarbenes and their rearrangement to 1',2',2'-trifluorostyrene, 1,1,2-trifluorobenzocyclobutane and trifluoromethylfulvenallene as well as ring expansion to trifluoromethylcycloheptatetraene, which dimerises to the corresponding heptafulvalene.

O'Hagan et al. (University of St Andrews, Scotland) describe fluorovinyl thioethers as putative biomimetic surrogates for the enols of thioesters. Fluorovinyl thioethers are prepared by reaction of acetylene thioethers with pyridinium (poly)-hydrogen fluoride, whereby titration with pyridine is important for the selectivity of the reaction. Without titration, the corresponding gem-difluoroethyl thioethers are formed. With titration, the reaction can be stopped at an intermediate stage



fluorovinyl thioether has steric and electronic characteristics similar to thioester enols. A fluorovinyl thioether representing the terminus of the pantothenoyl chain of acetyl-CoA is also prepared.

Chris Easton and Samuel Fraser (ANU) describe the utilisation of native and engineered ribosomal protein biosynthesis to produce a range of fluorinated  $\alpha$ -amino acids for incorporation into peptides and proteins, where they can act as substitutes for natural and unnatural amino acids. Fluorinated peptides with a range of diverse properties have been synthesised in this way, and the methods described are amenable to routine application as alternatives to conventional peptide synthesis.



James Gardiner (CSIRO, Clayton) reviews industrial uses of fluoropolymers, which have influenced all areas of industry since their discovery in the 1930s. The historical development of the fluoropolymer industry is highlighted with a focus on traditional fluoroplastics. The production, processing, and properties of these fluoropolymers are discussed, together with examples of the specific uses in the chemical industry and in manufacturing, electronics, architecture, energy, health and domestic sectors. Fluoropolymers such as fluoroelastomers, perfluoropolyethers and fluorosurfactants are also mentioned, and environmental aspects as well as the current state of the fluoropolymer industry are summarised.

Lidia Matesic et al. (ANSTO) report on the optimisation of [ $^{18}\text{F}$ ]-fluorination and fully automated production of the melanin-targeting positron emission tomography (PET) radiotracer the 5- $^{18}\text{F}$ -nicotinamide derivative [ $^{18}\text{F}$ ]MEL050 by using  $^{18}\text{F}$ H on Kryptofix[2.2.2] in a commercial continuous-flow microfluidic system. The process was translated to production scale, and [ $^{18}\text{F}$ ]MEL050 (35–150 GBq) was obtained in approximately 43% radiochemical yield in about 50 min.

Kassiou and co-workers (University of Sydney) describe how a plethora of indole-based, illicit, synthetic cannabinoids (SCs) have emerged in recent years, their structures evolving continually in attempts to elude detection and circumvent scheduling laws. The methodologies used to prepare the latest generation of SCs are based on patent literature describing bio-isosteric fluorine-for-hydrogen replacement reactions commonly used in medicinal chemistry. Unlike the case with traditional pharmaceuticals, the illicit SCs are peddled for recreational consumption with no prior testing and little or no knowledge of potential health risks.

Curt Wentrup FAA, FRACI CChem (wentrup@uq.edu.au),  
[http://uq.edu.au/uqresearchers/researcher/wentrupc.html?uv\\_category=pub](http://uq.edu.au/uqresearchers/researcher/wentrupc.html?uv_category=pub)

# Super resolution microscopy

$$\lambda = \frac{2n \sin \alpha}{2}$$

It's all about the molecules

2014 Nobel Prize in Chemistry I

Ernst Abbe memorial, Jena University.

BY **PETER KARUSO**

Microscopy has been the purview of biology for some 400 years. This year's Nobel Prize in Chemistry marks the crossing of light microscopy to the molecular level, revealing incredible secrets of the nanoworld.

**O**n 10 December 2014, the Nobel Prize in Chemistry was given to Stefan Hell (Max Planck Heidelberg), William E. Moerner (Stanford University) and Eric Betzig (Jenalia Research Farm) 'for the development of super-resolved fluorescence microscopy'. Fluorescence microscopy allows scientists to explore the inner workings of a cell, and its immense popularity arises to a large extent from the ability to specifically label biomolecules with specific fluorophores.

## The developing microscope

Dutch spectacle-maker (**Zacharias Jansen**) is credited with inventing the simple (1590) and compound (1618) microscopes, but this is debatable.

Another claim is that **Hans Lippershey**, Jansen's neighbour and spectacle-making competitor, invented the microscope. The truth is that the microscopy was probably invented many times in Europe between 1262, when **Roger Bacon** first wrote about the magnifying properties of lenses, and 1670, when **Antonie Philips van Leeuwenhoek** introduced the microscope to biology. In particular, the secretive art of spectacle making boomed in Holland in the 16th and early 17th centuries, where it was a lucrative business and it is not unreasonable to think that those engaged in grinding lenses would have noticed and applied their magnifying properties to looking at the micro-world.



Leeuwenhoek's microscope was brilliant and took advantage of glass blowing, not lens grinding. He used a trick, known to all chemists, of drawing out a glass rod in a hot flame to make two long 'whiskers' and then heating the end of the whisker to make a tiny sphere of glass that was then mounted into a brass plate. The smaller the sphere, the higher the curvature and the bigger the magnification. Leeuwenhoek realised that if his simple method for creating the critically important lenses was revealed, the scientific community of his time would jump onto the bandwagon and likely forget his role in microscopy. For this reason, he kept his microscopes secret and took the trick of making his lenses to the grave.

With his simple microscope, Leeuwenhoek was the first to observe bacteria, which he called 'animalcules' as they were intermediate in size between 'animals' and 'molecules', and led to his reputation as the father of microbiology. Leeuwenhoek's lens had very high magnification but also high chromatic aberration (where the different colours of light are refracted to different focal points. This was fixed by another Dutchman, **Christiaan Huygens** (1629–95), who invented the achromatic doublet – a compound lens that uses a crown and flint to correct for these aberrations.

**Galileo Galilei** (1564–1642) was not a Dutchman but he did get himself into trouble with the Church over some things he saw through the telescope. It is less well known that he also made the first useful compound microscope (microscopes that contain two or more lenses). It did not have the magnification of Leeuwenhoek's simple microscope but had much better image quality and was used to make the first published microscopic images of a bee, for example in *Persio tradotto in verso schiolto e dichiarato* by Francesco Stelluti (1630).

The optical microscope continued to develop over time and by the late 19th century, Thuringia (Germany)

was famous for precision glass and its capital, Jena, attracted great minds interested in optics. In particular, when glass chemist **Otto Schott**, instrument maker **Carl Zeiss** and physicist **Ernst Abbe** got together, they pushed optical microscopy to its limit. Through the companies Glastechnische Laboratorium Schott & Genossen (Schott & Associates) and Zeiss AG, the world's best microscopes were developed, but this also revealed a serious limitation of optical microscopy. Empirical observations found that, regardless of how precisely lenses are ground and aberrations compensated for, it was impossible to resolve anything less than about  $0.4\ \mu\text{m}$  in size. In 1873, Abbe figured out why. The limitation comes from the fact that light is a wave and as such diffracts when passing through a slit or aperture (like in a microscope or telescope), forming a diffraction pattern (Airy disc). Two close points create overlapping Airy discs at the focal point and Abbe calculated that the maximum resolution possible was about  $\lambda/2$ , or more precisely  $\lambda/2.n\sin\alpha$ , where  $n\sin\alpha$  is the numerical aperture (c.f. the  $f$ -stop on your camera lens) and  $\lambda$  is the wavelength of the light used. This is the so-called *Abbe diffraction limit*. Using visible light (400–700 nm), this means it would be impossible to resolve anything closer together than  $\sim 0.2$ – $0.4\ \mu\text{m}$ . In practical terms, this means simple light microscopy will never be able to resolve anything smaller than say mitochondria ( $0.6\ \mu\text{m}$ ) and definitely never viruses ( $<0.1\ \mu\text{m}$ ) or individual proteins ( $<0.01\ \mu\text{m}$ ).

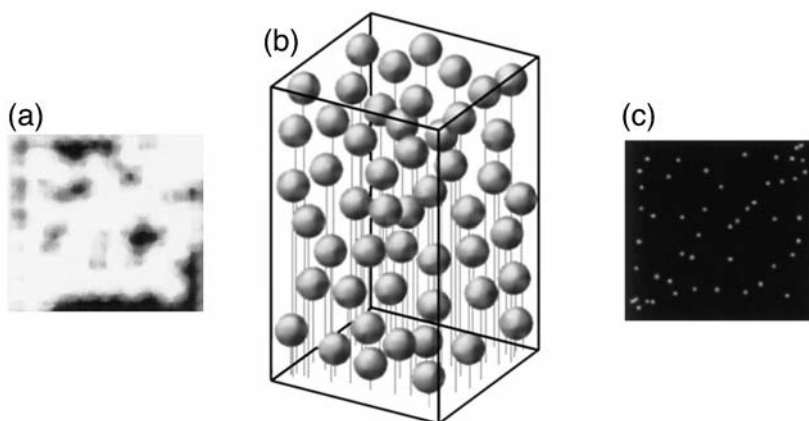
### Breaking the Abbe diffraction limit

**Richard Adolf Zsigmondy** received the Nobel Prize in Chemistry in 1925 for proving colloidal solutions were heterogeneous and for methods of studying these. He was inspired, in part, by dichroic glass, for example the late Roman 'Lycurgus cup', which appears green when illuminated from

the front and red when illuminated from behind. Zsigmondy, in collaboration with **Henry Siedentopf** (Carl Zeiss AG), developed the 'ultramicroscope' in 1902 to study colloidal solutions. By focusing sunlight to a single point inside a colloidal sample, Zsigmondy was able to count 4 nm colloidal particles from their reflections as long as they were more than 400 nm apart. Using this method, he was able to show that Roman dichroic glass was a colloidal suspension of gold or silver nanoparticles. While not strictly breaking the Abbe diffraction limit, this work inspired an Irishman to write to **Albert Einstein** in May 1928 with an idea on how the diffraction limit could be broken.

**Edward Hutchinson Synge** (Hutchie) studied mathematics at Trinity College Dublin (1908) but dropped out after three years of a four-year degree, travelled Europe and then returned to Dublin to become a recluse. He spent the last years of his life (1936–57) in a mental hospital but between 1928 and 1932 he came up with ideas, inspired by Zsigmondy's ultramicroscope and Einstein's photoelectric effect (Nobel Prize, 1921), that laid the groundwork for breaking the Abbe diffraction limit. The first idea was simple: if the microscope aperture was scanned across a surface and kept less than the wavelength of light away from the sample, the resolution was proportional to the aperture size and did not depend on the wavelength of the light used (E.H. Synge *Phil. Mag.* 1928, vol. 6, p. 356). The second idea was to scan an illuminated metal tip, capped with a  $\sim 10\ \text{nm}$  gold colloidal particle across a surface and observe the changes in the light-induced local field in response to changes in the sample. Again, the Abbe diffraction limit is bypassed because the resolution depends only on the size of the scanning nanoparticle. Einstein called his ideas '*im prinzipiell unbrauchbar*' (basically unusable) but theoretically





(a) A conventionally 2D image; (b) the same features after isolation of each emitting fluorophore; (c) reconstructed image based on the uncertainty of the centre of each feature in (b). Reproduced from Betzig, *Opt. Lett.* 1995, vol. 20, p. 238 with permission.

The Optical Society

sound (E.H. Synge, *Phil. Mag.* 1932, vol. 13, p. 297). So revolutionary were these ideas that they were completely forgotten and reinvented again some 50 years later by **Dieter Pohl** (IBM Research, Zurich) when he patented the idea in 1982. In 1984, Pohl published the first practical demonstration of the field of near-field microscopy (D.W. Pohl, W. Denk, M. Lanz, *Appl. Phys. Lett.* 1984, vol. 44, p. 651) by recording the first image with 10 times better resolution than the Abbe diffraction limit allowed.

Across the Atlantic a young **Eric Betzig** was completing his MSc in Engineering Physics (1985) and then went on to study for a PhD (1988) in the new (and exciting) field of near-field optics at Cornell University. He moved onto the famous Bell Research Labs to further develop near-field microscopy, where he recorded the first room-temperature single-molecule fluorescence image on a surface using Hutchie's aperture probe (J.K. Trautman, J.J. Maclin, L.E. Brus, E. Betzig, *Nature* 1994, vol. 369, 40), down to about 12 nm resolution. However, in 1996, disillusioned by the physical limitations of near-field microscopy and the unrealistic hype associated with the scientific bandwagon now following this technique, he decided to give up science and work for his father's machine shop. Besides, as a child,

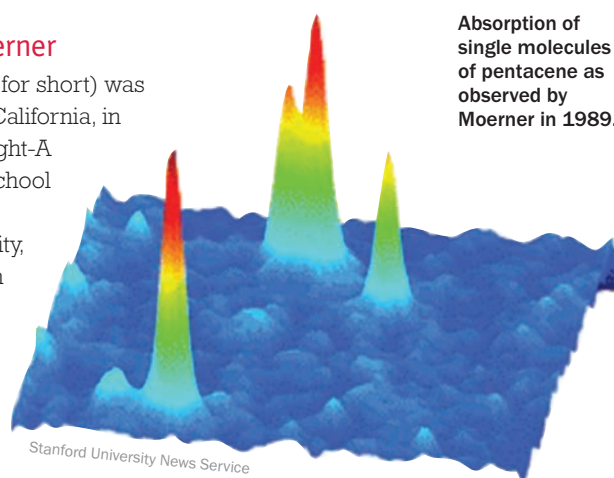
Betzig had told everyone that by the age of 40 he would be a billionaire and have a Nobel Prize. Now at the age of 36, neither seemed at all likely. Just before he left Bell Labs, he published a theoretical paper (E. Betzig, *Opt. Lett.* 1995, vol. 20, p. 237) that outlined how one might break the diffraction limit for far-field microscopy if it were possible to isolate the fluorescence from single molecules in a sparse matrix, mathematically determine the centre of every fuzzy ball of light and then overlay all the single molecule images to build a complete picture (see diagram). In 1996, it was not possible to isolate the fluorescence from individual fluorophores so Betzig left science, which was unfortunate because a year later **W.E. Moerner** published the key to making Betzig's idea a reality.

### William Esco Moerner

**W.E. Moerner** (W.E. for short) was born in Pleasanton, California, in 1953 and was a straight-A student all through school and university (Washington University, St Louis, Missouri). In 1975, W.E. earned three bachelor's degrees all with honours, in electrical engineering,

physics and mathematics, and then moved to Cornell for his MSc (1978) and PhD (1982) with **Albert Sievers**, finishing up at Cornell just a couple of years before Eric Betzig would arrive for his postgraduate years. W.E.'s PhD research was on single-molecule IR spectroscopy of  $\text{ReO}_4^-$  ions trapped in KI crystals.

He then joined **Gary Bjorklund** at the IBM Research Labs in San Jose, California, looking into the application of photonics in information storage. The general idea was to use single molecules to store data in some way but the research was to have unforeseen far-reaching implications. In 1989, he published a landmark paper (W.E. Moerner, L. Kador, *Phys. Rev. Lett.* 1989, vol. 62, p. 2535) that described UV absorption of a single molecule (defined by W.E.'s research group as '1 gaucumole' ( $1/(\text{Avocado's number})$ ), a much more useful concept than the equivalent 1.66 yoctomoles ( $1/(\text{Avogadro's number})$ )) of pentacene in a crystal of *p*-terphenyl. A year later, **Michel Orrit** (Leiden University) did exactly the same thing but using fluorescence (M. Orrit, L.J. Bernard, *Phys. Rev. Lett.* 1990, vol. 65, p. 2716). This was a very significant paper because it showed that fluorescence from one molecule greatly increased the signal to noise compared to absorption because the incident and detected wavelengths are different for fluorescence



Absorption of single molecules of pentacene as observed by Moerner in 1989.

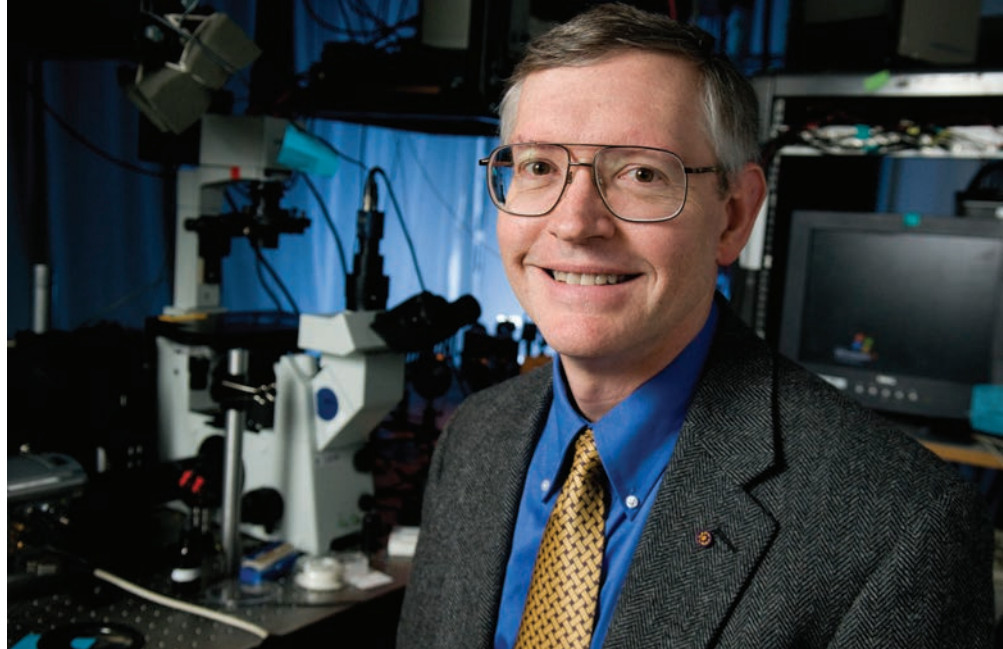
Stanford University News Service

spectroscopy. None-the-less, W.E. was the first to show that it was possible to detect a single molecule and study its stochastic modes of action.

However, these results were not useful at this point for super resolution microscopy as the technique requires liquid helium temperatures and individual fluorophores to be separated by well over Abbe's diffraction limit; but they were a step in the right direction. Buoyed by these results and wishing to pursue more fundamental research, W.E. moved to academia in 1995 (Department of Chemistry and Biochemistry, University of California, San Diego) and continued to work on single molecule detection.

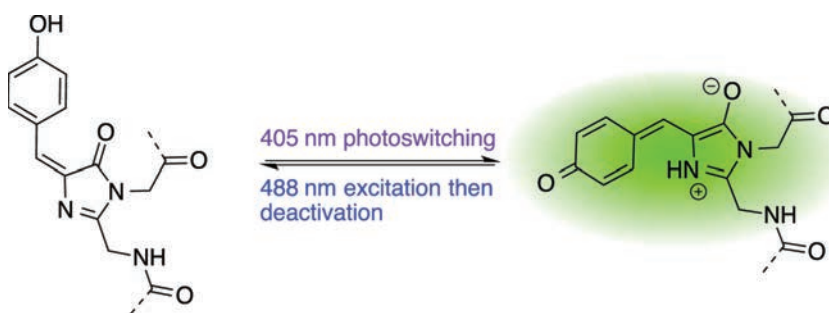
The breakthrough that Betzig was waiting for came in 1997, completely by accident. Moerner's postdoc (**Bob Dickson**; now at Georgia Tech) was studying a mutant green fluorescent protein (GFP) that he had obtained from his departmental colleague **Roger Tsien** (Nobel Prize, 2008; see October 2009 issue, p. 26). This mutant (S65G/S72A/T203Y) was chosen for single-molecule fluorescence only because it absorbed strongly at 510 nm (instead of 395 nm for the wild type) thus could be readily excited by the powerful blue argon ion laser (488 nm). He noticed that when individual molecules of GFP, trapped in a gel, were irradiated at 488 nm, they would fluoresce for some time and then turn off and then turn back on again. This 'blinking' behaviour is common in fluorophores but this is the first time it had ever been observed because this phenomenon is invisible for an ensemble average of millions of fluorophores. Only at the single molecule level could such behaviour be seen.

The really interesting thing though was that after some time the individual GFP molecules stopped blinking and just turned themselves off *but* if you irradiated the sample with a 405 nm violet laser for 5 minutes, the fluorophore would turn itself back on



W.E. (William E.) Moerner, Harry S. Mosher Professor of Chemistry and Professor, by courtesy of Applied Physics Biophysics Program and Molecular Imaging Program.

Linda A. Cicero/Stanford University News Service



Switchable GFP mutant

again (R.M. Dickson, A.B. Cubitt, R.Y. Tsien, W.E. Moerner, *Nature*, 1997, vol. 388, p. 355). Moerner concluded the paper with the possibility of using this new phenomenon in optical storage devices, something that he was quite familiar with, that could take advantage of stable, individually addressable molecules. Clearly he was unaware that this addressability was exactly what **Eric Betzig** was looking for to make his idea for a microscope that broke Abbe's diffraction limit a reality.

In 1998, Stanford made W.E. an offer he couldn't refuse and he moved his lab from San Diego up the coast to Palo Alto, where it has remained to this day. W.E.'s current research includes development of new single-molecule fluorophores for cellular imaging, exploration of biological chaperonins, diffusion in cell membranes and trapping devices capable of

overcoming Brownian motion to allow extended study of single biomolecules in solution.

This year's Nobel Prize in Chemistry recognises W.E. Moerner for creating a new field of science – single-molecule spectroscopy and imaging – by being the first to observe a single molecule in condensed matter. This discovery had broad interdisciplinary impact and led directly to the development of super resolution microscopy. Part II will look at the influence of W.E.'s research on **Eric Betzig**, and at the third recipient of the 2014 Nobel Prize in Chemistry, **Stefan Hell**.

**Peter Karuso** FRACI CChem is the Professor of Chemistry at Macquarie University, Sydney. Part II will be published in the March issue.





# Transport of sodium cyanide in Australia

BY **PETER DRYGALA**

**Control measures can bring both excellence in safety and public reassurance in hazardous goods transport.**

**A**n uneasiness exists for some residents near roads and rail routes used for sodium cyanide transport. This is understandable – potential toxicity hazards are significant and loom large in the mind, more so than the fact that the actual risk to people is low.

In reality, the wide range of robust safety controls in place make sodium cyanide no riskier to transport than many other dangerous goods.

## Importance of sodium cyanide to Australia

Globally, some 80% of sodium cyanide produced goes into making organic polymers such as nitrile, nylon, acrylic plastics and synthetic rubbers. However, in Australia nearly all sodium cyanide is used by the gold mining industry. Gold is Western Australia's second most valuable mineral commodity – the annual *DMP Statistics*

*Digest* lists the total sale of gold in Western Australia in 2013 to be \$8.7 billion, making Western Australia by far the biggest gold-producing state in Australia with more than two-thirds of Australia's production. Significant production also occurs in Queensland, New South Wales and the Northern Territory.

Orica's sodium cyanide plant in Gladstone in Queensland and the Kwinana-based Australian Gold Reagents Pty Ltd in Western Australia are the only Australian producers of sodium cyanide. They utilise the Andrussow process, reacting methane, ammonia and air over a platinum/rhodium wire mesh catalyst at 1000–1100°C to produce hydrogen cyanide gas, then absorbing the cyanide into a solution of sodium hydroxide.

With an annual output of about 160 000 of a global half a million

tonnes, Australia is one of the world's biggest producers of sodium cyanide. Approximately two-thirds is exported widely, a welcome example of the success of Australia's chemical industry in global markets. The use of sodium cyanide to extract as little as one or two grams of gold from a tonne of ore is an example of how the Australian mining industry competes globally – our mining engineers, explosives makers, chemists, chemical engineers and process metallurgists use cutting-edge technologies.

## Hazards during transport

Solid sodium cyanide is a white solid with a high melting point (563°C). The solid is manufactured in the form of briquettes, because they are less sensitive to moisture and generate little dust. Each pillow-shaped briquette weighs 20–30 grams. It must be kept away from water and should be



protected from high humidity to avoid the generation of poisonous hydrogen cyanide gas. Sodium cyanide is not flammable or explosive, but must be segregated from acids and oxidising agents.

Sodium cyanide is also transported as a 30% solution. Accidental spillages on top of acidic soils or dilution in water can evolve toxic hydrogen cyanide gas. The solution evolves hydrogen cyanide gas unless the pH is kept highly alkaline at all times. Caustic soda (0.5%) and sodium carbonate (3.5%) maintain the pH at 13 during transport.

Sodium cyanide does not persist long in the environment due to a variety of detoxification mechanisms including volatilisation, complexation, thiocyanate formation, oxidation, photolysis, hydrolysis and biodegradation.

Although sodium cyanide is acutely toxic, available evidence suggests that it is not mutagenic, teratogenic or carcinogenic. Severe poisoning can be lethal, but complete recovery happens after sublethal doses. Poisoning by the gas is by inhalation. Poisoning by the solid is through accidental ingestion or inhalation of the dust or from skin absorption of the dust, although in the briquette form the dust problem is minimised. Poisoning by the dissolved cyanide solution poses a greatest danger than from the solid because of:

- greater skin absorption hazard
- greater ingestion hazard, e.g. animals drinking contaminated water
- inhalation of sodium cyanide gas evolving from a solution of low pH.

### Australia's safety record

Australia has an excellent safety record in sodium cyanide transport. The number of transport incidents for solid and solution has been very small compared to the large number of journeys over long distances by road and rail.

Over the past 25 years, only three loss-of-containment incidents have occurred; only one of those, the Tanami Desert incident in the Northern Territory in February 2002, resulted in harm from the toxic nature of sodium cyanide.

During the Tanami Desert incident, 3000–6000 litres of dilute sodium cyanide solution was released from a sparge tank (see p. 20) due to a procedural failure: not locking the input and output valves. A large number of birds and one dingo died after drinking the dilute sodium cyanide solution spilled at the roadside.

The other two loss-of-containment incidents involved solid sodium cyanide in composite intermediate bulk containers (see p. 20), which suffered high-energy impacts in traffic accidents:

- In July 1992, near Condobolin in New South Wales, a freight train carrying 120 tonnes of sodium cyanide derailed after colliding with a semitrailer at a level crossing. Forty tonnes of sodium cyanide was spilled.
- In February 2007, an accident involving a triple road train occurred on the Stuart Highway north of Tennant Creek in the Northern Territory. Two of the three shipping containers tipped over and briquettes of sodium cyanide fell into a non-flowing watercourse.

### Transport safety controls

The transport of dangerous goods in Australia is regulated by nationally uniform regulations.

In Western Australia, the Department of Mines and Petroleum administers the Dangerous Goods Safety (Road and Rail Transport of Non-explosives) Regulations 2007, which require compliance with the Australian Code for the Transport of Dangerous Goods by Road and Rail, seventh edition (ADG7.3) ([www.ntc.gov.au/heavy-vehicles/safety/australian-dangerous-goods-code](http://www.ntc.gov.au/heavy-vehicles/safety/australian-dangerous-goods-code)).

ADG7.3 is maintained by the states and territories under the leadership of the National Transport Commission. It is regularly updated to keep it harmonised with international transport codes, especially the International Maritime Dangerous Goods Code. ADG7.3 contains mandatory requirements relating to, for example, design, construction and approval of appropriate packaging, containers and tanks, consignment procedures, labelling of packages, placarding of vehicles, stowage, constraint and segregation of loads, transport documents and emergency procedure guides and safety equipment (see box).

In Western Australia, additional environmental protection conditions are in place under Environmental

### Emergency response

Emergency plans and how to put them into action are mandatory. A fast and effective emergency response is especially important for sodium cyanide – exposed solid cyanide needs to be recovered before rain sets in, and spilled solution has to be contained and neutralised before it can flow into watercourses. Transport of sodium cyanide requires recovery equipment, neutralising agents and the capacity to efficiently respond to emergencies such as roll-overs and derailments. This can only occur with trained responders and regular emergency response exercises.

In the event of a spillage, any emergency responders in the immediate vicinity of the spillage site require personal protective equipment including breathing protection. Responders set up a small exclusion zone around the spill site to exclude members of the public until the spill has been cleaned up or neutralised. Neutralisation methods use various oxidising agents, most commonly ferrous sulfate and sodium hypochlorite.



**Top: Composite intermediate bulk container with solid briquettes of sodium cyanide.**

**Middle: Sparge tank on a truck with solid briquettes of sodium cyanide.**

**Bottom: An isotainer on a truck carrying sodium cyanide solution.**



Ministerial Statement 700. One of the conditions is the presence and regular review of a Transport Management Plan, which includes procedures for the safe transport, use of carefully selected approved transport routes, effective communication with vehicles, location of neutralizing agents, annual emergency exercises with the Department of Fire and Emergency Services and external and internal audits of the plan.

## Containment systems

The choice of transport containment is a critical part of safety and must comply with ADG7.3. The prescribed standards for containment are high and in keeping with a toxic dangerous good of Packing Group I. Australia uses the following three containment systems (in order of technological emergence):

- *composite intermediate bulk containers (CIBCs)*: These contain 800–1200 kilograms of sodium cyanide briquettes, filled into a hermetically sealed polyethylene bag with a second woven polypropylene bag used on the inside or the outside of it. The double bag is then placed inside a wooden outer box with lid and integral pallet base, which is strapped horizontally and vertically. All CIBCs are then placed inside a steel freight container, which typically holds 20 CIBCs.
- *portable tanks (isotainers)*: Many mine sites prefer the manufacturer to provide solution rather than solid sodium cyanide. However, this is only economical within a limited radius from the manufacturing plant because of transport costs. Isotainers have a capacity of 18 kilolitres and are internationally approved tanks that are twist-locked onto road or rail platforms. These heavy duty 6 millimetre steel pressure vessels are impact and rollover resistant and are protected within a substantial box end-frame. There are no loading or unloading



connections at the bottom of the container, which prevents accidental leakage. Any hydrogen cyanide vapour above the solution is fully contained and unable to vent, except through a special safety valve. The valve only vents under extreme pressure caused by extreme fire impingement on the tank, which is not a credible accident scenario.

- **sparge tanks:** Transport to ports and by ship occurs in CIBC's, but CIBC transport to mine sites is being replaced by heavy duty solid-to-liquid tanks called sparge tanks, because of the superior security and safety features both during transport and handling operations on the mine site. 'Sparging' is the remotely controlled dissolving of the solid sodium cyanide in water in a closed system of dissolving tanks inter-connected by pipes. It removes the mine worker from exposure to sodium cyanide and avoids the need for manual handling of solid sodium cyanide. Manual handling is associated with hour-long wearing of a cumbersome protective suit and breathing apparatus in a potentially hot and stressful environment. 'Sparging' avoids the need to dispose of sodium cyanide contaminated CIBC packaging. Sparge tanks offer the safest method of transport:

- Transporting solid is inherently less hazardous than solution.
- The sparge tank is more impact-resistant than CIBC in freight containers.
- The sparge tank carries 20 tonnes of dry sodium cyanide compared to only 6 tonne of dry sodium cyanide dissolved in 18 000 litres in an isotainer – the larger payload reduces transport risk, because of the reduced journey distance for a given amount of sodium cyanide.

## Codes and voluntary commitment

To maintain their excellent safety record, Orica, AGR and their transporters have to work hard and diligently and apply a large range of safety controls. Many of these safety controls are mandated by legislation, but the application of the voluntary International Cyanide Management Code is equally important.

AGR and Orica are fully accredited to the third-party-audited Code for both the production plants and for the safe management of the Australian transport supply chains to help them maintain high levels of safety. The Code is developed under the auspices of the United Nations Environment Programme and the International Council on Metals & the Environment. The reason for the Code is to prevent spills, such as the Baia Mare incident in January 2000 at a Romanian gold mine, which killed many fish in the rivers of Romania, Hungary and Yugoslavia.

Accreditation to the ICMC is a voluntary commitment shared with leading gold mining companies to ensure maintenance of the highest standards of safety and environmental protection during the processing, transport, handling, storage and disposal of sodium cyanide. For comprehensive third party audit summary reports of all accredited companies, and references related to sodium cyanide chemistry, toxicology, effects on the environment and wildlife, visit [www.cyanidecode.org/about-cyanide-code/faq](http://www.cyanidecode.org/about-cyanide-code/faq).

For another useful reference, especially for a record of early sodium cyanide transport accidents in Australia, visit [www.nicnas.gov.au/\\_data/assets/pdf\\_file/0018/4392/PEC\\_31\\_Sodium-Cyanide\\_Full\\_Report\\_PDF.pdf](http://www.nicnas.gov.au/_data/assets/pdf_file/0018/4392/PEC_31_Sodium-Cyanide_Full_Report_PDF.pdf).

**Dr Peter Drygala** FRACI CChem is Principal Adviser Explosives and Dangerous Goods, Department of Mines and Petroleum.

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# Medicinal chemists

## Central to drug discovery

BY **CHRISTOPHER J. BURNS**

In the midst of drug discovery are chemists with the knack of drawing many disciplines together.

The process of drug discovery is an extraordinarily complex and multidisciplinary undertaking. Among others, it involves biomedical researchers (molecular and cell biologists, structural biologists, biochemists, pharmacologists), drug development specialists (such as scale-up and formulation chemists, and clinical researchers) as well as intellectual property, business development and commercialisation experts.

At the front and centre of the discovery of small molecule drugs are medicinal chemists. To put it simply, drugs are designed by medicinal chemists, and medicinal chemistry is the central science devoted to the discovery of chemicals that can be developed as drugs. By fusing inputs

from such disparate areas as organic chemistry, biochemistry, pharmacokinetics, toxicology, pharmaceuticals and intellectual property, medicinal chemists choose a molecule to make and test, then they take that test data and repeat the process iteratively until they identify a candidate compound with the desired overall properties.

A good medicinal chemist is a polymath. Generally with a strong background in synthetic organic chemistry, they also have a working knowledge of the biology of their therapeutic area of interest; drug screening and biochemistry; drug metabolism and distribution; the interface of chemistry and toxicology; and intellectual property and competitive positioning.

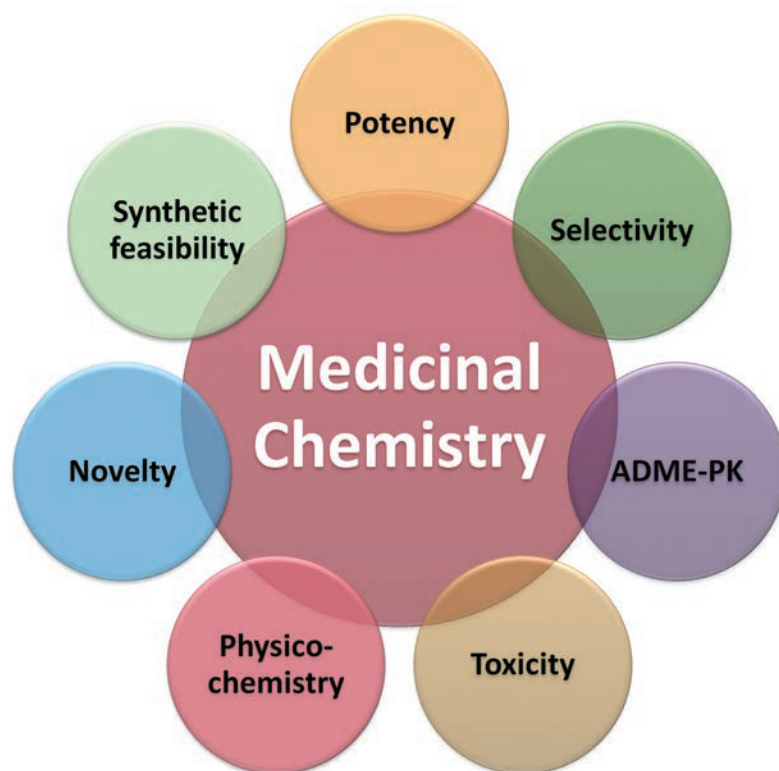
A drug is the combination of a number of properties, and the medicinal chemist is responsible for making sure all these requirements are met. For example, a compound should:

- be potent against its target – to minimise the dose required
- be selective over other biological processes – to reduce risk of toxic side-effects
- display good pharmacokinetics – so that dosing can be convenient
- possess an acceptable safety profile – so that it can be dosed without undue toxicity
- possess acceptable physicochemistry – so that the drug is stable and can be formulated
- be patentable – so that it can be commercialised
- be synthetically feasible – so that it can be manufactured on large scale.

Here I will focus on small molecule compounds with a MW < 1000 Da, rather than larger biochemicals such as proteins, which themselves constitute an important drug class.

### Finding a chemical lead

A drug discovery project starts with identifying a biological process that can be modified to therapeutic benefit.



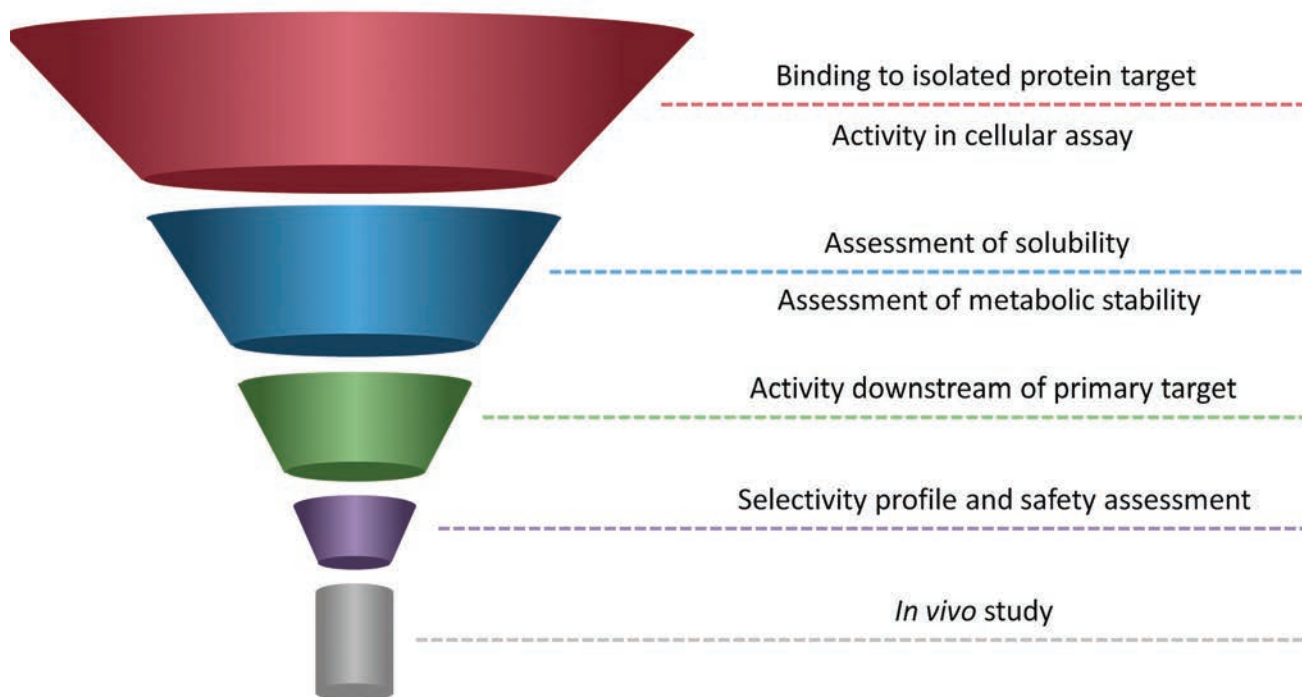
Typically, this will be inhibition of the function of a protein (or protein complex) (e.g. ion channel, receptor, enzyme) that has been shown to drive the disease pathology. Once the drug target has been identified, it is then necessary to find chemical compounds that interact with the target thereby blocking the aberrant activity associated with the disease. Generally this is achieved by testing large numbers of compounds against the target in a simple biochemical or cellular assay, in a process known as high-throughput screening (HTS). Technological developments (robotics, miniaturisation) in screening laboratories over the last 20 years has made it possible to conduct HTS of thousands of compounds per day, so

that a library of 1 million compounds (now available commercially or through a company or institute's legacy collection) can often be screened in a matter of weeks.

### A silk purse from a sow's ear

Compounds that are identified from HTS as interacting with the target – known as 'hits' – are typically a long way from being a drug that can be taken by humans. First, hit compounds rarely have the desired potency against the target, and selectivity over other targets, that enables them to be taken safely and in acceptable doses. Furthermore, many hit compounds will often have poor pharmacokinetic properties – if dosed to people (or animals), the drug will not reach

**The process of drug optimisation is basically a systems development cycle of design–synthesis–test–analysis, and while the testing is typically performed by biologists, the other activities are chemistry-led.**



concentrations in the target tissue to exert a sufficient therapeutic effect. The medicinal chemist's job therefore is to modify the hit compounds to address these issues of potency, selectivity and pharmacokinetics.

The process of drug optimisation is basically a systems development cycle of design–synthesis–test–analysis, and while the testing is typically performed by biologists, the other activities are chemistry-led.

- **Design:** At each turn in the cycle, compounds are designed to improve the desired properties while balancing potential risks to the compound's overall properties that result from making changes to the compound. Molecular property predictions (e.g. lipophilicity, basicity, molecular weight) are used to increase the likelihood that new compounds will possess good physicochemistry and ADME-PK (absorption, distribution, metabolism, excretion and pharmacokinetics). Molecular modelling may be used to predict compounds that best fit into a protein target to block its action. Chemical novelty is also considered

to ensure that compounds prepared can be patented.

- **Synthesis:** Designed compounds are typically synthesised on milligram scale for initial testing; however, the synthetic methods must be suitably robust to allow scale-up for further studies if required. Compounds must also be synthesised in an efficient manner to ensure that analogues can be easily prepared.
- **Testing:** Preliminary screens will test potency and selectivity in basic biochemical and cellular assays. Further study is then undertaken on the basis of a specific project's screening funnel (see figure).
- **Analysis:** Data for a suite of compounds from the assays undertaken is analysed to determine the effect of each individual chemical modification on the overall activity profile of the drug.

### Compound screening funnels

The very best medicinal chemistry design, however, is working in the dark without quality assays in which to assess the compound's activity and properties. Drug discovery projects

typically establish a screening funnel so that only compounds with an agreed activity cut-off progress to the next, often more complex, assay. A typical screening funnel is shown here. Compounds that successfully make it through the funnel are then ready for more elaborate preclinical profiling which may include broader toxicity assessment, studies with human material (where available) and process chemistry development, prior to formal preclinical studies as required by regulatory authorities.

### Innovations and new approaches

The development of HTS technologies in the 1990s was ostensibly a consequence of dealing with the large compound libraries prepared using combinatorial chemistry techniques. Combinatorial chemistry itself, however, is less widely practised these days with chemists preferring to make smaller, focused libraries around existing lead compounds. The development of flow chemistry techniques is likely to have a significant impact on library synthesis, given the benefits of automation and



the modular approach to synthesis employed. The potential advantages of having the synthesis of a lead compound optimised for flow chemistry also has the advantage that compound scale-up is straightforward – just run the flow chemistry longer!

Much has been written in recent years about 'drug-likeness' and effort continues to identify measurable or predictable molecular parameters that predict whether a compound is more likely to succeed as a drug. No hard and fast rules exist; however, these guidelines (which focus on measurable properties such as number of rotatable bonds, polar surface area, fraction of  $sp^3$  carbons etc.) can help the medicinal chemist prioritise compounds for actual synthesis.

Improving the quality of HTS screening libraries has also been the focus of considerable effort in recent years. Thus, removing compounds that often appear as false positives in

screens, or that possess functionality known to lead to toxicity or non-specific pharmacology, should reduce the risk of chemistry programs attempting to optimise leads unlikely to yield developable compounds.

The process of fragment-based screening, as an alternative to finding hit compounds for a new target, continues to grow in popularity. In this process, small ( $MW < 300$ ) weakly binding compounds are identified through biophysical screening methods such as NMR, SPR (surface plasmon resonance) and X-ray crystallography. These small fragments can then be 'grown' to fill out the binding pocket of their protein of interest. The success of the clinically approved kinase inhibitor vemurafenib, for the treatment of melanoma, which was discovered by fragment screening, acts as a clear endorsement of this approach.

Phenotypic screening, as opposed to target-based drug discovery, is

making a firm comeback after being cast aside with the molecular biology revolution in the 1980s. In this approach, compound libraries are screened in cell assays that have been engineered to read out for a particular phenotypic response, for example the upregulation of a gene, or decrease in a cell signalling event. Active compounds from such screens with demonstrated selectivity are then used to identify the specific molecular target responsible for the response, while at the same time acting as lead compounds for medicinal chemistry optimisation.

Despite the developments in biopharmaceuticals over the last two decades, small molecule therapeutics continue to be an important part of the pharmacopeia for many diseases and will do so for many years to come.

**Dr Christopher J. Burns** FRACI CChem is a laboratory head at the Walter and Eliza Hall Institute of Medical Research.

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BY **OLIVER JONES**

**The possibility of food contact materials in what we eat has prompted regulation and some innovative analytical chemistry.**

**'S**cientists warn of chemical dangers in food packaging', announces one news headline. 'Using recycled cardboard in food packaging risks contaminating food with mineral oils', declares another. Thousands of substances are approved for use in food packaging, and they regularly face media scrutiny. What does the research tell us about health risk, and what are the regulations?

The practice of storing food in containers dates back thousands of years. The ancient Greeks and Egyptians stored food in sealed earthen jars and the oldest known wine, a 1664-year-old (Roman era) vintage, is sealed with wax. It has been

displayed at the Pfalz Historical Museum in Germany for more than a hundred years.

In the late 18th century, the first bottled food was sold, with canned food arriving in the early 19th century. In the 1890s, crackers were sold in sealed waxed paper bags, heralding what might be considered the modern age of food packaging. However, the materials used were still relatively natural substances. Synthetic materials such as plastics did not begin to appear until the 1920s and 30s, and even then the packaging materials were limited.

Fast forward to today and more than 6000 different manufactured substances are now approved for use



# Chemical migration from food packaging

as packaging – or food contact materials (FCMs), to use a more modern term – in the US and Europe alone. Food packaging prevents contamination from microorganisms and hence prevents deaths from food poisoning caused by bacteria such as *Salmonella*, *E. coli* and *Listeria*. It allows food to be transported easily and with minimal damage, and it extends shelf life, as well as providing a surface for labelling and easy identification of products, all properties that consumers want and indeed demand.

FCMs include all substances that may be in contact with food: the packaging in which food is purchased, the containers that we use for food at home, even processing equipment

used in factories and food outlets, such as a coffee machine. Additives used to prevent spoilage are also classified as FCMs (see [tinyurl.com/o69836e](http://tinyurl.com/o69836e) for more detail).

Regulators in most countries are well aware of the potential for chemical migration into food from the packaging and have implemented strict controls on how much FCM is allowed in food. However, sometimes even older technologies can spring a surprise or two.

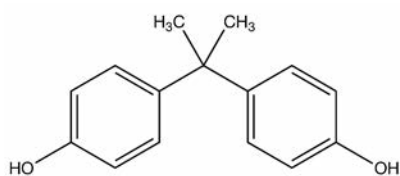
In 2011, analytical chemist Dr Konrad (Koni) Grob and his team at the Official Food Control Authority of the Canton of Zurich in Switzerland released a study that gave the food packaging industry quite a surprise. They showed that mineral oils can be transferred to dried food from the ink printed on cardboard containers at concentrations of between 10 and 150 mg/kg ([tinyurl.com/pye37c8](http://tinyurl.com/pye37c8) and [tinyurl.com/mt5zyk7](http://tinyurl.com/mt5zyk7)). This followed their study, 20 years earlier, which showed that foods transported in jute bags can become contaminated by batching oil (see below) at levels of between about 5 and 500 mg/kg ([tinyurl.com/mkc457w](http://tinyurl.com/mkc457w) and the video at [tinyurl.com/org7x3p](http://tinyurl.com/org7x3p)).

Jute fibre is made from plants in the *Corchorus* genus. A natural, sustainable product, it is used to store foods such as coffee, cocoa, nuts and

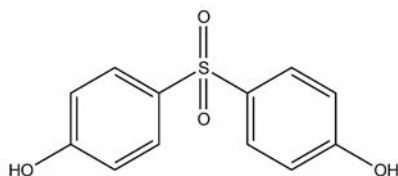
rice. The raw material must be processed before use, usually by treatment with high boiling point mineral oils (batching oil) to render them flexible enough for making fabrics. Such oils may be generally classed as one of two forms: the mineral oil saturated hydrocarbons (MOSH) consisting of linear and branched alkanes and naphthenes, or mineral oil aromatic hydrocarbons (MOAH), which are mainly alkylated compounds. From Grob's study came the realisation that people can potentially ingest MOSH and MOAH.

The potential presence of MOSH and MOAH in food has led to some innovative analytical chemistry. Gas chromatography, often with flame ionisation detection (GC-FID), is a common method for oil analysis. Analysis of oils by GC tends to feature large humps, usually referred to as unresolved complex mixtures (UCM). Multidimensional GC and even liquid chromatography (LC)-GC have been developed ([tinyurl.com/km6tqn8](http://tinyurl.com/km6tqn8) and [tinyurl.com/n2dqueq](http://tinyurl.com/n2dqueq)) to identify substances within the UCMs. During multidimensional chromatography, two chromatography columns of different phases are used in sequence; the total peak capacity of the system is the product of peak capacities of each dimension. Both gas and liquid chromatographic systems (GC and





**BPA**



**BPS**

#### Chemical structure of BPA and BPS

LC) can be linked in this way, greatly increasing their separation and resolution power. LC-GC is a particularly powerful technique because it couples the high sample capacity and the wide range of separation mechanisms of LC with the high efficiency of GC, and the potential applications of the method go beyond food analysis.

More easily detected and more widely known and studied is the FCM bisphenol A (BPA). It is used in water bottles, baby bottles, dental fillings, spectacle lenses, DVDs and CDs, household electronic and sports equipment, the lining of some food and beverage packaging and as a print developer in the thermal paper used in cash register receipts ([tinyurl.com/lf8urr6](http://tinyurl.com/lf8urr6)). The primary concern regarding BPA has been its potential as an endocrine disruptor, and it has also been implicated in a host of potential health problems including asthma, brain function and cancer ([tinyurl.com/pk53dgm](http://tinyurl.com/pk53dgm)). Small

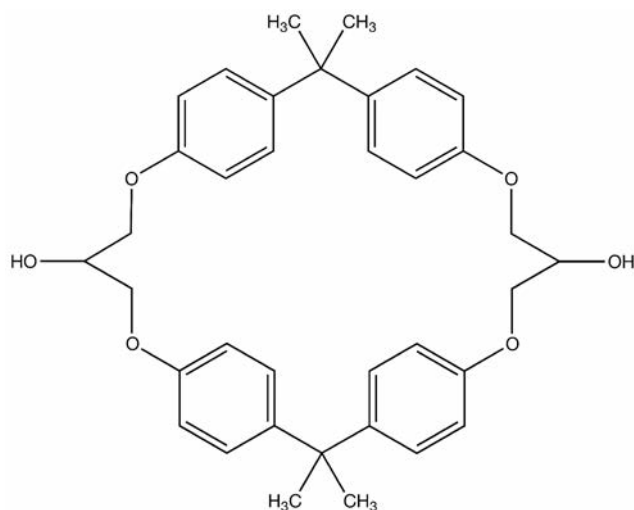
amounts of BPA are known to migrate into food and beverages from containers, but extensive testing and review by relevant authorities of the US, Europe and Australia and New Zealand has shown no adverse effects at current regulatory limits of exposure ([tinyurl.com/pdwkadi](http://tinyurl.com/pdwkadi)). Studies suggest that BPA does not remain in the body for more than a few days because, once ingested, it is metabolised to the glucuronide form (which does not exhibit oestrogenic activity and is excreted ([tinyurl.com/ole9ssa](http://tinyurl.com/ole9ssa))). However, because we may be continually exposed to low levels of BPA and a mixture of other weakly oestrogenic compounds, some members of the public and some scientists are worried about the long-term effects of exposure.

The precautionary principle (action on a perceived potential risk before scientific confirmation) has been applied to BPA, with its use in baby bottles now prohibited in many

countries, and it is banned from all food packaging in France from 2015. Many BPA-free products (e.g. water bottles) are now publicly marketed as such, implying that they are safer than BPA-containing products, but many BPA-free products contain bisphenol S (BPS), which acts as a plasticiser to replace BPA. This is chemically very similar to BPA and is more stable to heat and light, but it has not been as extensively tested as BPA for potential health effects.

Regulations for FCMs primarily cover only the starting materials and not potential reaction products such as those produced from epoxy resins, polyesters, organosols and trimellitic acid resins. For example, cyclo-di-(bisphenol-A-monoglycidyl) ether is formed from BPA and BPA-diglycidyl ether (BADGE) during the production of epoxy resins. It was recently found in 50% of samples of canned fish oil tested ([www.ncbi.nlm.nih.gov/pubmed/9829047](http://www.ncbi.nlm.nih.gov/pubmed/9829047)). It has never been made in amounts sufficient for toxicity assessment because it forms during food processing. European framework Regulation 1935/2004 ([tinyurl.com/ko47mvq](http://tinyurl.com/ko47mvq)) does, however, require the safety of all substances migrating from FCMs into food to be assessed, stating that no more than 60 mg of packaging materials should leach into each kilogram of food. Reaction products may well have to be studied and analysed further in future.

Other seemingly well-characterised materials may have un-assessed risks. Epoxidised soybean oil (ESBO) is used as a non-toxic replacement for phthalates in polyvinyl chloride (PVC) based plastics. ESBO serves as a plasticiser and as a scavenger for hydrochloric acid liberated from PVC when the latter undergoes heat treatment. This reaction creates an oil with a hydroxy group and a chlorine atom bound to a fatty acid. Such a compound has never existed in nature – again, because it is not deliberately added to the product and has never been made in large amounts, it has



**cyclo-di-(bisphenol-A-monoglycidyl) ether**

## Small amounts of BPA are known to migrate into food and beverages from containers, but extensive testing and review by relevant authorities of the US, Europe and Australia and New Zealand has shown no adverse effects at current regulatory limits of exposure.

never been tested. Such compounds are classed as non-intentionally added substances (NIAS).

Research on the contamination of food from FCMS and packaging is interesting from both a scientific and regulatory viewpoint. Research indicates that the material migrating from packaging may well be much higher in food, in terms of physical amount, than either pesticides or environmental pollutants. Also, control

of FCMS often lags behind the standards set up for other sources, mainly because people tend to be more worried about pesticides and also because the extent of the problem is unknown.

FCMS are likely to be present in some foods, but at very low levels. The standard approach to chemical risk assessment is to multiple toxicity by likely exposure level. Given low exposure level, overall risk from FCMS

is likely to be low, even if toxicity were found to be high. Nevertheless, this is an area in which a lot more chemistry would be useful. Until we have more information about FCMS, the full picture – unlike many food containers – is not clear.

**Dr Oliver Jones** MRACI CChem is a senior lecturer in Analytical Chemistry at RMIT University. He still uses a plastic lunch box for his sandwiches. Oliver would like to thank his good friend Dr Gregor McCombie, of the Official Food Control Authority of the Canton of Zurich, for the inspiration to write and conduct research on the topic of FCMS.

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## Jack Cannon AM

### Organic chemist and promoter of international co-operation

In recognition of service to science and technology in the field of chemical research and education and in the promotion of international co-operation among chemists in Australia and South East Asia.

This citation on the Order of Australia website neatly summarises but grossly understates Dr Jack Cannon's contributions to chemistry in general and to the development of chemistry in the Asia-Pacific region.

Jack Cannon was born in Sydney on 1 October 1927, the first child of Gerald and Elsie. His father, Gerald Robinson Cannon was an artist in Epping. Jack entered the University of Sydney in 1945 on a Public Exhibition and graduated with First Class Honours in Organic Chemistry in 1948. In his final two years, he was supported by a Timbrol Scholarship for Pure and Applied Chemistry. He completed his MSc in 1950 and worked as a teaching fellow in the Department of Organic Chemistry in 1950–51, undertaking research with Dr Ern Ritchie at the start of the national phytochemical project. Jack then proceeded to Emmanuel College, University of Cambridge as an Overseas Scholar of the Royal Commission for the Exhibition of 1851. Jack and Goldie Sunderland married on 10 September 1955. Goldie and their three children Jan, Jim and Ian survive him.

At Cambridge, he worked with A.R. Todd (later Baron Todd of Trumpington) on the elucidation of the structure of vitamin B<sub>12</sub>. He returned to Australia in 1955 to take up a position as a research officer in the CSIRO Division of Industrial Chemistry at Fishermens Bend. In 1959, he moved to the University of Western Australia as a senior lecturer in organic chemistry and, along with his teaching responsibilities, established an active research program. He was promoted to associate professor in 1973 and retired in 1992. He was a senior honorary research fellow until 1997 and remained involved in chemical affairs for the rest of his life. Jack joined the RACI in 1959, was elected Fellow in 1964 and given an Honorary Fellowship in 1996. Jack was an outstanding teacher, researcher, research mentor and the godfather of many.

Jack Cannon's long involvement in Asian chemistry started in 1969 when Pichaet Wiriyachitra did his BSc Honours work with Jack at the University of Western Australia on the chemistry of natural products. After completing his PhD in 1972 at the University of Tasmania with John Bremner and Ralph Bick, working on bisbenzylisoquinoline alkaloids, and postdoctoral work in the US, Pichaet returned home and was soon established at the Prince of Songkla University (PSU), Hat Yai campus in Southern Thailand. In late 1973, Jack visited PSU to help set up a phytochemical survey of plants in Southern Thailand based at PSU and to explore opportunities for collaboration. He also enlisted the support of Vichai Reutrakul, a former Colombo Plan student, at Mahidol University in Bangkok. His network had commenced.

Jack accepted the position of World Bank Visiting Expert at PSU and returned to Hat Yai in December 1978. Jack described his three months in the position as '... one of the busiest and happiest periods of my life.' He was able to represent Professor Arthur Birch at the 4th Board Meeting of the UNESCO Regional Network for the Chemistry of Natural Products in Southeast Asia, December 1978, and then served as Australia's National Point of Contact from 1978 to 1983. The network provided a comprehensive analytical service including spectra and X-ray crystal structures free of charge to research groups in the less well-endowed institutions. Jack represented the RACI at a meeting in December 1978 concerned with a UNESCO proposal to establish a Federation of Asian Chemical Societies (FACS). Jack was also present at the inaugural meeting of the FACS at Mahidol University in Bangkok in August 1979 and was awarded an FACS Citation in 1991 for his role in creating the FACS.

Jack was an enthusiastic supporter of the Asian Symposium on Medicinal Plants, Spices and Other Natural Products (ASOMPS), the 14th (Golden Jubilee) conference of which was held in Karachi in December 2013. By the time of ASOMPS IV in Bangkok, Thailand, Jack's persuasive powers were in full swing with seven Australians participating. Jack was Chair of the International Advisory Committee of ASOMPS from 1980 to 1997.

An outcome of ASOMPS in 1992, initiated by Jack and UNESCO, was the Manila Declaration on the Ethical Utilization of Asian Biological Resources. This ethical approach informed Jack's later phytochemical work with Western Australia's indigenous communities.

In 1982, Jack persuaded the Australian Development Assistance Bureau to support a new Network for the Chemistry of Biologically Important Natural Products (NCBNP). This would act as an adjunct to the UNESCO Regional Network, concentrating on Indonesia, Malaysia, The Philippines and Thailand. Through this network, Jack was able to assist countless scientists and institutions in the region. In 1980, he was awarded an honorary DSc from Prince of Songkla University, Thailand, by His Majesty King Bhumipol Adulyadej. He served as a long-term adviser to UNESCO and to the Stockholm-based International Foundation for Science. He was awarded the UNESCO Einstein Silver Medal by the Director General UNESCO, Dr Federico Mayor, in Bandung, Indonesia in January 1989.

Jack was both a trailblazer and a 'behind the scenes' influencer. All of us who have been involved in chemistry in the Asia-Pacific region have been well aware of his opinion on our activities and grateful for his advice on how to do things better. He died on 8 August 2014 and will be sorely missed right across the region.

**Tom Spurling** FRACI CChem, with inputs from **John Bremner** FRACI CChem, **Mary Garson** FRACI CChem, **Barry Noller** FRACI CChem, **Ian Rae** FRACI CChem, **Rob Toia** and **John Webb** FRACI CChem



# Chirality research in Australia

## Special issue 2014

President of the RACI ACT Branch Associate Professor Ashraf Ghanem FRACI CChem (University of Canberra) was the editor of a special issue of *Chirality* (2014, vol. 26(11)), covering chirality research in Australia. This is the first time *Chirality* has showcased such Australian research.

Life on Earth is based on chiral biomolecules. For example, all mammalian cells contain DNA in the form of a right-handed double helix, carbohydrates are derived from D-sugar, and proteins are composed of L-amino acids. Drug developers are designing drugs to target D-amino acids in bacteria cell walls without affecting the L-amino acids in humans (selective toxicity). These very complex chiral molecules are the building blocks for biological macromolecules such as proteins, DNA and RNA. Both DNA and RNA are incapable of complementary pair bonding if they are not homochiral. Furthermore, the receptors in our bodies are proteins; hence they are chiral, which consequently makes the internal biological environment chiral.

Rosetta, the robotic space probe built and launched by the European Space Agency recently landed safely at the comet Tschuri in the Philae module to take probes that may give an indication about the start of life on our planet. A Chirasil-Dex coated capillary chiral column previously developed in Bayer and Schurig's group at the University of Tuebingen, Germany, is on board to possibly detect and determine L-amino acids in space. Coordinator Professor Meierhenrich confirmed that a measurement with the column has already been performed but data has not yet been disclosed.

Contributors to the special issue include Fei Liu, Macquarie University, who discusses the upside of downsizing and the utility of cooperative design in enabling enhancement of both enantioselectivity and rate to develop future generations of organocatalysts in biomimetic asymmetric catalysis.

Roselito Quirino and Paul Haddad from the Australian Centre for Research on Separation Science (ACROSS), University of Tasmania, describe a significant preconcentration of chlorpheniramine maleate using a combined stacking approach of field-enhanced sample injection and micelle-to-solvent stacking.

The third article comes from the second node of ACROSS in Victoria and is written by Philip Marriott et al., Monash University. It describes an enantioselective comprehensive hyphenated two-dimensional gas chromatography (eGCxGC) coupled to quadrupole-accurate mass time-of-flight mass spectrometry (QTOFMS) for the determination of the chiral composition of several monoterpenes in cardamom oil.

Stuart Khan, University of New South Wales Water Research Centre, describes an interesting study about the enantioselective analyses of effluents from municipal wastewater treatment plants and from untreated sewage overflow.

The fifth article by Malcolm McLeod et al., Australian National University, describes the osmium-catalysed oxyamination of chiral acyclic allylic alcohol derivatives bearing mono- and 1,1-di-substituted double bonds with benzyl *N*-(4-tosyloxy)carbamate.

The last six articles are either from the chirality group at the University of Canberra or a result of collaboration with the Australian Defence Force Academy (ADFA), University of New South Wales Canberra or CSIRO. The chirality group at the University of Canberra is a unique Australian specialised group dealing with all aspects of chirality from catalysis to analysis. The nano LC facility supported by Dionex (now Thermofisher) and Shimadzu is remarkable. They are focusing on industry research oriented for commercialisation.

The group's first article discusses the first facile one-pot in situ preparation of lipase-based polymer monoliths in capillary columns of 150  $\mu\text{m}$  internal diameter for the enantioselective nano liquid chromatographic separation of racemic pharmaceuticals.

Their second article is in collaboration with the Plasma Nanoscience Centre Australia, CSIRO Materials Science and Engineering, and reviews the preparations and chiral applications of organic/hybrid nanoparticles and single-walled carbon nanotubes.

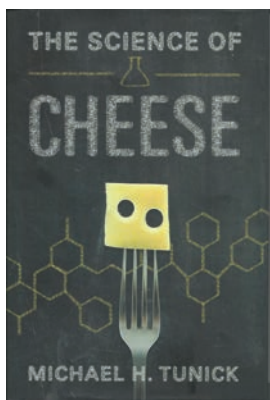
The third article is a comprehensive literature review covering the recent advances in the utilisation of two of the most important classes of dirhodium(II) paddlewheel complexes, dirhodium(II) carboxylates and carboxamides as chemzymes in inter- and intra-molecular asymmetric cyclopropanation, as well as cyclopropanation reactions.

The chirality group also describes the synthesis of a new series of dirhodium(II) tetracarboxylate derived from *N*-1,2-naphthaloyl-(*S*)-amino acid ligands with lower symmetry used in the asymmetric synthesis of chiral cyclopropylphosphonates.

The group's fifth article is in collaboration with Anthony Day's group from the University of New South Wales Canberra and ADFA, and brings together past and current methods for synthesising a relatively new family of macrocycles commonly known as cucurbit[*n*]uril (Q[*n*]) with structural variants and derivatives. The group's final article discusses a comparison between the conventional Chiralpak ID vs capillary Chiralpak ID-3 amylose tris-(3-chlorophenylcarbamate)-based chiral stationary phase columns for the enantioselective HPLC separation of pharmaceutical racemates.

This special issue will provide an overview for the scientific community worldwide about some of the research conducted in the field of chirality in Australia. We sincerely thank all authors for their enthusiastic support and contributions, which drove this special issue to such a great success.

Ashraf Ghanem FRACI CChem



## The science of cheese

Tunick M.H., OUP, 2014, hardback, 279 pp., ISBN 9780199922307, \$37 (approx.)

This is a very readable, informative and enjoyable book. The author, Michael H. Tunick, is a research chemist with the US Department of Agriculture. The claim is that the book itself is aimed at a non-scientific audience, although my feeling is that this is a somewhat ambitious claim. There are certainly bits of the book where a modicum of scientific knowledge would ease a lot of

perspiration. In any event, you do not need to be a food scientist /technologist to thoroughly appreciate this treatise and gain a lot from it. If cheese is your nibble, or indeed your passion, then this book can only enhance your pleasure. The author certainly has a Whey with Curds.

and other mammals, not only in terms of water, fat, protein and lactose but in terms of vitamins and minerals present. It takes two hours to extract a gallon (about 4 litres) from a moose, but then moose cheese will cost you \$1000 or so for a kilo. You are unlikely to find it in your local supermarket, even if you do fancy trying it. How do you milk a moose? Well, probably, carefully, but you'll have to look in some udder place for a definitive answer. Human milk won't coagulate properly because it contains so little protein (~1%) and although people have apparently derived cheese from a 50 : 50 bovine/human milk blend, there are undeniably better uses to which human milk can be put.

Each chapter of the book starts with a brief quotation about or involving cheese, taken from the literature and there is plenty of leavening of 'heavy' material with interesting facts and anecdotes, so that reading the book is never a chore. The differences between types and varieties of cheeses is fully explored, both in terms of their composition, trace components

**... if you have ever endured a less-than-ideal cheese, perusal of this book will inform your understanding on what exactly went awry in its manufacture.**

The scope of the book ranges from history to agricultural statistics, to microbiology, to physics to chemistry and lots of other places besides. In fact, chemistry is really central to this story of cheese and there is a goodly amount of information about the chemicals responsible for the aroma and taste of a wide variety of cheeses and what causes off aromas and flavours. I found this fascinating, although I confess that I did wonder for a brief instant what the MSDSs would have to say about some of the compounds (gloves, glasses, coats and fume hoods I suspect!) but given that their influence heavily outweighs their mass in your cheese, you probably won't come to too much harm at the dinner table, particularly if an appropriate oenological fluid is co-consumed. Additionally, if you have ever endured a less-than-ideal cheese, perusal of this book will inform your understanding on what exactly went awry in its manufacture.

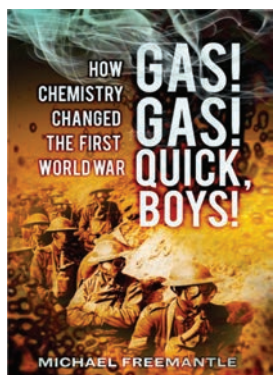
Statistical information on cheese consumption is quite intriguing: Americans eat about 15 kilograms per head per year; we in Australia eat just a tad less; but in Greece they each eat about 31 kilograms per year. Equally interesting is the volumetric production and milk composition of various bovine

and method of manufacture. Finally, there is a chapter entitled 'Do Try This at Home', if you have a yearning to try your hand at some cheese making. The chapters are well referenced and appropriately illustrated, mostly with black and white photography.

The book uses American units throughout: gallons, pounds, inches, Fahrenheit, for examples. There are explanatory/conversion tables in the book, but this is a bit of a nuisance for Australian readers born pre-1966 and possibly a cause of more substantial consternation for post-1966ers! The section on laws, regulations and appellations is largely only relevant to the US.

If you want to know about cheese, in general, how different cheeses are made and what molecules and processes give them their distinctive tastes and textures, you'll love this book. It provides a painless, fun way for learning about something we nearly all like in some form or other. There is even a Periodic Table of Cheeses in the front of the book! Read it: you won't be sorry!

R. John Casey FRACI CChem



## Gas! Gas! Quick, boys! How chemistry changed the First World War

Freemantle M., The History Press, Stroud, hard cover, 240 pp., ISBN 9780752466019, approx. \$40

The title of Michael Freemantle's book alludes to a poem *Dulce et Decorum Est* by Wilfred Owen, a great English poet, killed in World War I, just seven days before its end. A short extract is appended below:

GAS! Gas! Quick, boys! – An ecstasy of fumbling,  
Fitting the clumsy helmets just in time;  
But someone still was yelling out and stumbling,  
And flound'ring like a man in fire or lime . . .  
Dim, through the misty panes and thick green light,  
As under a green sea, I saw him drowning.

*Gas! Gas! Quick, boys!* is a book about the chemistry of warfare during World War I, with chapters that cover nearly every conceivable angle of chemistry. Michael Freemantle is the author or co-author of about ten books that relate to chemistry including *Chemistry in action* (1987), a very useful school textbook.

*Gas! Gas! Quick, boys!* is a scholarly work of patient endeavour that provides great detail with thorough and accurate references. The author's introduction considers that it's a work for the general reader; he does introduce and explain many of the chemical terms used and provides some definitions. However, in my view it's a work mainly of interest to chemists, because the general reader will likely find this book too technical. The book consists of 11 chapters (240 pages) and includes 16 pages of black and white war photographs. These help the reader visualise and better appreciate some of the situations referred to in the text.

In Chapter 1, entitled *The chemists' war*, the point is made that all warfare throughout recorded history has relied on scientific and technological expertise to provide an advantage over the enemy. For instance, Antoine Lavoisier had helped the French Government to improve the quality of gunpowder but was nonetheless guillotined in 1794. After his death, the role of the chemist in improving weapons, both for attack and defence, became increasingly important. Various chemists whose discoveries influenced the history of warfare are mentioned, with particular attention paid to Fritz Haber (1868–1934) and Carl Bosch (1874–1940). The portraits of both these scientists are included in the photographic section. Haber's significance is detailed for his work on the fixation of nitrogen needed for agricultural production and also for the production of explosives. His role in the use of chlorine as a poisonous gas in trench warfare is explained in Chapter 6.

Chapter 6 describes some of the history of the uses of poison

gases in warfare, including the possibility that Adolf Hitler may have been gassed when serving in World War I. There is a section on the pros and cons of chemical warfare. The different classes of agent – lachrymators, sternutators, choking agents, vesicants and blood agents – are described. Examples of each of these classes are given, often with details of their chemistry, preparation and physiological effects. Attention is also focused on Wilfred Owen's poem, which provides the title of the book and of this chapter. Finally, several sections of this chapter deal with methods of protection against poison gas attack, including gas masks and their development and improvement. One redeeming aspect expressed during this chapter is Freemantle's use of British, French, American and German accounts to provide an overall picture of how each nation viewed gas warfare.

Chapter 4, 'The Highs and Lows of Explosives', discusses the main explosives used in the World War I. Chemists may find this topic, which mentions the manufacture of gunpowder, brown powder, fuses, gun-cotton, nitro-glycerine, dynamite, gelignite, ballistite and cordite, of particular interest. The exploration of explosives is then followed by an account of the actual chemicals used in explosive manufacture. For instance, the manufacture of acetone from grain by a fermentation process discovered by Chaim Weizmann, in time the President of Israel. Acetone was an essential chemical in the manufacture of cordite. The huge quantities of explosive manufactured during the World War I was extremely impressive. New factories were built and workforces were trained. Factory workers previously inexperienced in safety procedures had to change long-established habits, such as wearing wooden rather than metal buttons to prevent accidental explosions (though these did occur).

Chapter 5, 'The Metals of War', is also likely to be of interest to many chemists, given the number and variety of metals and alloys used. Not only are the metals actually used in making guns, rifles and other obvious weapons of war explained, but for example, platinum was used as a catalyst in the manufacture of sulfuric acid, which is itself used in the manufacture of many other war-related chemicals.

Chapters 8–10 consider the use of chemicals used to preserve wounded soldier's lives, to ease pain and to fight infection, a major cause of the loss of soldiers' lives. It was good to see the emphasis given to chemistry's positive role in relieving human suffering.

Different readers will find that different parts of the book are of specialist interest to them as they observe examples relating to organic, inorganic and physical chemistry. I found that Freemantle's extensive use of science history in every chapter added greatly to the relevance of the book.

I can thoroughly recommend *Gas! Gas! Quick, boys! How chemistry changed the First World War*.

Bill Palmer



## Fire on earth: an introduction

Scott A.C., Bowman D.M.J.S., Bond W.H., Pyne S.J. and Alexander M.E., Wiley Blackwell, 2014, paperback, 413 pp., ISBN 9781119953562, \$40 approx.

There is only one planet in our solar system where fire exists, and we are on it. For many thousands of years, Australia's indigenous people used fire to control and manage their environment, while more recently, we have seen substantial areas of Australia ravaged by devastating bushfires and large sections of South East Asia enveloped in an acrid cloud of smoke from indiscriminate clearance of tropical rainforest for agricultural activity. We regularly learn of major fires in parts of the US, particularly California, as well as in Mediterranean Europe.

Fire is an important aspect of life on Earth: it controls our landscape and ecology; it influences the very air we breathe; it terrifies us with its awesomeness while at other times being our faithful and very useful servant. Fire, then, would seem to be an important phenomenon to understand. The problem is, of course, as Salmon Rushdie so eloquently put it in *Midnight's children*, '... if you want to understand just one life, you must swallow the world.' And fire has many 'lives', and their importance varies with the stance of the observer. (Didn't Thomas Kuhn more-or-less say that?)

This book is a brave attempt to pull together the varied disciplines that share an interest in Fire. The authors range from London (Scott), to the United States (Pyne) and Canada (Alexander), to Australia (Bowman), to South Africa (Bond). The subtitle, *An introduction*, belies an observation that this is a 'serious' book, extensively referenced and not to be taken lightly: it is a long way from light bedtime reading. There is a lot of information in it and there are a lot of concepts to grapple with and think about. It appears, although it is not explicitly stated, that different authors tackled different sections of the writing task and that leads to a variety of subtle differences in style throughout the book. We all have our pet foibles, and one of mine is an annoyance associated with having explanatory text on one page and the associated diagrams, graphs or pictures on another. The book is certainly not the worst I've come across in this regard, but it could certainly be better.

Is this a chemistry book? No, it isn't. There is, however, a lot of underlying chemistry that is integral to the understanding of ignition and propagation as well as the controlling of fire. Some of this is present, but an extra section discussing the physical and organic chemistry in detail would be a valuable addition to the book.

The book is divided into four parts, each of which is subdivided into a number of chapters. The first main subdivision, Part 1, 'Fire in the Earth System', covers the nature and classification of fire, fire in the fossil record, and the geological history of fire. Part 2, 'The Biology of Fire', deals with pyrogeography, the interactions of fire with flora and fauna, the role of fire as a process in the ecosystem, and the

anthropogenic environmental change wrought by fire. The last is further explored in Part 3, 'Anthropogenic Fire', while Part 4, 'The Science and Art of Wildland Fire Behaviour Prediction', brings home the processes of wildfire propagation, the modelling and estimation of the processes of wildfire behaviour and the strategies for understanding, predicting and controlling wildfire. This is, indeed, part science and partly an art, as people who lived through the various devastating bushfires that have ravaged Australia in recent times can well attest. There is an associated website, [www.wiley.com/go/scott/fireonearth](http://www.wiley.com/go/scott/fireonearth), which contains downloadable PowerPoints of all the figures in the book and PDFs of all the tables in the book. There are also links to key fire websites, videos and podcasts, as well as additional teaching material.

For environmental scientists, geographers and others with a professional interest in Fire, this is an important book, synthesising and organising information from a diversity of disciplines into a coherent, scholarly and convenient form. As a textbook for tertiary students, it contains a plethora of readily accessible information as well as extensive guides to further information. For lecturers, the website is a latter-day form of manna from heaven.

For chemists, other scientists and technologists, and, indeed for non-scientists too, this book is a fascinating and educational adventure. Given that we live in one of the more fire prone areas of the world, and accepting that climate change might be real, which means things can only get worse, then this book can only be worth your while reading. As Michelangelo put it, *ancora imparo*: I'm still learning.

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R. John Casey FRACI CChem

**John Wiley & Sons books are now available to RACI members at a 20% discount. Log in to the members area of the RACI website, register on the Wiley Landing Page, in the Members Benefits area, search and buy. Your 20% discount will be applied to your purchase at the end of the process.**

## Cultivating curiosity

I am honoured to be an occasional contributor to this new column about chemistry in the realm of plants. I am certainly not a horticultural or gardening expert, and (having retired from academic chemistry and pedagogy ten years ago) I doubt if I'm a chemistry expert either. However, I have been encouraged to be 'chatty'; I can do chatty.

I have learnt about gardening experientially because botany and horticulture are two of the few science subjects I never got to study in a classroom. Nevertheless, I have always had a fascination for all natural systems. Although my family had no experience in gardening, I often chose horticultural themes for my high school science projects; and as a teenager I diligently tried to improve our clay soil by experimenting with different types of compost. Then later, I learnt more about gardening from my very enthusiastic husband whose family has always grown things. Lots of things. In my retirement, I now help with growing Gondwanan proteaceae for the Sydney markets, here at the Centre of the Universe (defined as equidistant from anywhere we want to go, in any direction; and equally as inconvenient to get to those places.)

Professionally, I have been a chemist and a sometime biochemist. My earliest research involved synthesising analogues of natural products; and later, in collaboration with horticulturalists, biochemists and biologists, I extracted and investigated various compounds directly from plants.

I'd like to offer some personal observations gleaned from these diverse interests, sometimes highlighting unanswered questions regarding the chemistry of plants. If these stimulate even one further research project, that will be A Good Thing. Some topics I hope to cover are odours; plant communication (yes – really); colours; primary school children's projects; and phosphorus.

When we first thought of a flower farm as a hobby, we sought advice from those already in the business. I was amazed to find how many of our helpful contacts were originally trained in chemistry or chemical engineering. Obviously, chemists can do anything.

One influential person whom I never actually met was John Wrigley AM, author of *Australian native plants* (written with Murray Fagg). Since botanical keys are a total foreign language to me, I need pictures and descriptions to identify plants, so I relied heavily on various editions of his book. I did not know he was a chemist, but perhaps that fact explains why he could communicate so well with non-botanists like me.

I recently read his obituary (*J. Aust. Plants Soc. NSW Ltd*, 2014, vol. 49(4), pp. 4–6) and learnt that he had been planning the Australian Botanic Gardens in Canberra during the years I was an undergraduate roaming those very slopes of Black Mountain, at the times I needed a break from studying chemistry. I guess this is an almost-brush with fame.

Another obituary I read earlier, when I had changed research direction after a hiatus, was that of Professor A.N. Hambly,

**When we first thought of a flower farm as a hobby ... I was amazed to find how many of our helpful contacts were originally trained in chemistry or chemical engineering. Obviously, chemists can do anything.**

foundation Head of the Department of Chemistry at ANU, who made statistical thermodynamics seem logical, if not actually easy (*Chem. Aust.* 1997, vol. 64(4), pp. 31–2). He had been very kind to me. When I was an undergraduate at ANU, his wise counsel ensured that I stayed to do honours in chemistry in 1969, which turned out to be one of the happiest years of my career. I learnt about chemical synthesis as well as the relation between lichens and their secondary metabolites while working with the young lecturer Dr Jack Elix (later Professor and Head of Department when my son did his degree there). At the end of that year, Professor Hambly facilitated a process for me to submit my thesis on time after I had become ill six weeks before the final deadline.

I did not know that he also enjoyed growing Australian plants. Had I known, would I have made the effort to contact him to tell him of my similar interest, to let him know about my chequered career, and to thank him for his mature advice years earlier when I was a stubborn young thing? Maybe? Anyway, I hope that somehow he did know. Perhaps the plants told him.

**Dr Deidre Tronson** FRACI CChem used to be a mad scientist, but is now the Good Little Banksia Lady who, in retirement, is an enthusiastic member of Scientists and Mathematicians in Schools at a local primary school. She has proudly raised three science graduates. She has had separate careers in research and teaching, culminating in a position as part-time senior lecturer at the University of Western Sydney, Hawkesbury campus.



## Incentives for innovation

The Global Innovation Report 2014 (Cornell University, INSEAD and WIPO) reiterates what has long been well understood – Australia lags behind other countries in terms of protecting and commercialising intellectual property. The report shows that while Australia fairs reasonably well in the funding of research and development, there is a real inability to translate innovation into commercial outcomes. Given universities are at the forefront of Australia's research, and patenting this research is often the first step to a successful commercial result, the key question arises: how can patenting in Australian universities be incentivised?

Australia was ranked a disappointing 17th in respect of its global innovation index – just fourth in the Asia-Pacific region. Leading the rankings were Switzerland, the UK, several Scandinavian countries, and the US. In terms of R&D expenditure, Australia is ranked 13th with a gross expenditure of 2.4% of GDP. This falls well behind the rankings leader, the Republic of Korea, with a gross expenditure of 4.4% of GDP. The issue becomes most evident from a direct comparison to the US and UK figures; Australia is simply less efficient in translating R&D expenditure into commercial outcomes.

	Global Innovation Index		Gross expenditure on R&D
	Score (0–100)	Ranking	(% of GDP)
Australia	55.01	17th	2.4
US	60.09	6th	2.8
UK	62.37	2nd	1.7

Further compounding the issue, the report also detailed that although Australia published an impressive 48 scientific and technical articles per billion dollars of GDP (ranked 12th; USA published 21 and UK 43), Australia had a mere 2.7 patent applications (ranked 40th, with the USA at 16.6 and UK at 6.7). Again, our patenting performance in comparison to our counterparts is, to put it politely, rather dismal.

Where Australian universities are concerned, the patenting story is perhaps unsurprising given the above statistics. In October 2013, IP Australia released its pilot assessment of the patenting activity of Australian universities, as well as the impact of Australian university patents (*Research performance of university patenting in Australia: a pilot assessment*). The study was based on a cross-section of 12 Australian universities, and identified 4056 university patent applications relating to 1293 inventions over the period of the study (1 January 2006 to 30 June 2012). All in all, Australian university patenting activity averaged just 16 new inventions per university per year. This is most concerning when you consider that the University of California obtained almost 400 granted US patents in 2013.

The information suggests that while many Australian universities file patent applications, the rate at which they are pursued to grant is low. Given the cost of the patenting process and the current financial pressure on Australian universities,

who would be surprised by this?

So how can patenting in universities be incentivised? One approach, as proposed by the Minister for Industry, Ian Macfarlane, is to base university grants on the number of patents that are obtained by researchers, not on the number of scientific articles they publish. The statistics show that Australian researchers are consistently publishing world-class research, so it would seem logical that they can patent this research as a means to potentially obtaining commercial outcomes. However, this proposal is flawed in practice.

It's not a surprising revelation that patents are expensive. There are substantial costs associated with getting a patent to grant, and these costs increase with every country in which patent rights are sought. Do universities have this financial capacity? As a former university researcher, I can tell you that they simply do not.

Conversely, publications are free. They're also peer-reviewed, and, most importantly, provide an international standard of measuring research success. Government funding of research is not globally uniform, and so a free system that enables researchers to be 'ranked' on the basis of their professional research publications serves as a global indicator of the quality of research being undertaken.

Many would argue that radically reforming the Australian research-grant process to incentivise patenting, as proposed by Minister Macfarlane, with the view of increasing the protection of intellectual property and hopefully commercialisation, is a far more complex issue than he appears to have given credit. Any scheme to increase patenting in Australian universities would require a considerable contribution by the Australian Government to get the ball rolling. That is, Australian universities will need to be in a position where they are exploiting several patented inventions and have commercial outcomes before they can self-fund future patenting ventures.

In view of the Australian Government's continuing decrease in R&D funding, it seems unlikely that, at least in the short term, Australian universities will receive any contributions of this nature. As such, incentivising university grants based on granted patents is not the solution. So what is an alternative option?

One option would be to adopt a 'patent box' scheme. This is a tax incentive in the form of a reduced company tax rate applied to profits made on the commercialisation of patents. It was first introduced in 2000 in Ireland, and shortly thereafter adopted by the French in 2001. Today, the patent box, or a variation of it, is effective in the UK, the Netherlands, Belgium, Switzerland, China and Spain, among others. The US is now considering its own patent box scheme, with legislation introduced into the House of Representatives on 28 June 2013. A patent box scheme was the lone IP-related initiative taken into the most recent federal election. However, Treasurer Joe Hockey appears to have back flipped on the issue, recently



calling for other countries to amend their own patent box rules in November's G20 Summit in Brisbane.

How would such a scheme affect Australian universities? Australian companies will no doubt be more willing to support and commercialise patented university research if such an incentive exists. In doing so, they will have the opportunity to receive reduced tax rates of between 5 and 15% on profits attributable to this intellectual property. In essence, if a company invests in university research, in developing and/or commercialising intellectual property that is subject to patent protection, any profit attributed to this is eligible for a reduced tax rate. A patent box scheme provides a direct incentive to invest in innovation.

There is a real need to drive revenue from Australia's intellectual property, though to do this, we must first have it. Offering grants to researchers based solely on their patenting record, without significant initial contributions from the Australian Government, is not a feasible solution. One avenue of incentivising use of the patent system would be to financially support those companies that successfully exploit

## ... a 'patent box' scheme ... is a tax incentive in the form of a reduced company tax rate applied to profits made on the commercialisation of patents.

granted patents – especially those from our prolific academic sector. A way of doing this may be through the adoption of a patent box scheme, a step which has proven successful in several other jurisdictions. Doing so would incentivise investment in innovation and commercialisation in Australian universities.



**Dr Brittany Howard** MRACI completed her PhD in medicinal chemistry at the Monash Institute of Pharmaceutical Sciences before undertaking a postdoctoral position with the National Institutes of Health (US), and has since commenced as a trainee attorney with Watermark Patent and Trade Marks Attorneys.



Caricature by David Green  
([www.davidgreen.com.au](http://www.davidgreen.com.au))

## Chemistry

in Australia

### Congratulations to Ian Rae on 30 years of columns in *Chemistry in Australia*.

To read some letters of appreciation from Ian's readers, published in May to mark this special occasion, visit [chemaust.raci.org.au](http://chemaust.raci.org.au) and click on Special issues under Other resources.

## Waste not, want not

A new year is underway and, after the usual summer break, many of us are back at work. The Australian summer coincides with Christmas, which is probably the last of the traditional Christian feasts that is observed with feasting. Food production is a significant part of the Australian economy, and there is a higher than usual rate of consumption during the Christmas and New Year festivities. Accompanying the higher consumption is a higher rate of waste generation. The environmental impacts of this waste can be managed in several ways.

A number of papers at the 4th International Industrial and Hazardous Waste Management Conference held on Crete in September 2014 looked at the management and re-use of olive oil production waste, giving the event a local flavour. In Greece, there are approximately 550 olive mills, which produce oil for local consumption and export; they also generate a large amount of waste. Many of these mills are small, family-run businesses, with limited resources to adequately deal with their wastes. The papers presented mainly looked at two aspects of waste management – resource recovery and enhancement of biodegradation. Olive oil waste is relatively rich in phenolics and other anti-oxidants, so extraction could make them available for other food industries and a range of industrial applications. Olive waste is quite woody, and biodegradation can be a slow process. Some studies looked at pre-treatment methods to enhance the biodegradation, and others looked at encouraging methane formation from the waste to be used as an energy source.

The last of these aspects reminded me of some research I heard of back in the 1980s as a postgrad student. A colleague in biochemistry was looking at the use of whey waste from cheese production as a source of hydrogen, again for use as an energy source. Unfortunately, despite the research being an industry partnership project, the dairy company was reluctant to disclose the identity of various microbial strains used in cheese making, and the research faltered.

Used edible oils, particularly restaurant and café wastes, have been used in Australia as a feedstock for biodiesel production. The production process involves base-catalysed hydrolysis and methylation of the triglycerides in the oil, with the formation of fatty acid methyl esters having combustion characteristics suitable for use in diesel engines. The feed oils come from a range of waste oil collection contractors, and the hydrolysis process avoids the need to purify the oils before re-use as fuel. Some edible oils can also be used directly in diesel engines, but the environmental benefits of such an approach need to be balanced against the loss of natural vegetation as more land is cultivated for oil seed production, and also the possible diversion of oils from the food supply.

Traditional production of grain crops also has an element of optimisation of resource use. In this case, after the grain has been harvested, the stalks are cut for hay. After the hay has



iStockphoto/godunk13

been collected, the stubble remaining is given over to livestock grazing. Few would have thought that a similar approach was possible with sugar cane waste, but my local nursery sells sugar cane mulch neatly bundled into 10 kg (25 litre) blocks. The price works out at about \$1200 per tonne, but I suspect that the cane grower sees very little of that.

Another paper at the Crete conference looked at the use of bio-char derived from coffee grounds to adsorb zinc from water. Zinc is often present as a natural constituent of groundwater in Australia, and, in urban environments, the widespread use of galvanised steel over a century and a half has resulted in some elevation of zinc concentrations. Base metals processing facilities also tend to introduce zinc into the environment. The solubility of most zinc salts means that it can be hard to clean up. So, the use of one waste material in the treatment process that removes another waste is an example of thinking outside the square.

Coffee grounds aren't the first food or crop waste to be used for the production of carbonaceous adsorbents. Coconut husks have also been used to make activated carbon for use in the recovery of gold from the cyanide-based carbon-in-leach (CIL) process. The surface chemistry of the two carbonaceous materials must be different, given that zinc is adsorbed from solution where it is present in cationic form, and gold is present in the CIL solution as the dicyano complex anion. However, I suspect that the surface properties of the carbon owe more to the production process than to the carbon source, noting that the coffee beans are roasted before use, and before conversion to char.

The old farmers' saying about using everything from the pig but the squeal still seems to have some currency, which may be food for thought when we sit down to a traditional leg ham next Christmas.



**Paul Moritz** MRACI CChem (Paul.Moritz@douglaspartners.com.au) is a Principal Contaminated Land Consultant with Douglas Partners, and an EPA-appointed Environmental Auditor in Victoria and the Northern Territory.

## Volatile sulfur compounds and wine aroma

Volatile sulfur compounds (VSCs) in wine fall into two distinct aroma groups. A positive aroma profile is obtained with the so-called 'fruity' thiols, while the other group generates unpleasant smells or off-odours commonly described as *rotten egg*, *cooked cabbage* and *garlic*. This month, I will concentrate on the fruity aromas and next month I will discuss the 'reduced aromas' that result from hydrogen sulfide and methane thiol, among others.

Several VSCs have been identified in Sauvignon Blanc wines, including 4-mercapto-4-methylpentan-2-one (4MMP), 4-mercapto-4-methylpentan-2-ol, 3-mercapto-3-methylbutan-1-ol, 3-mercaptohexan-1-ol (3MH) and 3-mercaptohexyl acetate (3MHA). Some of the early research on these compounds came from Bordeaux, where Sauvignon Blanc is an important cultivar for white wine. Over the last 10 years, there has been considerable research activity at the Australian Wine Research Institute (AWRI) in Adelaide with a focus on 4MMP, 3MH and 3MHA (see Natoiya Lloyd's summary of this research at [bit.ly/14tqCQo](http://bit.ly/14tqCQo)).

The detection threshold (the concentration at which the taster is aware of something, but not necessarily able to identify it) for these compounds is very low: 3 ng/L for 3MMP, 60 ng/L for 3MH and 4 ng/L for 3MHA. The aroma descriptors depend on the amount of each substance in the wine. Common descriptors include *passionfruit*, *grapefruit*, *gooseberry*, *blackcurrant*, *lychee*, *guava* and *box hedge* when assessed individually, and *tropical* (pleasant) and *cooked green vegetable* (not so pleasant) when assessed in combination. As the amount of 3MHA increases in the sample, the aroma descriptor changes from *passionfruit* and *box hedge* to *sweaty* to *cat urine*, the last-mentioned far from making a positive contribution!

Understanding the origin of these three compounds and how their concentrations can be manipulated through viticultural and wine-making practice has been examined at the AWRI. Volatile thiols are found only in wine and exist in a cysteine-bound, non-volatile form in grape juice. For example, Cys-4MMP has a cysteine group attached to the sulfur atom in 4MMP and the action of carbon-sulfur lyases in yeast cleaves the C-S bond to release 4MMP during fermentation. In an intriguing study, an engineered wine yeast with overexpressed C-S lyase gene resulted in a concentration of 4MMP 10 times higher than that in the control wine after fermentation. 3MHA is formed from 3MH by yeast-derived alcohol acetyltransferase. Similar gene overexpression studies confirmed the pathway from 3MH to 3MHA. There is a good review on thiol release linked to yeast activity by Hentie Sweigers and Sakkie Pretorius (*Appl. Microbiol. Biotechnol.* 2007, vol. 74, pp. 954–60) with more specific detail on yeast engineering in *Yeast* (2007, vol. 24, pp. 561–74).

The chemistry associated with these thiols, and perhaps with 3MH in particular, is fascinating. There is a glutathione conjugate of 3MH in addition to the cysteine conjugate and work at the AWRI on synthesis of the two conjugates and

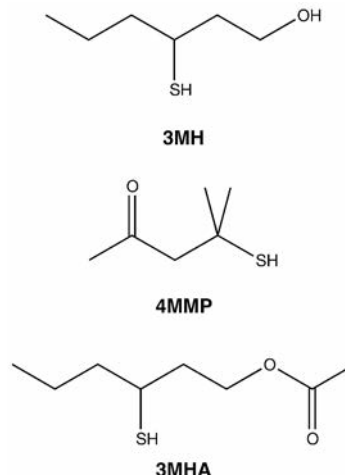
analysis of their enantiomeric forms has provided greater insight into the processes that transform the conjugates extracted from the grape into the volatile thiol. This work has also allowed linking stereochemistry to aroma: the (*S*)-form aroma is more passionfruit, while the (*R*)-form shows more grapefruit or citrus peel characters. Some great examples for teaching stereochemistry here.

Check out the publications on the AWRI website ([bit.ly/1EQAPTV](http://bit.ly/1EQAPTV)) for more detail.

Localisation of the volatile thiol precursors in the berry can affect the amount of the thiols themselves in the finished wine. There is considerable evidence from winemaking studies with and without skin contact (the latter being more common in white-wine making) that the precursors of 3MH are higher in the skins, while those for 4MMP are higher in the flesh (pulp) of the berry. In one AWRI study, the transport of machine-harvested Sauvignon Blanc grapes from the Adelaide Hills to the Riverina resulted in higher concentrations of the 3MH precursors, reflecting the skin/juice contact that would have occurred. There are a range of other winemaking and viticultural practices that can affect the total concentration, as well as the individual isomer amounts, of the 3MH and the 4MMP precursors. These are described in the AWRI publications.

These studies on volatile thiols provide a great example of the associations between analytical science, synthetic chemistry, oenological science and practice, and sensory science. This is then linked to the market place, as the science allows the potential to fine-tune viticultural and winemaking practice to provide more or less of the thiols, according to consumer demand. The country of origin also needs to be considered. Sensory scientists use the 'odour activity value' (OAV, the measured concentration of a substance divided by its sensory threshold) as an indicator of the relative importance of a compound to aroma. For 3MH, the OAV is up to 210 in Australia and up to 310 in New Zealand. For 3MHA the OAV is up to 195 in Australia and reaching 625 in New Zealand. Maybe this reflects the attraction towards NZ Sauvignon Blanc wines in the market place.

**Geoffrey R. Scollary** FRACI CChem ([scollary@unimelb.edu.au](mailto:scollary@unimelb.edu.au)) was the foundation professor of oenology at Charles Sturt University and foundation director of the National Wine and Grape Industry Centre. He continues his wine research at the University of Melbourne and Charles Sturt University.





## Too small to succeed?

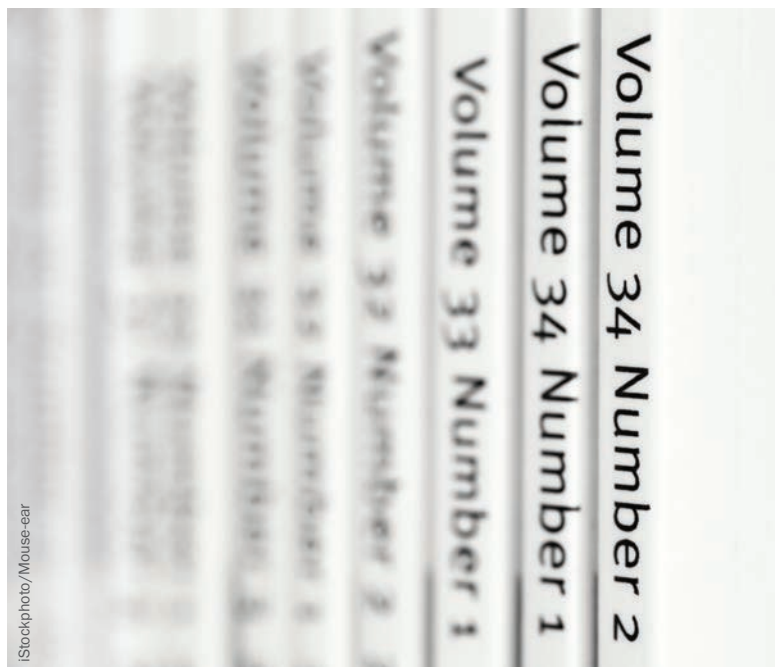
A few months ago I mused in this column on how, given the prestige of their previous publications, the most renowned academic professors and institutions are more likely to win research funding than less well-known ones. This in turn leads to them having a more impressive research output and thereby winning further grants. This self-perpetuating chain of events I likened to the phenomenon of *Too Big to Fail*. This may or may not be a bad thing both in the financial and academic worlds, but the corollary could be an undesirable outcome. If some institutions and people are too big to fail, does that mean that others are *Too Small to Succeed*?

I currently work at a very well-funded university in Europe. In the room behind my office, we have a thermogravimetric analyser, a differential scanning calorimeter, an isothermal calorimeter and a dynamic light scatterer; across the corridor we have two automated peptide synthesisers, three size-exclusion chromatographs and a high-pressure liquid chromatograph coupled to a mass spectrometer. This represents a fraction of the equipment we have at our disposal. We can perform a very broad range of analyses on just about anything in the lab. This in turn means that the research we generate can be published in prestigious journals, which will improve the standing of the group. All of this bodes well for members of our group, but I am painfully aware that we are the exception rather than the rule of scientists around the world.

My situation is especially poignant to me because I did not always have the fortune to work in such an opulent group. For my honours thesis, I performed every bit of analysis with a furnace, a spectrophotometer and an ageing scanning electron microscope (which we considered ourselves lucky to have). I'm proud of the work I did that year, but it certainly wasn't published in a prestigious journal. I consider myself fortunate to have had this experience because it allows me to appreciate my current situation even more. At the same time, I can't help but think of how the uneven distribution of equipment among researchers can be improved.

So here is my plan to level the playing field a little: a consequence of having so much equipment is that you never get 100% usage out of what you have. So we (and many other groups like us) have instruments idling away throughout the day. I've often wondered what would happen if we allowed less well-equipped groups some time on the instruments.

I envision this taking place as a collaborative process. Let's say Professor A lets Academic B run a few samples through his differential scanning calorimeter. Academic B gets valuable data with very little cost to Professor A. But it could go further than that. The professors could set up a collaboration. Their students could work on complimentary aspects of the same project or it could even be a way to generate new research interests within the group.



To be fair, this happens quite a lot at certain levels of academia, but it's often between pre-established colleagues, so it is far from optimised. I think in this digital age of shrinking boundaries, it can be taken even further. It may even be a good idea to have a national database of equipment (especially of those bought with public funds) so that academics (and I include students here) can reach out to each other and find a way to further their research in a way that would otherwise be unattainable within their institutes' budgets.

Of course, for this to work and be sustainable, there has to be some form of payback to the munificent professor other than simply the warm glow of helping a fellow scientist. However, since the current currency in academia is publications, I think there may indeed be a viable option. Collaborations often yield data much faster (and of greater depth) than solo efforts, so this could well be an excellent, symbiotic way to increase and improve research output.

It could also expose the students in the individual groups to others from another university, establish inter-institutional networks, get full use out of expensive, specialised equipment and, in general, make the most out of available resources. I certainly know that I've benefited greatly from the generosity of scientists with superior equipment and generous spirits and I can't wait to pay it forward as soon as I am a famous, well-funded academic, and minimise, if I can, the too small to succeed phenomenon.

The author is currently an unknown researcher in Lausanne who happily shares his fancy toys when he can.

## The scientific prime minister

I was once at a dinner where the Governor General of Australia, Sir Zelman Cowen, addressed the assembled chemical throng. Sitting near me at the end of our table was a man who was not a chemist but part of the GG's retinue. Despite the stifling conditions in the hall, he never removed his jacket, and I understood why when I caught sight of a hefty handgun in a shoulder holster. 'Must be an interesting job you have', I ventured in conversation. 'Not at all', he replied. 'I'm out at a dinner every night with people I don't know and with whom I have nothing in common'. And, of course, he was working as he gazed thoughtfully around the room.

Was there anybody like that at the Jubilee Dinner of the Chemical Society of London, now the Royal Society of Chemistry, when they sat down in February 1891? The contents of the commemorative volume published a few years later included the guest list and showed the seating arrangement only for 240 named guests and a menu (all in French) that included oysters, soup, *saumon avec frits*, veal sweetbreads, lamb, ham, potatoes and green beans, salad, and various desserts and puddings, all washed down with French and German wines, black coffee and natural mineral water.

The guest of honour was the Prime Minister of Britain, the Marquis of Salisbury. Speaking first, after the Royal Toast, the President, Dr W.J. Russell, said there had been 21 presidents before him and that nine were present at the dinner. In addition, he had 'a Scientific Prime Minister' on his right and 'a learned Attorney General on his left, and two hundred fellows of the Society "all expecting an interesting speech"'. Indeed, Lord Salisbury was a scientist of sorts, possessor of a home laboratory in which he explored the world of chemistry and later getting interested in electricity to the extent that he had arc lights in the dining room of Hatfield, his country house, and a primitive telephone system that allowed communication from room to room.

Speeches were limited to 15 minutes, but there were plenty of them, as can be seen from the commemorative volume where they were reproduced in full. Theirs was the first chemical society, said Russell, and owed its foundation to 'the enthusiasm for chemical study which Liebig was infusing into the whole of the scientific world' at that time. His potted summary of 19th-century chemistry emphasised its value to industry, a point on which Salisbury, speaking next, took him gently to task, regretting that it consists of 'a large amount of solid fact, and comparatively little of scientific imagination'. Taking a broader view of science, he said that in earlier times 'the atom reigned supreme; but now the atom has been dethroned, and the bacillus reigns in its stead' and he urged chemists to 'grapple more closely with the mysteries which separate organic and inorganic life'.

Claiming that he was 'an agriculturist, and a disciple of Dr Gilbert and others' Salisbury also turned his future eye on manures, and the elements they contribute, and asking

rhetorically 'why we have to go to Chili (sic), and why we cannot take them from the air around us'. To fill in the gaps, Liebig was a great proponent of manures, while Gilbert and Laws were responsible for work at Rothamstead that showed the essentiality of phosphorus and the value of 'superphosphate', and Chile was the source of nitrate fertilisers.

Other chemists to speak at the dinner were Sir Henry Roscoe, Professor Edward Frankland, Armand Gautier (President of the Société Chimique de Paris), Dr Will and Victor Meyer from the Deutsche chemische Gesellschaft, and Sir Frederick Abel. The commemorative volume includes the texts, in French and German respectively, together with English translations, from which I take it that the European delegates had spoken in their own languages. Praising Lord Salisbury for honouring the gathering with his presence, Roscoe said that if he 'had not unfortunately become a great statesman, and had followed the inclination of his own mind, he would have been a great chemist'. He went on to observe that 'the education of the upper classes in this country has for a long time been too restricted' and that 'science has not formed that element in education which is so necessary for its progress'. This was 1891, not 1991; Roscoe's views would no doubt receive support from chemists in 2015.

**Family members recall laboratory experiments that caused him to faint after inhalation of chlorine gas, and inflicted cuts from an unexpectedly vigorous reaction of sodium with water.**

Salisbury also spoke about chemistry's illustrious history in his address to the British Association for the Advancement of Science a few years later. In a Poo Bah (*The Mikado*, 1885) performance, he welcomed the Association as Chancellor of Oxford University, then donned another hat as the Association's President to thank the university for hosting the 1894 meeting.

Salisbury (1830–1903) was born Robert Arthur Talbot Gascoyne-Cecil, second son of a marquis. He was elected to the House of Commons as a Tory and served as Prime Minister for a few months in 1885 and then for the period 1886–92. Family members recall laboratory experiments that caused him to faint after inhalation of chlorine gas, and inflicted cuts from an unexpectedly vigorous reaction of sodium with water. His 'long beard and imposing bulk' (18 stone when he first led the country) resembled those of his contemporary W.G. Grace.

**Ian D. Rae** FRACI CChem (idrae@unimelb.edu.au) is a veteran columnist, having begun his Letters in 1984. When he is not compiling columns, he writes on the history of chemistry and provides advice on chemical hazards and pollution.



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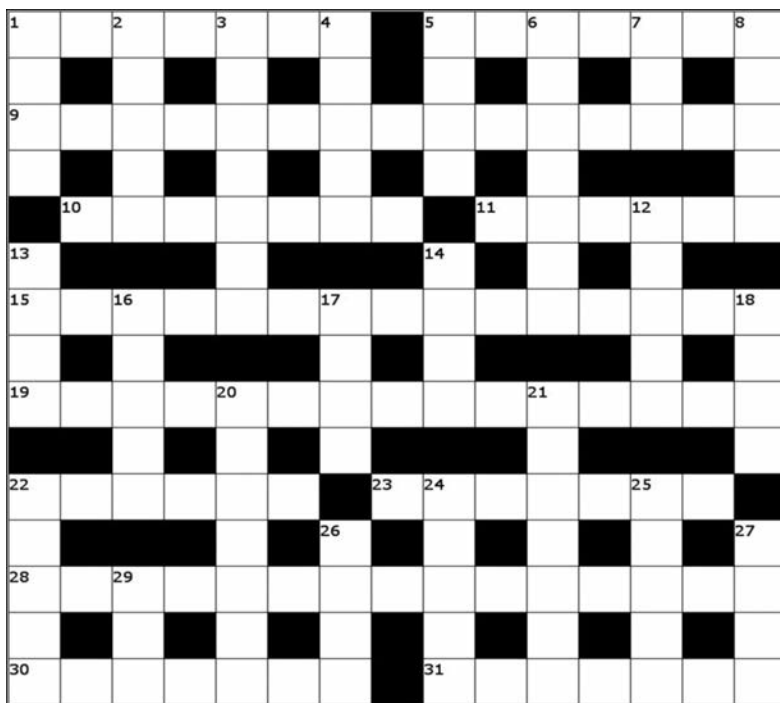
**IUPAC 2015**

48th General Assembly 6–13 August 2015,  
45th World Chemistry Congress 9–14 August 2015,  
Busan, Korea  
www.iupac2015.org

**Pacificchem 2015**

15–20 December 2015, Honolulu, Hawaii  
www.pacificchem.org

RACI events are shown in blue.



**Across**

- 1 Adjust tuner and metal at pH 7. (7)
- 5 *trans*-Butenedioic reacts if cumarin dropped in. (7)
- 9 Cloaks remodeled mixture which emits light coherently in pulses of extremely short duration. (4-6,5)
- 10 Edgy over bitter little title removal. (7)
- 11 Funny idea to make anion. (6)
- 15 A safe rural career, less radical, might stem from an important concept in electrode chemistry! (4,7,4)
- 19 Clod! His easy prac produced starch and cellulose? Perhaps. (15)
- 22 Old mass follows recent force. (6)
- 23 Lu/Pa/En/C filter for environmental remediation. (7)
- 28 Binary filtrates challenged assumption that a chemical property will have a similar value in a variety of different circumstances. (15)
- 30 Verbose about notice. (7)
- 31 Mess seen – try C<sub>8</sub>H<sub>8</sub>. (7)

**Down**

- 1 See 27 Down.
- 2 & 8 Down Is this where the definite integral combines cadmium, rhenium, vanadium, uranium, ruthenium and neon? (5,5)

- 3 New era lets accounts. (7)
- 4 Pub where the food helps you lose weight. (5)
- 5 Sounds like a small number will shortly make something that can provide energy. (4)
- 6 AFL coach discarded a couple of elements. Sweet! (7)
- 7 Alternate premise: quadratic mean. (3)
- 8 See 2 Down.
- 12 A group of investigators holds radical. Nasty! (5)
- 13 Net collar. (4)
- 14 Way cheap at half the price inside. (4)
- 16 Let everyone shout in pain. (5)
- 17 Stone swing. (4)
- 18 A capital sales ratio finally to boot. (4)
- 20 Clasp on so resolutely to hold backer. (7)
- 21 Liar! Dye mixed with ease. (7)
- 22 Functional group hears after-dark sequence. (5)
- 24 Pbs ahead. (5)
- 25 Three or four elements get together. (5)
- 26 See 27 Down.
- 27 & 1 Down & 26 Down A pyrene theme used to give instruction as to how to identify yourself. (4,4,4)
- 29 A33 atomic absorption spectroscopy. (3)

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Coming up

- Chlorophyll, carotenoids and other autumnal pigments
- Reflections on the RACI Congress
- The past lives of our Sun

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





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