NZC Chemistry IN NEW ZEALAND

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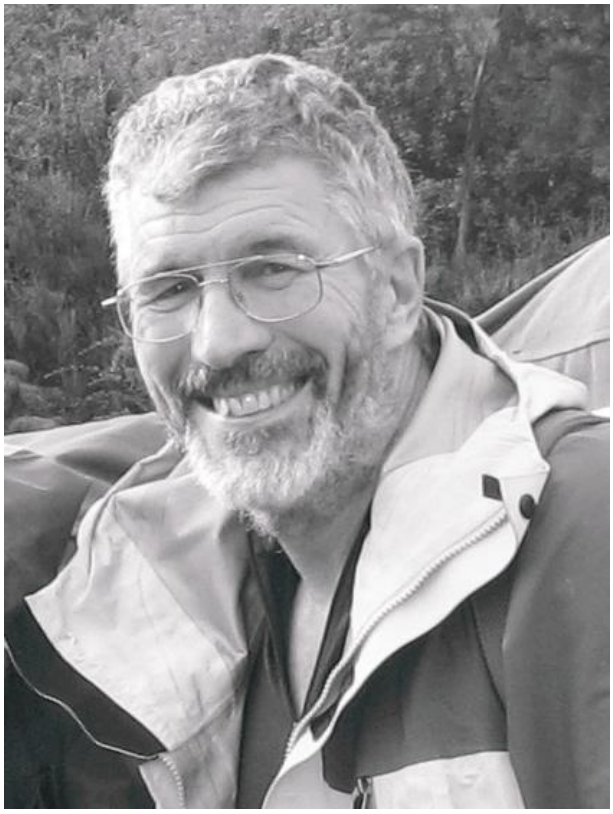
Articles and Features

Other Columns

Comment from the President



I'm delighted to lead the profession of chemistry in New Zealand in my role as NZIC President for 2015. The NZIC has a well-managed succession plan for the key leadership role of President that provides a two-year rolling start for all aspiring Presidential candidates. While supporting and serving the Institute in Vice-Presidential roles over the past two years I have learned and benefited from observing the strong leadership demonstrated by Michèle Prinsep throughout 2014 and Michael Edmonds in 2013. I trust that I can sustain and hopefully even further enhance the quality of our leadership in 2015. I'm sure that both Michèle and Mike would be the first to agree with me that while strong leadership is essential, the successful operation of our Institute is predicated on the remarkable efforts of Richard Rendle and Colin Freeman, in their roles as Honorary General Secretary and Treasurer. Richard and Colin keep our NZIC show very much on the road and we are grateful to you both for your ongoing support of our profession and our Institute.

A short introduction to you all at the outset of my tenure might help set the scene. For those that know me – jump to the next paragraph! For those that don't, here's a quick resume of my background and skill set. I have always been interested in the industrial applications and uptake of materials science, and materials chemistry in particular. I completed my PhD in Chemistry at VUW with Prof James Duncan in 1974, where perhaps unusually I studied glass chemistry. At the end of my degree James played the 'old boys network' card and I accepted the offer of a position in the Pilkington Brothers laboratories in Lancashire, England. At that stage Pilkington's had >20,000 employees in the UK and had a laboratory staff of over 600. I spent five great years exploring many aspects of glass materials science from the most strategic microstructure and glass reaction path studies through to working shifts in the wee small hours to implement new technologies in Pilkington's flat glass, fibre glass and optical glass subsidiary companies. I quickly learned the essential values of clear communication and hands-on personal demonstration to achieve good tech transfer! Returning to DSIR Chemistry Division in 1979 I worked on a succession of solid state materials chemistry projects over many years, spanning glass, mineral and fertiliser chemistry through the 80s then settling in to a sustained period of ceramic materials research through the 90s and 00s. While I have long maintained my interest in ceramic science I have also designed, written and led MBIE programmes in hydrogen materials, geothermal cement science and most recently in titanium materials. The common theme is one of relating very similar concepts in terms of materials processing and understanding the complex and iterative relationship between materials chemistry, microstructure and materials properties. I do hope that I can promote awakened interest in materials chemistry in New Zealand during my presidential tenure and I'll certainly be pleased to both talk about and demonstrate this fascinating and economically important field of chemistry to you all as the year unfolds.

I've had the good fortune to attend some of New Zealand's premier science award ceremonies in recent weeks, in part because I had acted as a member of the judging panel for some of the specific awards for both the Prime Ministers Science Prizes and the Royal Society annual science awards. It was a delight to hear a vivid and memorable acceptance speech for the Rutherford Medal from the extraordinary Peter Schwerdtfeger but it was equally remarkable to hear the composed and mature acceptance speech from 17 year old Tim Logan, who won the Prime Minister's Future Scientist Prize. Peter, of course, is one of our leading NZIC Fellows and offers a prime example of how the chemical sciences are a key plank to access and solve science challenges of an increasingly multidisciplinary nature. At a more local level I was pleased to attend the Wellington Branch AGM on 19 November where Michèle Prinsep presented a number of our annual NZIC awards to Wellington Branch members. While we correctly laud our medal and prize winners, I do want us to acknowledge our new 2014 NZIC Fellows, who represent all that is good about the diversity of our national chemistry talent. This year we have recognised the efforts of chemists who are business leaders, project and programme leaders at our institutes, accomplished academics and long contributing 'coal face' chemists whose skills underwrite so many of our best science teams. Well done to you all. I hope to see such a breadth and depth of applicants for NZIC Fellowship in 2015.

Finally, let me note that in my role as President for 2015 I will be the first researcher from Callaghan Innovation to hold this honour. It is 12 years since our predecessor organisation IRL was host to the NZIC Presidency in 2003

when David Bibby held the role during the year that he transitioned from IRL to VUW. Callaghan Innovation is home to a number of New Zealand's finest chemists and chemical engineers. Its mandate is to accelerate the commercialisation of innovation by firms in New Zealand but within that mandate there is great opportunity to undertake and apply high quality chemical science and engineering to benefit New Zealand. The rapidly changing face of chemistry in our many New Zealand research agencies may be bewildering to some and threatening to others but we must continue to educate our chemists to support those that wish to take career paths in Callaghan Innovation and in our CRIs. The fact remains that our research agencies need a long term supply of talented scientists who can innovate, lead and communicate science to our business leaders. A critical part of this education process is a broader student exposure to New Zealand's institutional research capabilities, via summer studentships, extended internships or sponsored post graduate placements. I'll be pleased to play my part in encouraging and supporting this educational pathway for our best and brightest.

Ian Brown
Callaghan Innovation
NZIC President 2015

From the Editor

Happy New Year! This issue gets the year off to a great start with an unprecedented number of contributions - so many in fact that some items have had to be held over to April due to printing costs. Thank you to everyone who submitted material so enthusiastically. I hope we can maintain this momentum throughout the rest of the year.

In addition to articles on a wide range of topics, the University of Auckland has provided an overview of the School of Chemical Sciences. I found this very informative, and other branches may wish to do something similar if it seems appropriate. Please also consider approaching distinguished visitors at your institution in the coming year who might be persuaded to provide an article that is relevant to our journal. Authors may also like to include a very short bio and photo with articles. This is done in a few journals already and I very much like the personal feel it gives. Author guidelines will be updated later this year to clarify the content, scope and length of articles but if you have any queries in the meantime, feel free to contact me directly.

As we were going to press, we received the sad news that Dr Tony Woolhouse of the Ferrier Institute had passed away very suddenly. Many readers will know Tony and we extend our sincere condolences to his family, friends and colleagues.

Best wishes for 2015.

Cath Nicholson

New Zealand Institute of Chemistry

supporting chemical sciences

January News

NZAS Awards

The New Zealand Association of Scientists (NZAS) presented its awards at the Royal Society of New Zealand in Wellington on 12 November 2014. Two chemists were amongst the award winners. Professor *Keith **Hunter*** of the University of Otago was the joint recipient of the Marsden Medal, awarded for a lifetime of outstanding service to the cause or profession of science. He is a recognised leader and innovator in environmental and chemical oceanography. His research is characterised by the application of fundamental chemistry to the investigation of oceanographic systems and the role of trace elements and, recently, CO_2 in ecological and biogeochemical processes. Associate Professor *Richard **Tilley*** of Victoria University of Wellington was the joint recipient of the Research Medal, awarded for outstanding fundamental or applied research in the physical, natural or social sciences published by a scientist under the age of 40. He has pioneered and developed the synthesis and electron microscopy characterisation of nanoparticles in New Zealand, with applications including the development of magnetic nanoparticles for MRI contrast agents in collaboration with the Malaghan Institute and Wellington Hospital.

RSNZ Award and Fellows

The Rutherford Medal was awarded to Distinguished Professor *Peter **Schwerdtfeger*** FRSNZ, FNZIC, Massey University, for his world-leading contribution to fundamental aspects of chemical and physical phenomena in atoms, molecules and condensed matter.

Two NZIC members have been elected as Fellows of the Royal Society of New Zealand.

Professor *Catherine **Day***, Department of Biochemistry, University of Otago, is a highly innovative protein biochemist and structural biologist who has made advances in understanding protein interactions that occur in programmed cell death and survival – critical in normal human development and cancer.

Professor *Alison* **Downard**, Department of Chemistry, University of Canterbury, is an internationally acclaimed scientist working in the fields of electrochemistry, materials chemistry and surface science. She

has made pioneering discoveries involving the chemical modification of surfaces at the nanoscale, leading to new electrodes with applications in energy storage and conversion.

AUCKLAND

The University of Auckland

Awards

The new chemistry undergraduate teaching laboratories at the School of Chemical Sciences have won a coveted international S-Lab Award for Laboratory Improvement and Innovation. S-Lab is a response to the need to create more effective laboratories arising from financial, customer, user, regulatory and other pressures, mainly funded by the Higher Education Funding Council for England (HEFCE).

Professor *David **Williams*** was named as the 2014 recipient of the U.R. Evans Award, which is the top international award of the UK Institute of Corrosion. It was first awarded in 1976 and is made for outstanding international achievements in pure or applied corrosion science. The award includes a mounted sword on an engraved plaque (!) and an Honorary Life Fellowship of the Institute.

Distinguished Professor *Margaret **Brimble*** won a Women of Influence Award. This is a partnership between Fairfax Media and Westpac, and celebrates the women helping shape the future of New Zealand.

MBIE and Marsden Funds

Four projects led by researchers from the School of Chemical Sciences were successful in the latest MBIE funding round. These were: *The biocide toolbox* led by Professor *Ralph **Cooney***, *High-density air quality measurement instruments* led by Professor David Williams, *Beam shaping for femtosecond laser machining* led by Associate Professor *Cather **Simpson*** and *Measuring pH with a RFID chip* led by Professor *Penny **Brothers***. The School also received one funded project in the 2014 Marsden round: *Unravelling the unprecedented architecture of the NZ natural product portimine using molecular chess* led by Distinguished Professor Margaret Brimble.

The New Zealand Institute of Advanced Study (NZIAS), Massey University, Auckland

Rutherford medal

Distinguished Professor *Peter **Schwerdtfeger*** received the Rutherford medal for his contributions to fundamental aspects of chemical and physical phenomena in atoms, molecules and condensed matter. The Rutherford Medal, named after Sir Ernest Rutherford, is the country's highest science honour. The selection panel described Professor Schwerdtfeger as one of New Zealand's "most brilliant and internationally highly sought-after scientists", adding that his research had provided a deep insight into how atoms and molecules interact at the quantum level.

Professor *Al **Nielson*** received the College of Science Lecturer of the Year Award as well as the Annual Albany Lecturer of the Year Award. *Elke **Pahl*** and Distinguished Professor Schwerdtfeger jointly received a Marsden grant for *Putting the squeeze on atoms and molecules - accurate quantum simulations of atomic and molecular phases under high pressures and temperatures*.

CANTERBURY

A Branch seminar was given on 11 September entitled *From land to sea and macro to micro: natural products from cyanobacteria and marine bryozoans* by Dr *Michèle R. **Prinsep*** of the School of Science, University of Waikato. Michèle's presentation illustrated the importance and relevance of natural products chemistry in our daily lives.

Another Branch seminar was given on 15 October entitled *Harmful algal blooms of Prymnesium parvum: an emerging threat to inland waters* by Professor *Bryan W. **Brooks*** of the Department of Environmental Science, Baylor University, Texas, USA (see http://www.baylor.edu/environmentalscience/index.php?id=56293). Since 2000, harmful algal blooms of *P. parvum* have increasingly produced devastating fish kills in inland waters of the United States and other countries. The talk covered assessment and management strategies as well as future perspectives and recommendations for research needs.

University of Canterbury

Events

*Samantha **Bodman*** and *Sarah **Masters*** have been busy with outreach work involving some rather different audiences. On 29 September they went to a holiday club in Papanui, with the children making sky in a bottle and testing the pH of Sprite. On 2 October they went to Peppers Clearwater Resort to talk to delegates from Airways. This is the air navigation service that develops and maintains all the software that keeps aircraft in the skies over New Zealand. The *Chemistry of Dessert* show

Distinguished Professor Peter Schwerdtfeger with Nicola Gaston on the left and Matthias Lein on the right

was a real hit with everyone.

Visitors

*Morkel **Zaayman*** graduated with a bachelor's degree in chemistry from the University of Pretoria in 2004 and has recently completed his Masters in Soil Science through Massey University in Palmerston North where he investigated the health risks of greywater in New Zealand. Currently he is doing a PhD through the University of Canterbury where, in conjunction with the Centre for Integrated Biowaste Research (CIBR) and NIWA, he is investigating the fate and behavior of emerging organic contaminants (EOC) from wastewater in constructed wetlands and on-site land application systems. The research aims to identify which types of EOCs are removed by wetlands, the removal and deactivation mechanisms involved, removal and deactivation mechanisms of EOCs in greywater applied to soil, and potential effects EOCs could have on soil health parameters following greywater application. *Sally **Gaw*** is his supervisor.

*Ye **Hui*** (Hector) has joined the Human Toxicology Research Group to carry out his PhD under Professor *Ian **Shaw*** on the effects of food fermentation production methods on estrogenic components (e.g. genistein in soy). Many Chinese foods utilise fermentation and Hector is interested in what the effect on their components might be, particularly from the point of view of their health-giving properties.

Awards and appointments

In August the Department welcomed *Alexander **Goroncy*** as Instrument Support. Alexander studies physics and chemistry in Germany (Bremen, Göttingen) and in the USA (University of South Carolina, Columbia) and has worked in universities in the US (Albert Einstein College of Medicine and Ohio State University) in Japan (Riken-Yokohama Institute) and in New Zealand (Massey University).

The postgraduate *Thesis in three* competition was held on 19 August and was won by *Anna **Farquar*** (Downard Research Group) in the final with her presentation entitled *Graphene: can we unleash its energy storage potential?* All the chemistry students (Anna, *David **Kim*** and *Gert-Jan **Moggre***) had a strong showing at the college final the preceding Thursday, with David Lim receiving an honourable mention at college level.

Prof Ian Shaw was awarded the University of Canterbury Students' Association Science Lecturer of the Year 2014.

Baira Donoeva and Daniil Ovoshchnikov both successfully completed their PhDs.

Professor *Alison **Downard*** was named as a newly elected Fellow of the Royal Society of New Zealand (RSNZ). This is a lifetime achievement, and this prestigious honour recognises Alison's excellent contribution to national and international science over many years.

Researchers from the University of Canterbury received a total of $4.43 million in funding over three years in the latest Marsden round, including chemistry Professors *Paul **Kruger*** and *Emily **Parker***.

MANAWATU

The Manawatu Branch held their AGM in November 2014, with a number of potential events for 2015 discussed. A more complete schedule of events for the year will be planned at the first Branch meeting of this year.

Massey University, Institute of Fundamental Sciences

Dr *Catherine **Whitby*** joined the Institute of Fundamental Sciences at Massey University as a Senior Lecturer in Chemistry on 28 October 2014. Prior to this she was an ARC Future Fellow and Senior Research Fellow in the Ian Wark Research Institute at the University of South Australia (UniSA). She completed a Bachelor in Science with Honours at the University of New South Wales and was awarded the University Medal in Chemistry in 1997. Catherine completed her PhD in Chemistry at the University of Melbourne in 2001. She then worked at the University of Hull in the UK and at the University of Sydney before being awarded a research fellowship at UniSA. Catherine is a physical chemist with expertise in colloid and surface chemistry. She investigates soft materials such as emulsions which are the liquid mixtures that form the base of creams, sauces and coatings. A focus of her research is on using nanomaterials to control the structure and performance of emulsions. She uses microscopy and rheology tools to probe how changes to the internal structure of emulsions alter their stability and flow behaviour. Her findings have been applied in food and pharmaceutical products and in drilling fluids. More information about her research group can be found at http://surfacechemistrylab.com/. Catherine also gave a presentation on her work to the Institute late last year.

The Plieger group is busy over the 14/15 summer with an additional four summer students. *Tom **Hall*** (working on quino-quinoline chemistry) and *Joseph **Corrigan*** (working on tri-pyridyl chemistry) are both funded through the Marsden grant *The good without the bad: selective chelators for beryllium*. In addition, *Jenna **Buchanan*** and *Ellie **Mclellan*** are sharing a summer scholarship working on salicylaldoxime magnetic materials and anion chelators respectively. PhD student *Nirosha **De Silva*** began to write up her thesis on iron cluster complexes and hopes to submit soon.

OTAGO

In mid-October the Branch hosted NZIC President *Dr Michèle **Prinsep***. She presented a research talk *From land to sea and macro to micro: natural products from cyanobacteria & marine bryozoans*, which was followed by the branch Annual General Meeting.

University of Otago, Department of Chemistry

Brookers Bunch is currently hosting three visiting research students, each for five to six months: two MSc interns, *Blue **Carter*** (Southampton) and *Katja **Dankhoff*** (Bayreuth), and a PhD student, *Christian **Herold*** (Mainz, as part of a collaboration with Eva Rentschler).

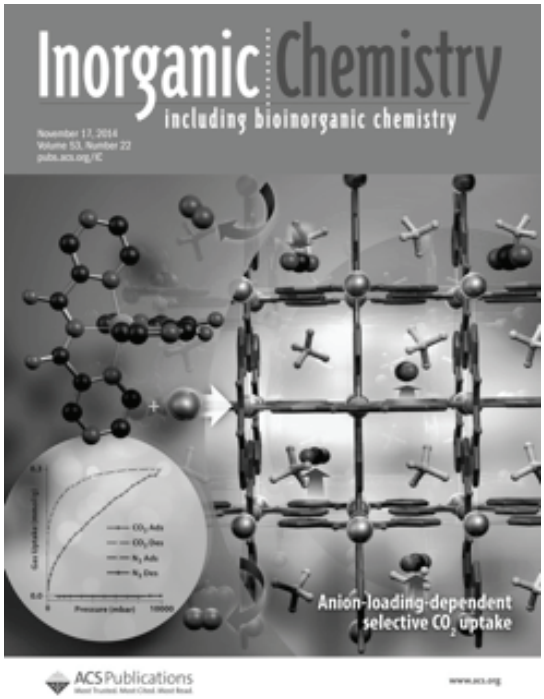
In a rapid and exciting development, the University of Otago takes delivery

of two new magnetometers early this year: a Lakeshore instrument based in Geology (operating at RT; ideal for measuring FORCs) and a cryogen-free Quantum Design Versalab instrument based in Chemistry (for 50-400 K).

In the first week of December, *Reece* ***Miller*** visited Cameron Kepert (Sydney), to make sorption measurements on his new metal organic framework (MOF), and also visited Simon Clark (Macquarie) to complete a pressure crystallography study. He then flew to Adelaide to present his research as a finalist in the Stranks best student lecture competition at the RACI Congress 2014. Reece recently completed our substantial collaborative study, started by *Matthew* ***Cowan***, into a pair of robust isostructural highly CO_2-selective MOFs, with Cameron Kepert, Peter Southon, Jason Price, Ozgur Yazaydin and Jo Lane. Specifically, they found that doubling the anion occupancy in the channels of the MOF (Ni^{II}-based MOF → Co^{III}-based MOF) further increases the observed adsorption selectivity for CO_2 over N_2 (*Inorg. Chem.* **2014**, *53*, 12076–12083). The group were thrilled to be invited to provide a cover image (see figure). This image was created by Michael Crawford (Dunedin) from a concept provided by Sally.

Another recent highlight for Sally was being one of seven researchers invited to meet with the German Chancellor, Angela Merkel, for a 45 minute discussion during her visit to NZ on 14 November 2014 (see photos from MFAT).

Anastasia ***Elliott*** finished her PhD (supervised by *Keith* ***Gordon*** and *Nigel* ***Lucas***) in September and is now working at VUW with *Justin* ***Hodgkiss*** helping to develop new methods of generating THz spectroscopy using ultrafast lasers. *Chris* ***Larsen*** (also supervised by Keith and Nigel) attended the Gordon Research Conference on Donor-Acceptor interactions, gave a flash presentation at ICCC 41, and presented his work as a talk at the RACI National Congress in December. *Holly* ***van der Salm*** (supervised by Keith) attended the International Conference on Raman Spectroscopy



The cover image created by Michael Crawford and Sally Brooker.

Top: Sally has just met the German Chancellor. Bottom: Chancellor Angela Merkel, Minister Steven Joyce and Ambassador Anne-Marie Schliech, during our discussions. Photos: MFAT.

(ICORS) conference in Jena, and has published a book chapter in Spectroscopic Properties of Inorganic and Organometallic Compounds (RSC), Vol. 45, with co-authors Keith and Anastasia. Holly got married in November.

Sara ***Miller*** (nee Fraser) finished up her PhD (supervised by Keith Gordon) in September and is now a postdoc in Helsinki working on spectroscopic methods to examine pharmaceutical materials. *Jeremy* ***Rooney*** finished his MSc (supervised by Keith) with distinction. He has just started a PhD with Blue Steel funding through a Callaghan Innovation fellowship. Jeremy's work on prescreening archaeological bone samples for stable isotope analysis was published in PLOSOne. *Daniel* ***Killeen*** (who works with Keith and *Nigel* ***Perry***) is currently writing up his PhD; in August he attended ICORS in Jena, Germany. He presented a poster on his work on herbicidal β-triketones which are compartmentalised in mānuka oil glands and were studied by Raman microscopy. The results of this research have just been published in New Phytologist. *Geoff* ***Smith*** attended ICORS and presented a poster on his work on component distributions in cheeses.

Jim ***McQuillan*** presented an invited lecture on IR spectroscopic analysis of TiO_2 photocatalysis at the 31st Congreso Latinoamericano de Química 2014 in Lima, Peru on 14 October, as well as giving a course of several lectures to postgraduate students on applications of attenuated total reflectance IR spectroscopy to investigations of the wet surface chemistry of metal oxide nanoparticles. Jim noted that this was the first chemistry conference he has attended at which English was not the official language, although many of the slides in the presentations were prepared in English. He had to apologise for not being able to deliver his talk in Spanish. However, the talk was well attended with a number of questions afterwards from an audience fairly familiar with English.

Guy ***Jameson*** has spent the last three months on sabbatical leave at the Manchester Interdisciplinary Centre at the University of Manchester, UK working with Sam de Visser, a very productive and enjoyable time for him. Guy was an invited speaker at the Asian Biological Inorganic Chemistry Conference held at the Gold Coast, Australia, in early December.

WAIKATO

Hill Laboratories

Bruce Morris, a Senior Technologist at Hill Laboratories, has won the inaugural "Excellence in Sample Prep" award at the annual North American Chemical Residue Workshop (NACRW) held in Tampa, Florida. Judging for the award was based on an oral presentation delivered to more than 300 conference delegates. According to Hill Laboratories founder and managing director Dr *Roger* ***Hill***, Bruce's presentation demonstrated the benefits of a new type of sample preparation for pesticide residues that Hill Laboratories has spent many years perfecting. Bruce and other members of his team developed a new 'clean-up' cartridge in co-operation with Hill Laboratories' US suppliers. Roger said, "We are extremely proud of Bruce for presenting and receiving this award and hope it will spark improved pesticide residue preparation methods carried out internationally." Bruce said the process was both exciting and daunting. "The NACRW is regarded as the best pesticide residue conference in the world. The people you are presenting to are experts in this field, so if you've got anything wrong, they'll know about it, and they'll tell you!" he said. "Having never presented to that many people before, it was a bit

Dr Bruce Morris with his award.

Wendy Jackson (right) with Faculty of Science and Engineering staff member Hine Ioane.

3MT final: 3MT overall and People's Choice winner Raymond Onyekachi (fourth from left) with other prize winners and judges.

Emeritus Professor Alistair Wilkins (left) with Deputy Vice-Chancellor Professor Alister Jones (second to left) and other awardees.

Left to right: NZIC Waikato Branch chairperson Michael Mucalo and NZIC President Michèle Prinsep with the winning team from Hamilton Boys' High School: Alex Paris, Soumil Singh and Lucas Sherlock.

unnerving. But it was also exciting to have had the opportunity to put Hill Laboratories, and New Zealand, on the international residue testing map."

University of Waikato

Wendy ***Jackson***, our long-serving University of Waikato technical officer (and Waikato Branch secretary) retired in September and staff celebrated her more than 30 years in the Chemistry Department with a well-attended farewell function. Wendy will be very sadly missed after her tireless enthusiasm and dedication to the job but she leaves for "greener pastures" to live in the Glasshouse Mountains near Brisbane. With family in Hamilton, however, she plans to come back and visit often.

PhD student, *Raymond* ***Onyekachi*** who works with *Bill* ***Henderson***, recently won the University of Waikato Three Minute Thesis (3MT) competition. Each PhD student has three minutes and a static Power Point slide in which to explain their thesis to three judges and a non-specialist audience. Raymond's presentation was entitled *The beauty without the beast: a chemical search for beryllium's partner*. His research looks at finding chemical agents that help remove beryllium from high-tech devices when they are disposed of. We are all very proud of Raymond who not only won $3000 and secured a spot in the Trans-Tasman 3MT next year in Australia but also won the People's Choice Award, based on audience votes.

Recently retired Professor Alistair Wilkins was awarded the title Emeritus Professor at a well-attended ceremony in October. Alistair came to the University of Waikato in 1975 as a lecturer, and retired in 2013. His work in the field of analytical chemistry is legendary and was of great importance in securing significant funding for the University to investigate the environmental effects after the grounding of the Rena in 2011. After the Rena struck Astrolabe Reef in the Bay of Plenty, Alistair worked to accommodate requests of the public, regional and central government for information about the oil and other contaminants coming from the ship.

His work in fingerprinting the oil was of prime importance to the Ministry for the Environment, Maritime New Zealand and the Bay of Plenty Regional Council.

In the annual ChemQuest competition held recently by the Department of Chemistry, Hamilton Boys' High School won convincingly for the second consecutive year to add to their earlier victory in the Analytical Chemistry competition (also for the second year running). Over 200 students from the greater Waikato region and Bay of Plenty participated. As usual, this was a fun-filled evening for students studying NCEA level 2 Chemistry.

Prizes were awarded as follows:

1st Place: Hamilton Boys' High School: (Alex Paris, Lucas Sherlock, Soumil Singh)

2nd Place: Hillcrest High School (Caitlin McEnigott, Harriet Plant, Emma Wardle)

3rd Place: St Paul's Collegiate: (Daniel Davis, Tobias Dean, Harini Meiyappan)

4th Place: St Paul's Collegiate: (Hugo Brown, Non Seehamart, Lara Wilson)

5th Place: Hamilton Boys' High School: (David Lee, Christopher Mayo, Visham Sathiyakumar)

The quiz was generously sponsored by the Waikato Branch of NZIC, Hill Laboratories, James & Wells Intellectual Property and the Faculty of Science and Engineering, University of Waikato. Question masters were Bill Henderson and *Michèle* ***Prinsep***, ably assisted by numerous other staff and students from the Department.

Professor Bryan Brooks (Erskine Fellow at the University of Canterbury) from Baylor University in Texas visited the chemistry department recently and gave a talk entitled *Lessons and opportunities from "fish on prozac" and other harbingers of an urbanizing water cycle* and Michèle Prinsep gave her Presidential address *From land to sea & macro to micro: natural products from cyanobacteria & marine bryozoans.*

WELLINGTON

We have been saddened to learn of the death on 31 December of Ferrier Institute Senior Researcher Dr Tony Woolhouse whilst in Greymouth on a cycling holiday. A full obituary will appear in the April issue.

The Branch congratulated Dr *Ian* ***Brown*** on assuming the Presidency of the NZIC for 2015, but is saddened to note the death of former long-standing member *Walter* ***Freitag***.

September 3 saw the release of the biography *Brian Shorland, Doyen of New Zealand Science* by Dr Joan Cameron, a former Branch Chairperson and 12-year editor of this Journal (1965-1976). Edited by Victoria Emeritus Professors Neil Curtis and Brian Halton, and published by the New Zealand Association of Scientists, the work provides a unique insight not simply into life in NZ in the early years but a kaleidoscope of science in this country in the post-WWI years through to Shorland's death in 1999 (see October 2014 issue of *Chemistry in New Zealand* and a review of this book on page 56 in this issue*)*.

September saw one of Victoria's PhD students return to deliver the Branch monthly lecture. Dr *Sujay* ***Prabakar***, who now works for the Leather and Shoe Research Association (LASRA) in Palmerston North, spoke on *Hell bent for leather: perspectives and future directions in leather research.* Sujay outlined the commercial nature and income derived from the NZ leather industry, pointing out that, while not as large as the meat industry valued at over 500 M p.a. it is surprisingly close, having Germany and the UK as its largest markets for the high quality leathers the country produces. After taking the audience through the process of leather manufacture from the beamhouse to a tanned skin, he discussed the worldwide difficulties associated with the reluctance of tanners to adopt alternatives to chromium(VI) (chrome) sulfate. This traditional process is quick and cheap but generates much Cr(VI) waste that has to be reduced to Cr(III) prior to conversion into a sludge for disposal in a landfill. The European Union is formulating regulatory directions away from this yet the industry leaders are reluctant to change. The important role the NZ leather processing industry has in ensuring that the best possible value is extracted from one of the larger volume by-products of our export meat industry was outlined. Moreover, changes in tanning practices that have emerged from an understanding of the chemistry were outlined. Sujay then focused on recent developments in cross-linking systems for tanning and inorganic/organic hybrid technologies for finishing leathers.

September 19 saw Professor *Douglas* ***MacFarlane*** (Monash University) deliver the 2014 RSC-RACI-NZIC Australasian Lecture *Ionic liquids for sustainable chemistry: applications in the chemical-, materials-, elec-*

Alison Shorland (left) with author Joan Cameron; courtesy Ian Linning, Primofoto (www.primofoto.co.nz)

tro- and bio-sciences. Yet again the organisers selected an outstanding speaker whose discourse held the attention of all for his all too short time. Douglas, another VUW graduate, explained that ionic liquids are simply organic salts that have melting points below 100 °C and that as liquid salts they offer a range of solvency properties distinctly different from normal molecular solvents; they are often very stable – thermally, chemically and electrochemically. Application in a wide variety of contexts from green, medicinal, electro-, and more recently bio-chemical and bioscience abound. He then discussed several recent examples from his group's work. He concluded by telling us that some ionic liquids have properties intermediate between molecular and ionic liquids for which the future developments could be enormous.

The inaugural *Halton Lecture* was given on Wednesday October 8 by Professor *Martin* ***Banwell*** (Australian National University), Brian's third PhD student. His topic was: *Is organic chemistry still relevant? Reminiscences, ruminations and ramblings of a graduate of the Brian Halton School of Organic Chemistry*. The Lecture has been established to acknowledge the enormous contribution Emeritus Professor Brian Halton has made to both chemistry and the NZIC. The large audience was treated to an entertaining and highly informative exposition of chemistry from a personal perspective. Martin paid tribute to Brian's work on strained organic molecules and his *Organic Photochemistry* text co-authored with Jim Coxon, while also demonstrating the vital importance of organic chemical synthesis for health and food production purposes. The named Halton Lecture is the second in a three-yearly cycle that began with the Mellor Lecture in 2013. Next year will see the inaugural Curtis Lecture to acknowledge the contributions of Emeritus Professor *Neil* ***Curtis*** to chemistry and to the NZIC.

The 2014 Branch AGM was held in mid-November and preceded the Presidential Address. *Michèle R.* ***Prinsep*** gave her lecture: *From land to sea and macro to micro: natural products from cyanobacteria and marine bryozoans* to a good sized audience. She spoke of the natural products (secondary metabolites) that are of interest to chemists (and others) from structural complexity, diversity and often very potent biological activity. Some of the natural products isolated by the Princep group at Waikato University, mostly but not exclusively cyanobacteria and bryozoans, were used to illustrate the importance and relevance of natural products chemistry (and chemistry as a discipline) to many aspects of our everyday lives. As usual, Michèle gave a very polished and enjoyable lecture.

Following her lecture the President presented Fellowship certificates to *Drs Paul* ***Bantes,*** *Gavin* ***Painter*** and *Philip* ***Rendle***. Absent was *Jenny* ***Mason***. NZIC awards were then made as:

Shimadzu Prize for Industrial and Applied Chemistry: Dr *Bradley* ***William*** (Ferrier Institute), the ABA Books Denis Hogan Chemical Education Award: Dr *Suzanne* ***Boniface*** (VUW) and the NZIC **Prize for Chemical Science: Dr** *Peter* ***Tyler*** **(Ferrier Institute).** Congratulations to all.

The Branch Officers for 2015 are as follows with the Chairperson and Treasurer continuing from 2014:

Chairperson: Dr *Suzanne Boniface*

Secretary: Dr *Robyn Fulton*

Treasurer: Dr *Ralf Schwoerer*

ESR News

Forensic Toxicologist Dr *Hilary* ***Hamnett*** attended the *22nd International Symposium on the Forensic Sciences* in Adelaide in early September. She provided two presentations, one on the use of LC-TOFMS in forensic toxicology, the other on publishing. She was awarded best oral presentation in toxicology and pharmacology.

Dr Allan Stowell has retired from ESR after 32 years of service. He will be sorely missed by the alcohol group and the wider ESR community. Dr *Wendy* ***Popplewell*** has returned from her maternity leave.

The Ferrier Institute

As noted above, five Ferrier chemists were recognised by the Institute. Professor Mike Wilson (Victoria's Pro-Vice-Chancellor of Science) said: "It's very gratifying to see our professional chemists being recognised by their peers. The Ferrier team has developed world-leading technologies in academic and industrial collaborations. These recognitions further solidify its position as New Zealand's foremost applied organic chemistry institute."

Victoria University - SCPS

Professor *Kate* ***McGrath*** has been appointed to the role of Vice-Provost (Research) at Victoria University. She took up her new position on January 20, but intends to remain research active and affiliated with the SCPS. Kate will remain Director of the MacDiarmid Institute until June unless a replacement is found earlier. Associate Professor *Martyn* ***Coles*** accepted the position of Associate Editor for the *Australian Journal of Chemistry* and took up his role early in September last year.

Following the inaugural Halton Lecture on October 8, Professor Martin Banwell delivered a research lecture on the 9th entitled: *Man vs wild: the application of chemoenzymatic and other methods to the total synthesis of biologically active natural products.* In this discourse he discussed the whole-cell biotransformation of certain aromatic substrates into the corresponding *cis*-1,2-dihydrocatechols by micro-organisms expressing dioxygenase enzymes. He pointed out that this has provided a particularly useful suite of enantiomerically pure starting materials for chemical synthesis and outlined recent research work carried out in Canberra concerned with the exploitation of such metabolites in developing total syntheses of a range of biologically active natural products.

Dr *Jonathan* ***Halpert*** has been awarded a Rutherford Discovery Fellowship and a Marsden Grant Fast Start grant. Other Marsden successes included standard grants to Dr *Bridget* ***Stocker*** and Associate Professor *Richard* ***Tilley***.

Eldon ***Tate*** has been awarded one of the ten $10,000 AMP Scholarships for work on the use of nanoparticles for water purification.

Kalpani ***Somarathne*** (Dr *Joanne* ***Harvey***) has successfully completed her PhD studies with a thesis entitled: *Synthesis of highly functionalised furo[3,4-*b*]pyrans; towards the fungal metabolite (−)-TAN-2483B* and *Hilary* ***Corkran*** (Drs ***Stocker/ Timmer***) with *Synthesis of small molecule inhibitors for the treatment of disease.* Both graduated at the December ceremony. Ms *Jessica* ***Siacci*** had her service as chemistry class representative recognised with one of the ten VUW Students' Association awards.

Suzanne ***Boniface*** attended the Australian Conference on Science and Mathematics Education (ACSME) at the University of Sydney in early October last. It was themed *Student engagement: from classroom to workplace* and brought together a wide variety of teachers from different disciplines and institutions with the common goal of enhancing the student experience and learning outcomes. Opportunities were provided to share ideas on the design and delivery of courses that encourage students to own and participate in their own learning, and to consider ways to re-imagine learning spaces and approaches in the light of the rapid growth of new technologies available for today's teachers and learners.

John ***Spencer*** returned from four months research and study leave at the University of York, UK, in late November. He was working with Professor Duncan Bruce on the synthesis of liquid crystalline tertiary phosphines for applications in the preparation of transition metal complexes with liquid crystal properties. The development of a facile route to liquid crystal phosphines could lead to many interesting areas for investigation at the interface of liquid crystal science and transition metal chemistry. York, a major centre of liquid crystal research in the UK, has outstanding facilities. While there, John was pleased to encounter Meghan Halse, a former physics PhD graduate of Victoria, who was recently appointed to the academic staff at York as a physical chemist.

The annual Massey-Victoria Chemistry Student Symposium was hosted by the SCPS at Victoria on 14 November and was attended by student (and staff) members of the Wellington and Manawatu Branches. Separately, members of the Wellington Branch attended the *Frontiers of biology: from protein structure and function to drugs* meeting in mid-November, a satellite of the combined NZ Microbiological Society/NZ Society for Biochemistry and Molecular Biology conference. It was organised by Brian Monk with support from Bill Jordan in VUW's Biochemical Sciences. The Centre for Biodiscovery annual symposium was held in late November at VUW and it attracted members of the Wellington Branch as well as speakers from Canterbury (*Emily* ***Parker***) and Auckland (Peter Shepherd and Jack Flanagan). The plenary speaker, Jerry Pelletier, from McGill University in Montreal, was supported by the Maurice Wilkins Centre. He spoke about the eukaryotic initiation factors as drug targets for preventing deregulated translation in cancer.

Article

The state of the School: a brief update on the School of Chemical Sciences at the University of Auckland

Kevin E. Smith, Professor and Head of School

School of Chemical Sciences, University of Auckland, Private Bag 92019, Auckland 1142
(email: *kevin.smith@auckland.ac.nz*)

Keywords: *School of Chemical Sciences, teaching, research, safety, centenary celebration*

Introduction

2014 was a singular year for the School of Chemical Sciences at the University of Auckland. We saw changes in leadership of both the School and of the Faculty of Science, changes in our academic and professional staff, and changes in the physical location of our research laboratories. We also saw extraordinary success in attracting external funding for research in the many areas of our diverse School. A notable event last year was my installation as the new Head of School in January 2014, and I take this opportunity to offer an update on the status of Chemical Sciences at Auckland.

Safety

The School of Chemical Sciences has an excellent reputation for performing its teaching and research missions in a safe environment. But safety in a laboratory environment is a dynamic process, and we continue to develop the culture of safety within the School. Monthly unannounced lab inspections, together with a process for documenting and addressing all safety incidents, are now an established part of the culture. An exciting development, led by the Deputy Head of School for Research, Christian Hartinger, is the introduction of a sophisticated software package for the tracking of hazardous and restricted materials "from cradle to grave". This software allows us to monitor what is ordered, whether the chemical is already in another lab on campus, the location of the chemical at all times, and finally its use or disposal. The School of Chemical Sciences will be the first academic unit at Auckland to use this software, and we will lead its installation across the entire university.

Teaching

We remain committed to the highest level of excellence in teaching, at both the undergraduate and postgraduate level. Numerous members of our staff have won university and national teaching awards. This year, our new undergraduate teaching laboratories won an international architectural award for excellence in scientific lab design, and Deputy Dean of Science, Jim Metson, was in London to receive the award on behalf of the university (for more details see the article by Katrina Graaf in this issue). The latest teaching innovation to originate from members of the School is the University of Auckland Science Scholars, an undergraduate interdisciplinary programme for the best and brightest undergraduates in the spirit of the "Honours Colleges" featured in many US universities. One of the leading founders of this program is Cather Simpson.

Research

The staff of the School have been very productive across our diverse areas of scholarship, from medical chemistry, through organic, inorganic, polymer and materials chemistry, to food science, wine science, and forensic science. This productivity is reflected in numerous external research grants and prizes. Among these are:

1. Ralph Cooney – Recipient of an MBIE grant, together with Margaret Brimble, Paul Kilmartin, Jianyong Jin, and Jadranka Travas-Sejdic.
2. Margaret Brimble – Won Westpac women of influence award in the science and innovation category, and awarded a Marsden grant.
3. Cather Simpson – Recipient of an MBIE grant.
4. Penny Brothers – Recipient of an MBIE grant, along with David Ware, David Williams and Margaret Brimble.
5. David Williams – Recipient of an MBIE grant.
6. Conrad Perera – Recipient of a Fonterra PGP grant.
7. Bruno Fedrizzi and David Barker – Recipients of a Bioresource Process Alliance grant.
8. Jonathan Sperry – Won a Thieme Chemistry Journal award in Feb 2014.
9. David Williams – named as the 2014 recipient of the U.R. Evans Award, which is the top international award of the UK Institute of Corrosion.

The School was also well represented in the recent round of CoRE awards. We were very pleased that the MacDiarmid Institute for Advanced Materials and Nanotechnology was funded again, since the School has 12 of our academic staff as Principal or Associate Investigators in the Institute. David Williams, Deputy Director of the MacDiarmid Institute, played a particularly important role in the successful proposal. We also note the success of members of our School in two other CoRE proposals: The Dodd Walls Centre, (Cather Simpson), and The Maurice Wilkins Centre (Margaret Brimble).

We made three new additions to the academic staff in 2014. Juliet Gerrard, Ivanhoe Leung, and Erin Leitao. Professor Juliet Gerrard trained at Oxford University, where she completed an Honours degree in Chemistry and a DPhil in Biological Chemistry. She joins our School as a joint appointment with the School of Biological Sciences and Callaghan Innovation. Juliet is FRSNZ, and Chair of the Marsden Fund Council. She is a distinguished protein chemist and has a particular interest in the self-assembly

of proteins into interesting functional nanostructures.

Dr Ivanhoe Leung arrived in October. His undergraduate, postgraduate, and postdoctoral studies were all undertaken at Oxford. He joins us as a Lecturer in Chemical Biology, and he will be critical for building our strength in chemical biology and macromolecular NMR.

Dr Erin Leitao joins us this year as a Lecturer in Inorganic Chemistry, strengthening our thriving Inorganic division. Erin earned her PhD from the University of Calgary, and was a Marie Curie Research Fellow at the University of Bristol.

Finally on the theme of research, a few comments on my own area of scholarship. My area of expertise lies in the x-ray spectroscopic study of the surface and bulk electronic structure of novel materials. Currently, six distinct classes of materials are under investigation: correlated solids (vanadates), organic semiconductors and metals (phthalocyanines), nitride semiconductors, transparent conducting oxides, rare-earth nitrides, and solid oxide fuel cell cathodes. The spectroscopies I use include numerous varieties of photoelectron spectroscopy (angle resolved photoemission, hard and soft x-ray photoemission, photoemission electron microscopy, and ambient pressure photoemission), x-ray emission spectroscopy, x-ray absorption spectroscopy, and resonant inelastic x-ray scattering. Almost all of my research is undertaken at synchrotron radiation facilities, and my group are heavy users of the Advanced Light Source at Lawrence Berkeley National Laboratory in California, the National Synchrotron Light Source at Brookhaven National Laboratory in New York, and the MAXLab facility in Lund, Sweden.

Centenary celebration

On Friday the 13th and Saturday the 14th of March 2015, the University of Auckland will celebrate the 100th anniversary of the establishment of the Department of Chemistry, now the School of Chemical Sciences. Our Centenary Celebration will feature:

- Lectures by Professor Robert H. Grubbs, 2005 Chemistry Nobel Laureate, from CalTech.
- A Lecture at the Auckland War Memorial Museum by Professor Russell Egdell from the Department of Chemistry, Oxford University, on Henry Moseley. Moseley, a student of Rutherford, is famous for his work on x-ray spectroscopy and the development of the modern periodic table. He was killed at the age of 27 at Gallipoli.
- A presentation by Professor Joseph Nordgren from Uppsala University in Sweden. A member of the Royal Swedish Academy of Sciences, he will speak on the history of the Nobel Prizes in Chemistry and Physics, and the process for selection of the Laureates.
- A lecture by Professor Tim Jones, Pro-Vice Chancellor for Research at the University of Warwick on the future of carbon-based solar cells, and on his entrepreneurial chemistry.
- The Chemical Sciences Research Showcase, where the innovative and exciting work of our postgraduate students will be presented.
- A guided tour of Goldie, the University of Auckland vineyard on Waiheke Island where the wine science students from the School of Chemical Sciences learn their craft.
- Lectures by our top researchers.
- Tours of our new award-winning teaching laboratories.
- And finally, on Saturday night, a gala black-tie dinner in the University Marquee.

All members of the NZIC are warmly invited to this event, and people are able to attend one or both days. The registration web site can be found linked at the School of Chemical Sciences web site: *http://chemistry.auckland.ac.nz*. I look forward to seeing many of you at our Centenary Celebration.

Summary

The state of the School of Chemical Sciences is strong. With well over 30 academic staff, over 110 PhD students, and thousands of undergraduates taking chemistry courses, we are thriving. Our culture of safety is embedded and growing, our excellence in teaching is established, and our externally funded research is going from strength to strength. We look forward to continued success in 2015.

Article

Award winning chemistry teaching laboratories at the University of Auckland

Katrina Graaf

School of Chemical Sciences, University of Auckland, Private Bag 92019, Auckland 1142
(email: k.*graaf@auckland.ac.nz*)

Keywords: *undergraduate chemistry laboratory, lab refurbishment, S-lab, award winning labs*

Fig. 1. Glass wall depicting an iron emission spectrum at the entrance to the new undergraduate laboratories

Introduction

In late 2010, the University of Auckland considered the feasibility of upgrading its outdated science sector buildings. It became clear that the podium block on the corner of Symonds and Wellesley Streets, which had been home to the chemistry teaching labs since the 1960s, was the best site for a new 11 storey building. This new building is due to be completed and ready for the start of teaching in March 2016.

Demolishing the podium block posed a dilemma of where to put the large chemistry teaching labs, which occupied this site, without disrupting any teaching. While Property Services, faculty staff and architects were trying to find the best site, the teaching staff researched lab design and course delivery at other universities. I visited the University of Western Australia and Curtin University in Perth and looked at their new labs. These had recirculating water for condensers and Curtin University had their water and power coming from the ceiling rather than through the floor, the advantage of this system being that it gives flexibility to future use of the room and reduces the number of drains, etc. fitted into a refurbished floor. Both these universities also had smaller interconnected pods rather than the large barn-type teaching lab that Auckland University had previously.

The technical staff noted ideas for potential improvements such as: Did we need the unsightly metal grids at the student bench that weren't used often and interrupted line of sight? Did we need running water and sinks on the student benches? Did we need natural gas and Bunsen burners? Should we have nitrogen taps in the fume cupboards? What type of power points did we need that could take two adapters as we had trouble plugging in all our equipment? Where would be the best place for the technician's office - inside or outside the lab? Did we need a gown up room (ante room) for the students? Did the students need a write up area in the lab or outside? Would a tote tray system be more flexible than individual student lockers for their equipment?

To explore these questions, a bench was set up in the old lab to trial new ideas so that by the time a new site was identified we knew what did and didn't work. The Gratnells system of trays was a must and also, yes, we still needed gas for Bunsen burners but not as many as we now use hotplate/stirrers for most experiments.

We were lucky that only one move was required. The new chemistry teaching lab (Fig. 1) is now on the first floor of the Maths/Physics building, which fortuitously was undergoing seismic upgrade with carbon fibre strengthening and refurbishment at the same time.

The design

As the new teaching labs were a refurbishment of an existing building, the architects had to design the lab around fixed walls and services in the existing 1960s concrete building with a similar structure and floor footprint to our old chemistry lab location. As this building project was fast tracked with tight deadlines (demolition started in late 2011 and the building was completed early in 2013), the construction and demolition was going on while changes to design and new ideas were still being discussed and implemented in building meetings.

Within the building constraints, the lab was opened up to the city, Albert Park and beyond by replacing some concrete walls with glass panels, thus enabling the students to have a view out and the general public to see into the building.[1]

The new undergraduate lab consists of two labs each with their own ante room (student lockers and gown up

area). Lab 1 (Fig. 2) caters for the larger taught classes, accommodating 128 students, and comprises 4 pods of 32 students separated by back-to-back 2 m common ducted fume cupboards (6 fume cupboards in each pod). The common ducting (manifolding) of the fume cupboards in this lab has allowed us to maximise the number of fume cupboards for the students while minimising the number of extract flues required. Lab 2 (Fig. 3) takes 80 students and is used for the advanced synthetic chemistry papers with 5 pods of 16 students, separated by back-to-back 1.5 m fume cupboards with a ratio of one fume cupboard to two students and nitrogen supplied on tap.

Each lab also caters for students with disabilities by having a low wheelchair accessible fume cupboard and an adjustable student bench opposite this cupboard (Figs. 4 & 5).

The two labs are separated by the prep room, analytical instrument room and routine instrument rooms. The technician's office is accessible from the lab 2 ante room and prep room with clear line of sight through to the analytical laboratory using glazed walls. The prep room has large preparation benches with Nederman extraction arms, ample storage with students' replacement equipment supplies located near or at the servery using Gratnells trays under the benches and pull out pantries. There are also custom built solvent cupboards, vented chemical stores and Compactus storage (Figs. 6 & 7).

The lab is now light and bright with increased visibility due to glazed walls (Figs. 8 & 9).[1] The modular pod system has worked out much better than was anticipated, particularly with the transfer of sound and how the group supervisors interact with their students.[1] Students in turn are no longer intimidated by the large barn-like old lab. There is excellent line of sight with the service shelves (Fig. 10).

The modular layout allows benches to be moved in the future as bespoke service shelves are suspended from the ceiling above the benches and house the electricity, recirculating water, vacuum and data points, meaning drains and sinks are no longer needed on the student benches.

The under bench tote tray cupboards allow the technicians to quickly clean up and set up the lab and allows flexibility.

Another design feature that makes the lab more flexible is the vented areas next to the fume cupboards which allows us to set up equipment such as rotary evaporators, ovens etc. on mobile benches (Fig. 11) which in turn allows us to quickly move them to different areas in the lab as needed.

The new teaching lab provides flexibility for the future needs of students with a high fume cupboard to student ratio. We now have a total of 58 fume cupboards.

Safety features

Improved safety was one of the top briefs given to the architects and lab designers and was achieved by the

Fig. 2. Lab 1

Fig. 3. Lab 2

Fig. 4. Disability fume cupboard

Fig. 5. Adjustable disability bench

Fig. 6. Preparation room benches

Fig. 7. Pull out pantry cupboards in the prep room

Fig. 8. Analytical instrument lab

Fig. 9. Lab 2 ante room with lab 2 in the background

Fig. 10. Suspended service shelves over student benches

Fig. 11. Mobile benches with venting next to the fume cupboards

Fig. 12. Teaching lab safety station

placement of the safety stations (Fig. 12) at the end of each fume cupboard bay. The safety stations were colour coded in red to be quickly identifiable.

Throughout the lab there are easily visible traffic lights; green indicates that the lab is safe, orange indicates a localised event such as a fume cupboard not working and red indicates that a serious incident may have occurred such as activation of the fire alarm and to evacuate the lab immediately and not to enter until the incident is cleared. The alarm events can be checked on a touch screen tablet in the technician's office which is outside of the lab zone with access from the lab 2 ante room. The air in the room, for example, can be purged using this touch screen as well as telling us if services such as vacuum and compressed air are working in the lab and the status of the gas bottles in the dedicated gas bottle storage rooms.

When the lab goes into red alarm, all lab gases and non-essential power is turned off and can only be restarted when the event has been cleared.

Good safety protocols and best practice have been achieved by having the ante room before the students enter the lab and lockers in which to leave bags. Hand wash basins are provided in the ante rooms and at safety stations in the labs.

The new undergraduate chemistry teaching laboratory opened in March 2013. In September 2014 the teaching lab was awarded first place at the international S-Lab awards in the refurbished laboratory section. S-Lab (Safe, Successful and Sustainable Laboratories) is based in the UK and aims to create more sustainable laboratories, and to raise sustainability awareness amongst staff and students.[2]

Summary

Architectus, Lab-works, Fletchers and Beca have worked closely together with University of Auckland staff to give us a lab that was ready on time for the start of the teaching semester even though there were tight time constraints for construction. The teaching lab is a pleasure to work in, is energy efficient with design features such as low energy fume cupboards, and water conservation with recirculating water as well as enhancing the teaching space where the students and staff are safe and students with disabilities are catered for.

Acknowledgements

The author would like to acknowledge the hard work of Jim Metson (School of Chemical Sciences), Colleen Seth and Ann Cook (Property Services) for ensuring the project went ahead and the following designers and contractors who gave us a well-built world class teaching lab delivered on time - project architect: Architectus, specialist laboratory design architect: Lab-works Architecture, project managers: RCP NZ, services engineer: Beca, construction: Fletcher Construction, fume cupboard manufacturer: Thermoplastic Engineering and joinery manufacturer: Novalab Systems.

References

1 Video prepared by the University of Auckland for the Awards Gala of S-labs UK, see https://www.dropbox.com/s/nxd53gfqqwfyx87/Labawards%20Master.mp4?dl=0

2 http://www.effectivelab.org.uk/awards.html (accessed 5/11/2014)

Erratum: Wohlman's waters and the Colonial Laboratory

Peter Hodder

Victoria Business School, Victoria University of Wellington *and* HodderBalog Social and Scientific Research, Wellington, New Zealand (email: *peterh@hodderbalog.co.nz*)

The last diagram of the above article was omitted when it was published in *Chemistry in New Zealand* vol 78, no. 4. It is provided below.

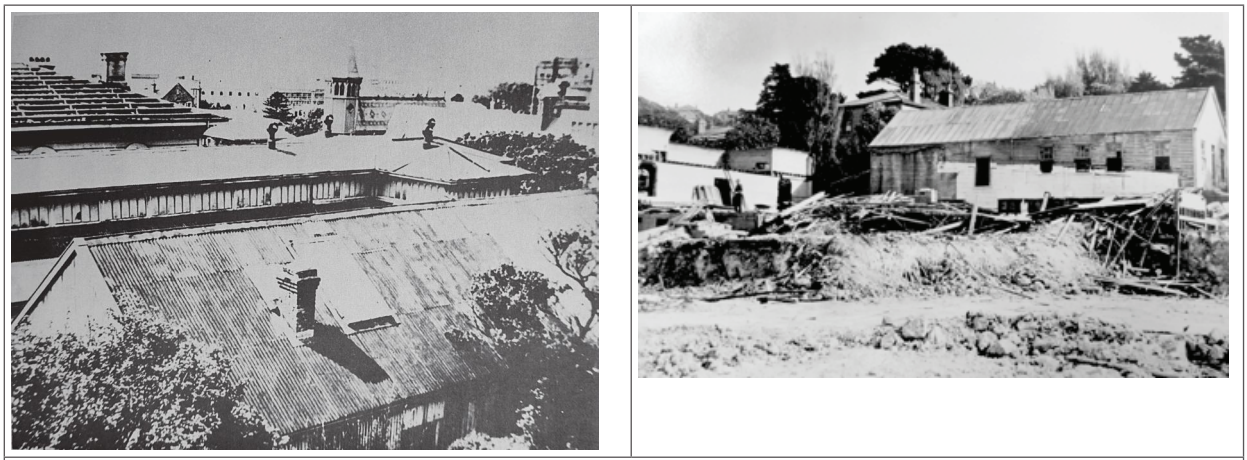


Fig. 7. *Left:* Of this photo, Hughson and Ellis (reference 16) wrote, "Early view of the sheds at the rear of the Colonial Museum that housed the Colonial Laboratory." In fact, the presence of the high-rise building – Kelvin Chambers – at upper right of the photo dates the photo to no earlier than the 1930s. Moreover, the exposed rafters at the upper left are inferred to be of the roof of the Colonial/Dominion Museum being demolished, which occurred in 1939. *Right:* The eastern side of the first Colonial Laboratory, revealed once more by the demolition of the adjacent museum (Alexander Turnbull Library, ref.: F55659 1/2).

Article

TBA-354: A new drug for the treatment of persistent tuberculosis

William A. Denny

Auckland Cancer Society Research Centre, School of Medical Sciences, University of Auckland, Private Bag 92019, Auckland 1142 *(*email: *b.denny@auckland.ac.nz)*

Keywords: *nitroimidazoles*, *pretomanid*, *TBA-354*, *tuberculosis drugs*, *drug development*

Introduction

Tuberculosis (TB), resulting from infection with the bacterium *Mycobacterium tuberculosis* (*M. tb*), is a resurgent and major worldwide health problem. TB was the principal cause of early death in Europe in the 17th and 18th centuries, and was still a greatly feared disease in the 19th and early part of the 20th century (the "white plague"), when there was no active treatment available. Yet by the middle of the 20th century it had essentially disappeared as a health issue in the developed world. This was primarily due to the introduction of an effective combination of the drugs isoniazid, ethambutol (bacterial cell wall synthesis inhibitors), pyrazinamide (energy metabolism inhibitor) and rifampin (bacterial RNA synthesis inhibitor); collectively known as "Rifafour" (Fig. 1).

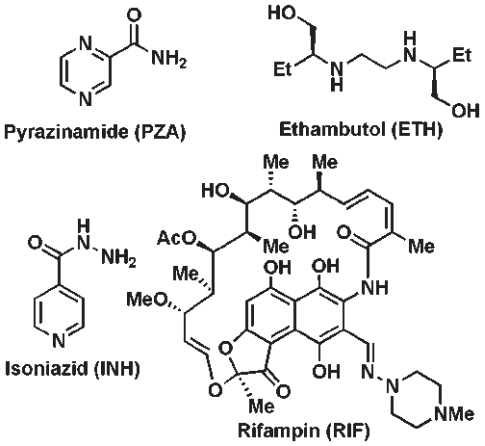


Fig. 1. Structures of the first-line drugs for TB

TB has always been a major disease in the less-developed world, and a major potential global issue, with best estimates suggesting that about 1 person in 3 worldwide carries a dormant infection. The large majority of these, with active immune systems, never develop the active disease. A suggested major factor in the recent resurgence of TB is the spread of HIV, which by weakening the immune system allows reactivation of latent disease. The current TB epidemic peaked in 1990, with an estimated 8 million new cases and 2.9 million deaths from the disease, but remains a major global health problem, with 8.6 million cases and 1.3 million deaths in 2012 (25% of the deaths being among HIV-positive people).[1]

However, a drawback to current treatment is the complex regimen and long duration needed (often more than 12 months), due to the limited activity of the front-line drugs against the "persistent" form of the disease, encapsulated in low-oxygen environments by macrophages.[2] Such treatment times result in levels of incomplete compliance which aids the development of drug resistance. This has given rise to a steep increase in cases of multi-drug resistant TB (MDR-TB; defined as resistance to isoniazid and rifampicin, the two most powerful first-line drugs), which comprised 5.2% of new TB cases in 2012 but nearly 14% of all TB deaths. Worse, in 2012 more than 90 countries reported cases of extensively drug-resistant TB (XDR-TB; resistant to all first-line and to many second-line drugs).[1]

The spectacular success of TB drugs in the 1950s meant that research efforts on improved drugs were not seriously undertaken until quite recently; the "Rifafour" combination remains front-line treatment after more than 50 years. Only recently, sparked off largely by global charities such as the Global Alliance for TB (GATB) and the Gates Foundation, have new drugs for TB started to be approved. Among these have been the nitroimidazole-based bioreductive compounds aimed at the "persistent" form of the disease, focussing on shortening and simplifying treatment, improving compliance and hopefully thus limiting the transition to MDR/XDR.

The nitroimidazole class of TB drugs

Nitroimidazoles such as CGI17341 have long been known to have anti-tubercular activity, but were too mutagenic to use (Fig. 2). The first of the clinically-useful compounds was the nitroimidazooxazine pretomanid (PA-824), initially discovered by the small company Pathogenesis[3] and developed to clinical trial by the GATB. Pretomanid showed substantial *in vitro* and *in vivo* activity against both replicating and non-replicating (low-oxygen) cultures of *M. tb*, while lacking the mutagenic profile of previous simpler and more hydrophilic nitroimidazoles. In a Phase IIA early bactericidal activity (EBA) trial (where a new drug replaces a standard drug in a combination for 14 days), a combination of pretomanid, pyrazinamide and the fluoroquinoline moxifloxacin was particularly effective.[4] It showed the most rapid onset of activity and was clearly superior to the standard Rifafour treatment. This pretomanid combination is currently in Phase III clinical trial.[5] A related compound, the nitroimidazooxazole delamanid, developed by Otsuka Pharmaceutical, has recently gained registration approval from the US Food and Drug Administration for use in TB treatment.[6]

Development of TBA-354

Introduction

Concomitant with their drug pretomanid beginning initial clinical trials in 2005, the GATB considered the development of a second generation analogue, looking for a combination of higher potency, better solubility, longer

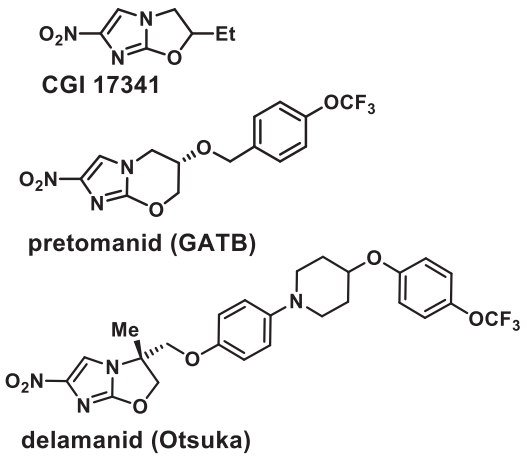


Fig. 2. Structures of nitroimidazole-based drugs for TB

half-life and, ideally, a broader spectrum of action. The Auckland Cancer Society Research Centre at the University of Auckland was selected for this work, due largely to our experience in nitroimidazole chemistry, gained previously in the development of hypoxia-activated bioreductive prodrugs for cancer therapy.

Variation of the nitroimidooxazine chromophore

When this work began, the molecular target of pretomanid was unknown, so we first focused on the nitroimidazooxazine chromophore. From the presence of the nitro group, and earlier work[2] that showed polar metabolites were produced when pretomanid was incubated with *M. tb*, it seemed likely that bioreduction was involved, so we first looked at varying reduction potential by changing the chromophore unit (Fig. 3; chromophore variations). The results showed that very limited alterations to the chromophore were permitted, and no correlation between reduction potential and activity was seen.[7] Furthermore, pulse radiolysis studies indicated that the active compounds (including pretomanid) showed unusual reduction of the imidazole ring in preference to the nitro group.[8]

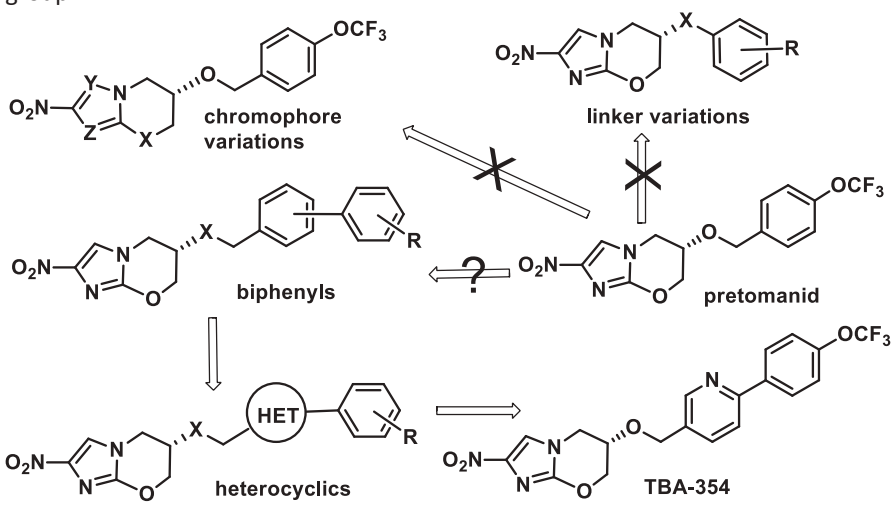


Fig. 3. The development pathway from pretomanid to TBA-354

At about the same time, a US group showed that the major stable metabolite from incubation of pretomanid with its putative *M. tb* target (now known as deazaflavin dinucleotide reductase; Ddn) was the des-nitro compound, which they surmised to be generated by initial reduction of the C2-C3 imidazole bond and hydride transfer to the 3-position to give the unstable intermediate M3, followed by release of nitric oxide (Fig. 4).[9] We later isolated M3 and confirmed its structure.[10]

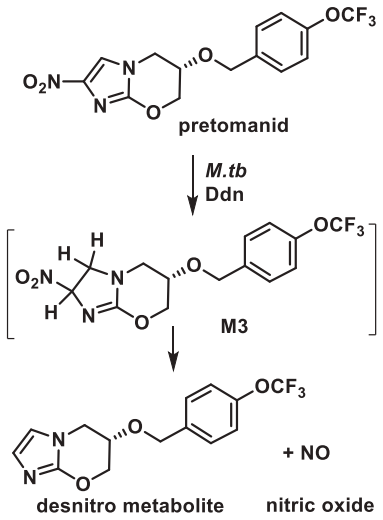


Fig. 4. Bioreductive metabolism of pretomanid

In an extensive study[11] of more lipophilic biphenyl analogues of pretomanid (Fig. 3; biphenyls) we showed that para-linked compounds were the most active, suggesting a reasonably linear and restricted lipophilic binding pocket in the target enzyme. The activity of the compounds (as the minimum inhibitory concentration for 90% inhibition of *M. tb* growth; MIC) correlated positively with overall lipophilicity (clogP) and the electron-donating ability of the R substituents.

Many of the biphenyl compounds also showed good efficacy in a mouse model of acute *M. tb* infection, using a once daily oral dose of 100 mg/kg for 5 days a week for 3 weeks.[11] Activity was measured as the ratio of the fold decrease in colony forming units (CFUs) recovered from the lungs of compound-treated mice compared to the corresponding fold CFU decrease achieved by treatment with pretomanid as internal control. By this measure, many compounds were >200-fold more effective than pretomanid. But with poor aqueous solubility becoming a limitation with the biphenyls, two ways of improving aqueous solubility were explored.

Variation of the side-chain: seeking solubility

One way studied to improve solubility was to replace the OCH_2 linker group with a wide range of more polar and/or more flexible groups, in both the pretomanid and biphenyl series (Fig. 3; linker variations). Previous studies by others on analogues where the benzyl ether linker was replaced by more hydrophilic (but less flexible) urea, carbamate and amide linkers showed these retained good *in vitro* potency,[3] albeit against *M. bovis*, not *M. tb*. We thus looked at

a significant number of new analogues with a wide range of both rigid[12] and flexible[13] linkers, both in the pretomanid and biphenyl series, but while many had excellent *in vitro* potency none approached the high efficacy of the biphenyls *in vivo*.

A second approach to improve solubility was to replace the first phenyl ring of the biphenyls with different 5-membered ring heterocycles, ranging in lipophilicity from thiophenes to tetrazoles (Fig. 3; heterocycles). Several of these series, most notably N-methylimidazoles and1,3,4-oxadiazoles, were substantially more soluble than the biphenyls, and many had comparable MIC values comparable to pretomanid against *M. tb* in culture, but none showed the extensive improvement in efficacy over pretomanid in the *in vivo* mouse assay demonstrated by many of the biphenyls.[14]

Success finally came by replacing one of the phenyl rings with a pyridyl unit.[15] With two rings, as well as the nature of the link between them to study, there were a large number of possible combinations, but it finally emerged that substitution in the first ring, particularly in the 3´-position, gave compounds that were significantly (>100-fold) more effective than pretomanid in reducing lung CFUs in the mouse model, among then TBA-354. The ionisable nitrogen also provided much more soluble compounds. Analogues with a pyridyl terminal ring were less successful and less soluble, the latter because an electron-withdrawing group was needed on this ring, thus lowering the pyridine pKa.

After this work was completed, the crystal structure of the truncated core protein of the target enzyme, *M.tb* Ddn, with the F420 cofactor bound, was published.[16] From this, the authors constructed a model of the putative binding site of pretomanid, locating it near the F420 cofactor binding site, with the nitro group H-bonded to several Ddn residues, which were shown to be important by point mutation studies. This model orients the side chain of pretomanid towards the N-terminus of the enzyme, where there are numerous aromatic residues potentially able to form van der Waal and charge-transfer binding interactions with the drug phenyl or biphenyl rings. This was supported by mutation of one or more of these residues to non-aromatic ones, which resulted in mutant enzymes of lower activity. It is also consistent with the observed structure-activity relationships of this class of drugs, where potency (due to more efficient metabolism by the enzyme?) is enhanced by lipophilic and electron-deficient biphenyl side chains. From this study it is possible to suggest a binding model for TBA-354 where the drug has opportunities for further binding contacts (Fig. 5).

TB-354 emerged as the preferred candidate from a small number of analogues that were extensively evaluated for activity in mouse models of chronic ('persistent") TB, and for pharmacokinetic, genetic and safety profiling. A comparison of TB-354 with pretomanid (Table 1) shows that the former has superior *in vitro* and *in vivo* activity against *M. tb* and appropriate pharmacokinetics, including a 4-fold longer half-life. These properties should have a favourable impact on the cost of goods - an important

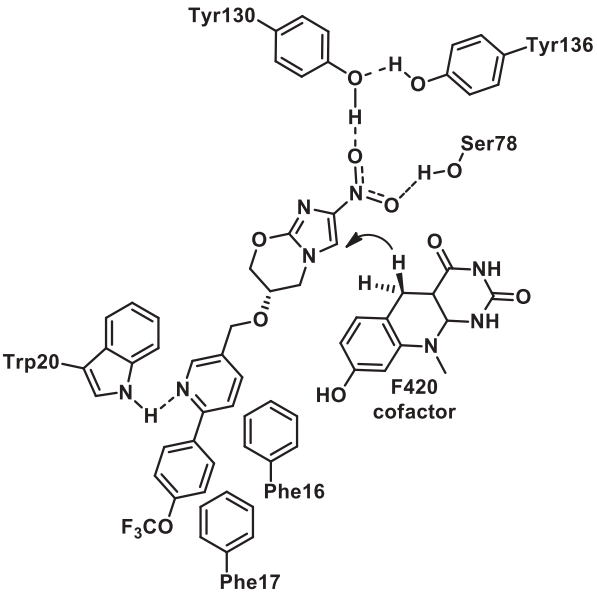


Fig. 5. Suggested binding mode of TBA-354 to Ddn (after Cellitti *et al*.[16])

issue for a drug which, if successful, will primarily be used in less developed countries. Finally, while the primary goal for drugs such as pretomanid and TBA-354 is to shorten initial treatment regimens to minimise non-compliance and the concomitant risk of drug-resistant TB, it is pleasing that both drugs retain activity against clinical isolates of human MDR and XDR TB (with TBA-354 retaining its potency edge) as compared with the front-line drugs rifampin and isoniazid (Table 2).[17]

Table 1. Comparative properties of pretomanid and TBA-354

Property	pretomanid	TBA-354
MW	359.3	436.4
clogP[a] (ACD v12)	2.79	3.49
tPSA[a]	95	107
Sol (μM) pH=2	30	104
Papp A->B[b]	24	24
aerobic MIC (μM)[c]	0.05	0.006
hypoxic MIC (μM)[d]	2.64	0.27
Fold redn CFUs[e]	1.00	>90
Microsome (%)[f]	82	83
HPP binding (%)[g]	81	97
$T_{1/2}$ (h) rat	4.2	24
AUC rat (h*ng/mL)[h]	7159	81266
F (%) rat[i]	81	62
Ames test	negative	negative
hERG (μM)[j]	20	8.2

[a]Calculated with ACD programme (v.12.02); [b]Permeability in a confluent monolayer of Caco-2 human colorectal carcinoma cells (x10^{-6} cm/sec); [c]Aerobic (replicating) *M. tb* assay; [d]Non-replicating *M. tb* assay; [e]Ratio of reduction in *M. tb* colony-forming units compared to pretomanid in a head-to-head study in mice, following drug dosing at 100 mg/kg daily for 15 days. [f]Percent drug remaining after 1 h exposure to human microsomes; [g]Percent binding to human plasma proteins. [h]Under fasting conditions. [i]Oral bioavailability. [j]Inhibition of the hERG potassium ion channel (cause of long QT syndrome)

Table 2. Potency of TBA-354, pretomanid, rifampicin and isoniazid against clinical isolates of human wild-type (WT), multidrug-resistant (MDR) and extensively drug resistant (XDR) *M. tb*

class	MIC (mg/ml)[a]			
	TBA-354	**preto**	**RMP**	**INH**
WT	<0.0063	0.042	0.033	0.047
MDR	0.016	0.25	10	4.77
XDR	<0.0075	0.14	>20	>1.25
XDR	0.015	0.25	>20	>20
XDR	0.013	0.21	>20	>20
XDR	0.015	0.21	>20	>20

[a]Data from ref. 17.

Summary

This research programme arose from a rather speculative offer to the GATB from the ACSRC to help with their PA-824 second generation development programme because of our expertise in nitroimidazole chemistry. A small part in the programme quickly morphed into our undertaking the entire drug design and synthesis role. Initial work on the chromophore showed that it was already optimal, and that activity depended on the initial site of reduction, contributing to an understanding of the mechanism of action. Increased potency (and insolubility) was seen with biphenyl analogues, and the rest of the programme really focused around solving the solubility problem. A number of approaches were explored, with the successful one being the introduction of an appropriate pyridyl unit in the side chain. Despite the lack of information at the start of the work about either a molecular target or a mechanism, the programme was able to recommend a clinical candidate in four years, although it took a few more years for the validation, safety and regulatory work to be completed (Table 3). We are extremely pleased that TBA-354 has recently been approved by the US Federal Drug Administration for clinical trial.

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To all the staff and students in the ACSRC and the Dept of Molecular Medicine & Pathology who contributed to this work; chemistry leader Associate Professor Brian Palmer, chemists Associate Professor Bob Anderson, Drs Adrian Blaser, Iveta Kmentova, Sujata Shinde, Hamish Sutherland, Andrew Thompson, pharmacologist Associate Professor Nuala Helsby, and students Mridula Dogra and Andreij Maroz. Primary screening against *M. tb* in culture was carried out in Professor Scott Franzblau's laboratory in the Institute for Tuberculosis Research, University of Illinois at Chicago. Funding for the programme was provided by the Global Alliance for Tuberculosis Drug Development, New York.

References

1. WHO global TB report 2013 (p ix) (http://www.who.int/tb/publications/global_report/en)
2. Stewart, G.R.; Robertson, B.D.; Young, D.B. *Nat. Rev. Microbiol*. **2003**, *1*, 97-105.
3. Stover, C.K.; Warrener, P.; VanDevanter, D.R.; Sherman, D.R.; Arain, T.M.; Langhorne, M.H.; Anderson, S.W.; Towell, J.A.; Yuan, Y.; McMurray, D.N.; Kreiswirth, B.N.; Barry, C.E.; Baker, W.R. *Nature* **2000**, *405*(*6789*), 962-966.
4. Diacon A.H.; Dawson R.; von Groote-Bidlingmaier F.; Symons, G.; Venter, A.; Donald, P.R.; van Niekerk, C.; Everitt, D.; Winter, H.; Becker, P.; Mendel, C.M.; Spigelman, M.K. *Lancet* **2012**, *380*(*9846*), 986-993.
5. Global Alliance for TB website (portfolio) (http://www.tballiance.org/portfolio).
6. Ryan, N.J.; Lo, J.H. *Drugs* **2014**, *74*, 1041-1045.
7. Thompson, A.M.; Blaser, A.; Anderson, R.F.; Shinde, S.S.; Franzblau, S.G.; Ma, Z.; Denny, W.A., Palmer, B.D. *J. Med. Chem*. **2009**, *52*, 637-645.
8. Anderson, R.F.; Shinde, S.S.; Maroz, A.; Boyd, M.; Palmer, B.D.; Denny, W.A. *Org. Biomol. Chem*. **2008**, *6*, 1973-1980.
9. Singh, R.; Manjunatha, U.; Boshoff, H. I. M.; Ha, Y. H.; Niyomrattanakit, P.; Ledwidge, R.; Dowd, C. S.; Lee, I. Y.; Kim, P.; Zhang, L.; Kang, S.; Keller, T. H.; Jiricek, J.; Barry, C. E. *Science* **2008**, *322*, 1392-1395.

Continued page 29

Table 3. Timeline for the development of TBA-354

Date	Event
mid-2005	First clinical trial of pretomanid (PA-824) by GATB. ACSRC wins one of the contracts to develop a second generation analogue
2006	ACSRC takes over the entire second generation medchem programme
2008	Independent papers from ACSRC and the US National Institute of Allergy and Infectious Diseases (refs 8 and 9) help define the mechanism of pretomanid
2009	Selection of SN 31354 as the preferred second generation clinical candidate; renamed TBA-354
Oct 2011	TBA-354 endorsed by international committee to proceed to IND filing
Sept 2012	First public disclosure of TBA-354 (symposium at the 52nd Interscience Conference on Antimicrobial Agents & Chemotherapy (ICAAC) in San Francisco
2014	Phase III trial of pretomanid/moxifloxacin/pyrazinamide combination begins
Sept 2014	US FDA approves the IND for TBA-354 to proceed to clinical trial
Late 2014	First clinical trial of TBA-354 expected to begin

Article

To RGB and beyond – not just a toy story

Adapting mobile imaging devices for chemical applications

Gordon M. Miskelly* and Jacob W. Martin

School of Chemical Sciences, University of Auckland, Private Bag 92019, Auckland 1142
(email: *g.miskelly@auckland.ac.nz*)

Keywords: *cellphone spectrometers*, *hyperspectral imaging*, *spectrophotometry*, *3D printing*

Abstract

The overlap in time of removable optical storage technologies (CDs and DVDs) and powerful personal electronic devices (ubiquitous smartphones with good quality cameras and readily available Apps) has created an opportunity for the widespread adoption of low-cost spectrophotometers. While such devices have been possible for decades, the barrier to implementation in teaching and research has never been lower. This article discusses current and future applications of consumer imaging devices in the chemical sciences, including how schools might take advantage of this accessible scientific instrumentation.

Introduction

Digital technology is changing the way we access and sense the world, whether it is the impact of Sony then Apple on music, Pixar Studios and Weta Workshop on film, or Adobe on the written word. Of most relevance to this article is the recent transition from film and traditional video to digital media, and the continuing evolution from standalone digital cameras to cameras within smartphones, to Google Glass, or similar personal electronic devices. Scientists are now thinking about how to leverage some of these technologies in teaching and research, and how to move from warnings saying "All cellphones must be switched off before entering this laboratory" to texts asking students to download the latest App before their next experimental session.

Scientists have been using electronic imaging devices for a long time: even if we only consider digital cameras these were developed in the 1960s and became widely available for space applications from the 1980s and microscopy from the 1990s. Many of the descendents of these cameras in current use might be laughed at by consumers, noting that they only have (for example) 1-4 million camera pixels. However, such cameras often have superior sensitivity to low light, lower noise levels, higher dynamic range, and faster "shutter speeds" (frame rates) than consumer cameras. Many of these scientific or machine vision cameras also are monochrome, because colour information is not needed or can be obtained by alternative means to that used by most consumer colour cameras. A consequence of the specialty nature and small size of the scientific market is that many of these cameras are expensive compared to a moderately equivalent consumer camera.

The recent large expansion in digital imaging has been driven by the high volume, competitive consumer electronics market in digital cameras and more significantly smartphones, tablets, and related devices. While there are compromises inherent in photography with smartphone cameras due to factors including their small sensors and lenses, their ubiquitous presence (most readers of this article probably have at least one digital imager with them most of the time) requires that we consider how we can best utilise such devices. The presence of additional sensors such as microphones, accelerometers and GPS increases the potential applications of smartphones.

The idea of using colour digital cameras in chemical applications is not new, but the ready availability of appropriate low-cost accessible cameras and accessories such as LEDs and diffraction gratings, together with suitable image acquisition and analysis software means that this technology can now move from being accessible only to specialists to having a much wider user base. This article gives selected references and website links to low-cost complete systems available either from websites or from commercial companies. The companies and websites chosen are indicative of the resources available, and do not represent endorsements of the companies, organisations, or individuals involved. A few of the cited websites recommend removing filters from cameras or altering the firmware in cameras. Since such procedures could void camera warranties, readers should use discretion when deciding whether to follow such procedures.

From RGB to spectral imaging

Digital color imaging has many associated terms and acronyms. Inside a digital camera is a chip (image sensor) with an array of light-sensitive regions that we will refer to as camera pixels. Each of these camera pixels initially provides a signal proportional to the intensity of light / number of photons of visible light which fall on it during the selected exposure period. There are two competing technologies for camera sensors (charged-coupled devices (CCDs) and complementary oxide semiconductor (CMOS) devices), although almost all modern small consumer electronic devices contain CMOS sensors. Most colour cameras in consumer devices have an array of filters (usually in a Bayer pattern, Fig. 1a) in front of the image sensor, so that each individual camera pixel only sees light corresponding to the red, green, or blue region of the visible spectrum, hence the descriptor "RGB imaging". The Bayer pattern results in twice as many green camera pixels as red or blue, to match the

relative sensitivity of the human eye. The "raw, unprocessed" image from a camera sensor with a Bayer filter array looks somewhat like a grey checkerboard or piece of grey tartan cloth, Fig. 1b. Lower priced consumer cameras usually only give you access to processed images, although some groups have developed approaches that can allow access to the raw images for some cameras, such as the chdk toolkit for Canon cameras.[1] On some higher-level consumer cameras it is possible to save this raw unprocessed image (CR2 and NEF files for Canon and Nikon respectively) and process it yourself. This processing can be within a programme designed primarily for photographers (e.g Adobe Photoshop) or using scientific software (e.g. the commercial software program Matlab (www.mathworks.com.au) or the open source ImageJ (imagej.nih.gov/ij/)). One of the earliest (first published in 1992) and best known books on using digital cameras for scientific purposes is The Imaging Handbook by John Russ [2] – indeed it guided our first forays into this field. A good tutorial on the many processes required to take a raw image to a viewable image using Matlab is available on the internet.[3] These processes include the following: the relative responses of all the red and blue pixels with respect to the green pixels can be adjusted ("white balance"), the overall brightness and the relationship between the original camera pixel brightnesses and the pixel brightnesses to be saved or displayed can be altered ("brightness", "levels", "curves" "gamma corrections" etc.) and, perhaps most importantly the image information has to be interpolated so that there is red, green and blue information corresponding to every camera pixel position. The simplest interpolation would just use the surrounding pixels of a given colour (say red) to estimate the red value at one of the green camera pixels. However, this can lead to undesirable geometric effects (including Moire patterns) and poor image quality as discerned by the human eye. Interpolation algorithms implemented in consumer cameras combine information from different colours, based on (for example) the fact that hue does not usually vary suddenly in a natural image. While the interpolation algorithms embedded in cameras or photographic software work well for most scenes the general public would photograph, they can result in artefacts when used for laboratory experiments. For example, if we shine only green light on a substrate and look for orange or red fluorescence using a cut-off filter that only allows light of wavelengths longer than that corresponding to green to pass there should be little or no information in the blue channel (ignoring the low sensitivity of the blue channel to other wavelengths). However, some interpolation algorithms in consumer cameras will result in apparent information appearing in the blue channel.

Unmodified colour digital cameras have been used to acquire information from chemical systems, including studies of changes in hue as liquid crystals respond to temperature,[4, 5] using a function related to hue to monitor degradation of photonic crystals,[6] and using the colour response for quantitative chemical analysis.[7] There are also reports of smartphone use in forensic science for monitoring of illicit drugs.[8]

Illumination

A key component of any imaging system, yet one that is frequently ignored by those entering the scientific imaging field, is the illumination. In two of the early areas of scientific digital imaging the illumination was reasonably well-controlled: a microscope would have one or more well-defined illumination systems, while satellite imagers rely on sunlight, which has a well-defined spectral distribution with well characterised variations due to such factors as atmospheric absorption. When imaging is performed on "intermediate" scales (i.e. mm – 100 m) we have to consider the illumination explicitly – and be aware that our eyes cannot provide adequate information about the illumination. A good example of these considerations is that while we perceive the colour of white paper to be the same indoors under an incandescent lamp or outdoors, a film photograph that was taken inside under a tungsten (incandescent) light often has an orange cast since most film was optimized for images taken outdoors. Digital cameras have a manual or automatic system which tries to adjust for the temperature of a broadband illuminant, where the automatic system usually relies on there being a significant portion of the image that is close to a neutral grey. However, many light sources have more spectral structure than this: for example a fluorescent light will typically have very intense narrow spectral bands of red and green, and broader less-intense components in other spectral regions, while "white" LEDs will often have a sharp intense band in the blue and a broad emission over the red-green part of the spectrum. While the human eye will rapidly adjust to compensate for differences in illumination, the camera system is not as adept. It is therefore very important to choose an appropriate illumination and use it consistently in measurements. If a camera has manual white balance setting these can aid in consistency for scientific imaging. Automatic white balancing can cause significant problems in scientific imaging if a large portion of the image is a single colour or a large portion of the image changes colour since the camera will automatically adjust the image white balance. Most digital cameras will automatically adjust for the brightness of the scene, although some cameras also allow manual exposure control. Again, this autoexposure usually works well for typical consumer images but can cause problems in some scientific applications – such as trying to photograph small regions of light (such as spectra) in an otherwise dark image. These problems are alluded to in the some of the literature describing use of consumer cameras for scientific applications,[9] but appear to be overlooked by many authors.

Moving beyond RGB

There are a couple of "next steps" beyond RGB imaging using consumer cameras. One is near-infrared imaging, which involves removing the infrared filter permanently fixed in front of most color camera sensors and then placing a long-pass filter that blocks visible light in front of the camera lens. While some user groups are interested just in imaging in the near-infrared, others are trying additional processing such as mimicking the normalised differential vegetation-index (NDVI) imaging made available

by satellites such as LANDSAT for monitoring plant health by removing the infra-red blocking filter and replacing it with a red-blocking filter.[10, 11] Another possibility is to develop multispectral imaging within the visible region but not just constrained to the standard red, green, and blue of a commercial camera. Instead, custom regions of the visible wavelength range are imaged and processed together. This might be done by placing filters in front of the camera, by using spectrally filtered light sources, or a combination of both. Another partial approach is to use the light output from an LED computer screen as a light source, since the red, green, and blue diodes have narrower spectral bands than the RGB filters on a typical camera.[12]

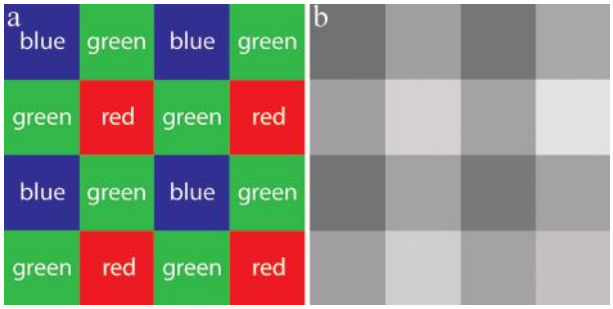

Fig. 1. (a) Diagram showing the layout of red, green, and blue-sensitive pixels in a Bayer pattern. (b) Greyscale image showing the light brightness detected by the camera pixels corresponding to the Bayer pattern shown in (a) when imaging a yellow/orange object.

Our interest in multispectral scientific imaging with consumer cameras started with the MSc (Forensic Science) studies of John Wagner in 2000, which coincided with Canon's release of the first "prosumer" digital SLR camera, the D30. This was a moderate cost CMOS camera that could be equipped with high quality lenses, and we decided to study whether multispectral imaging could add information for a forensic scientist. We started by looking for traces of blood, using the Soret absorption of hemoglobin which lies in the far violet part of the spectrum (around 410-420 nm). Unlike the absorption bands of most coloured items in our everyday lives, this Soret absorption is quite narrow. We therefore took photographs of bloodstains using three narrow-band filters in front of the camera lens: one matching the wavelength of the Soret absorption band and two others that bracketed this wavelength. The difference between the image taken centred on the Soret band and the average of the images obtained with the bracketing images was then calculated. This processing enhanced any blood in the image while suppressing the effect of different brightness (or shading) and common coloration. [13, 14] This bracketing approach gave the best selectivity, discriminating blood from the background. However, since the shortest wavelength imaging was problematic (see below) in later studies we only used a longer wavelength image (ca 440 nm) together with an image at the Soret wavelength, with results as shown in Fig. 2. The success of this approach led us to apply this imaging technique to forensic evidence that had been chemically enhanced.[15] While this imaging sounds simple, we struck many problems along the way, many of which are of relevance to new chemical applications with digital cameras. A significant problem for us was changes in the intensity of our light source and the sensitivity of the camera with wavelength. The sensitivity of a consumer digital camera drops rapidly as the spectral region of interest moves towards the ultraviolet, and usually also when it moves into the deep red / infrared. Indeed, as noted above most consumer colour cameras have an infrared cut-off filter permanently fixed in front of the sensor. Also, even though we were using a specialty forensic light source (Rofin Polilight) with increased intensity in the blue compared to most common light sources, its intensity still dropped by over a factor of 10 moving towards the ultraviolet across the range of wavelengths we were using to bracket the Soret absorption. The net result was that for our three images to have similar aver-

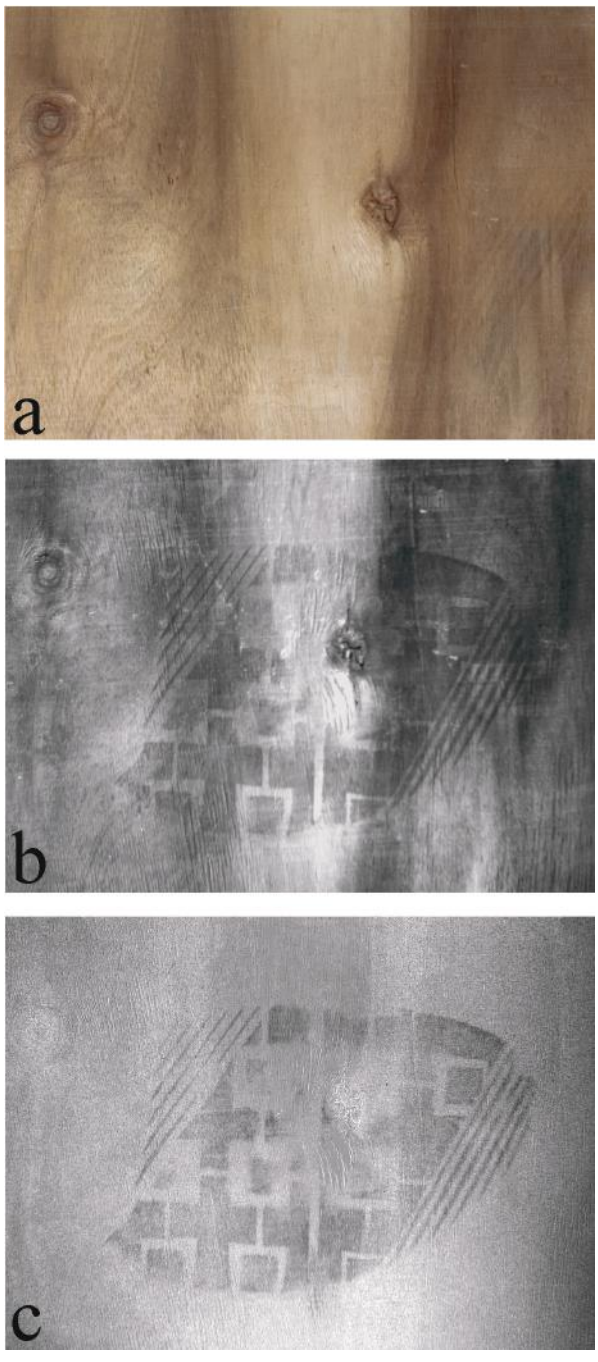

Fig. 2. (a) Colour photograph of a shoe mark in 50-fold diluted blood on a piece of wood. (b) Image of the shoe mark taken with a 415 nm filter. (c) Ratio of the image taken with a 415 nm filter to one taken with a 440 nm filter. Note: image (a) was taken with a different camera and is slightly displaced from the other two images.

age brightness values the exposure times for the images differed by a factor of 100. This prevented the technique being adapted to a hand-held instrument. About 4 years later we tried a different approach to blood imaging, this time using a light source containing multiple LEDs with peak emissions at 435 and 420 nm, together with an imager that consisted of two scientific-grade monochrome cameras, each with a bandpass filter in front, viewing the scene through a beamsplitter. This came closer to the concept of a handheld imager, but was expensive and impractical due to its slow imaging and weight.[16, 17] Improvements in LED brightness and small cameras since that time mean that this concept could be revisited. The blood imaging approaches had additional problems in that the filters placed in front of the camera(s) slightly distorted and/or displaced the image, so that the images had to be "registered" prior to the pixel arithmetic. This presents challenges for real-time analysis using the limited computing power and memory capacity that might be found in a smartphone.

Hyperspectral measurements with consumer cameras

Hyperspectral approaches measure light from many different regions of the visible spectrum. This article divides these hyperspectral approaches into two: (a) methods where no spatial information is obtained in each image, and (b) methods where both spatial and spectral information is obtained. While the term "hyperspectral" is almost always used in conjunction with "imaging" (i.e. case (b)), we are broadening the use of the term to include case (a) (which would more typically be called spectrophotometry).

Spectrophotometer or spectrograph?

Several independent reports describe turning smartphones into devices with capabilities similar to those of a recording spectrophotometer, with the provided references representing an early report, an integrated system, and a publicly-available device.[9, 18-20] Strictly speaking, these are all digital imaging spectrographs, since spectral information is dispersed using a grating, and then this dispersed light is detected by a camera or camera sensor (i.e. without a lens). However, since their function is designed to replicate that of a laboratory spectrophotometer, and "spectrophotometer" is how they are referred to in much of the literature, we will use this term for these devices. The published approaches range from modified cardboard boxes and videotape boxes to custom-made iPhone adapters. The dispersion element may be a purchased transmission diffraction grating or a portion of a CD-R or DVD-R in reflection or transmission modes. Scheeline wrote one of the first scientific articles describing cellphone-based spectrophotometers, describing both the construction of the physical device and giving links to a simple computer program that could analyse the acquired images.[18] Devices similar to those reported by Scheeline are now available on-line (with video tutorials) from Public Lab, with an open source App.[20] It should be noted that Scheeline has moved beyond this simple approach, and has a company called Spectroclick that is developing a more sophisticated device that used second and higher order diffractions from several diffraction gratings.[21] This approach is designed to mitigate one of the drawbacks of smartphone-based spectrophotometers which is their limited dynamic range, so that part of the spectrum might be saturated (overexposed) while other parts are too underexposed to obtain useful information. A further issue with simple approaches to constructing spectrophotometers is the lack of physical rigidity and reproducible positioning of the components. A promising approach to solve this problem is to 3D print the spectrophotometer housing with fixed positions for the camera, slit, and grating.

The integrated iPhone spectrophotometer device reported by Smith et al.[19] has been developed further by Cunningham et al., with their main aim being developing methods to monitor subtle changes in reflectance from a photonic crystal as a function of exposure to biomolecules or other analytes.[22] This device includes a light source and diffraction grating within a wedge-shaped body that clamps on a smartphone.

Cellphone spectrophotometers in the classroom

The University of Auckland's ultra-fast laser facility, the Photon Factory, recently hosted a group of students from Onehunga High School to learn about spectrographs as well as make their own cellphone spectrophotometer. Providing students with access to such simple spectroscopic devices gives them greater opportunities to explore analytical chemistry when they return to the classroom. A week before the students visited, project information was published on an online blog (http://nznano.blogspot.co.nz/2014/06/onehunga-high-school-visit-to-photon.html) including relevant videos and links for ideas and explanations of spectrograph design and construction. During the visit, the students spent the morning designing the spectrograph layout and used the internet to research the specifications of their final cell phone spectrophotometer design. The housing for the spectrograph was then printed on a Felix 3.0 3D printer, (printing time ca. 1 h) using a design the students prepared using FreeCAD (an open source computer-aided design package (http://www.freecadweb.org/). The entrance slit for the spectrograph was made by cutting a fine slit in a piece of Al foil and hot-gluing the foil to the front of the housing. A DVD was cleaved in half and a square of the resulting transmission grating was glued on the exit of the housing. Fig. 3 shows the steps involved and the resulting spectrograph. The spectrograph was designed to be integrated with the camera found on the current models of smartphone to form the complete spectrophotometer. Thus, the camera lens assembly was placed in contact with the spectrograph's grating and the spectrograph slit was pointed at a light source. The students then investigated the spectra of different light sources in the room (an LED, an incandescent bulb, and a fluorescent light), Fig. 4. The intention is that the cellphone spectrophotometer they made will be used in school science fair projects, with possibilities including algal growth monitoring in the Manukau Harbour, nitrate/nitrite and ammonia testing of stormwater, and infrared imaging of plant health.

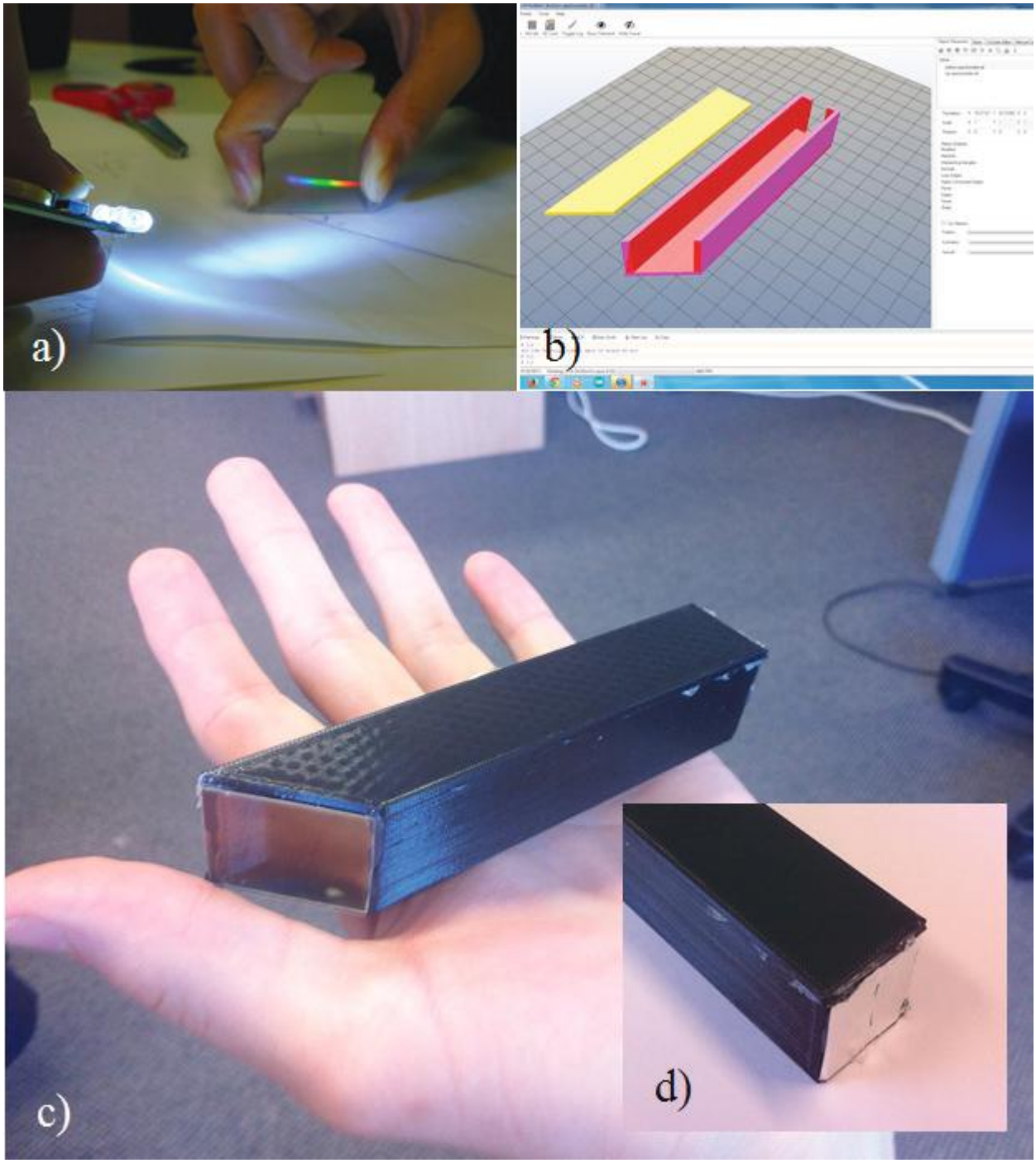

Fig. 3. Construction of a 3D printed spectrograph. (a) Determining the required geometry using an LED and a DVD diffraction grating. (b) Designing the housing. (c) The completed design showing the diffraction grating glued in place. (d) The Al foil with slit at the front of the spectrograph.

The Photon Factory is planning to produce kits to enable production of 3D printed cellphone spectrophotometers for the United Nations 2015 Year of Light, and these will be sent to participating New Zealand schools. These kits will include a spectrograph like the one shown in Fig. 3 and a spectrophotometer using an LED and light-dependent resistor. Instructions and files for 3D printed spectrographs are already available online (https://www.thingiverse.com/thing:537293/). Many schools have 3D printers and would be able to make their own model or New Zealand companies exist that can print the design for a small fee.

As an alternative approach to the spectrophotometer-based-on-a-student's-phone model, companies such as RSpec supply all-in-one systems consisting of integral units with consumer-grade camera and diffraction grating together with computer software, for classroom demonstrations.[23]

Imaging spectrophotometers

Devices that can collect both spatial and spectral information in the visible region are referred to as imaging spectrophotometers or hyperspectral imagers. They can have multiple designs, but three of the most common are (i) whisk-broom (or spot measurement), where a complete spectrum is measured at a single point, and the sensing device is swept in the x and y dimensions relative to the

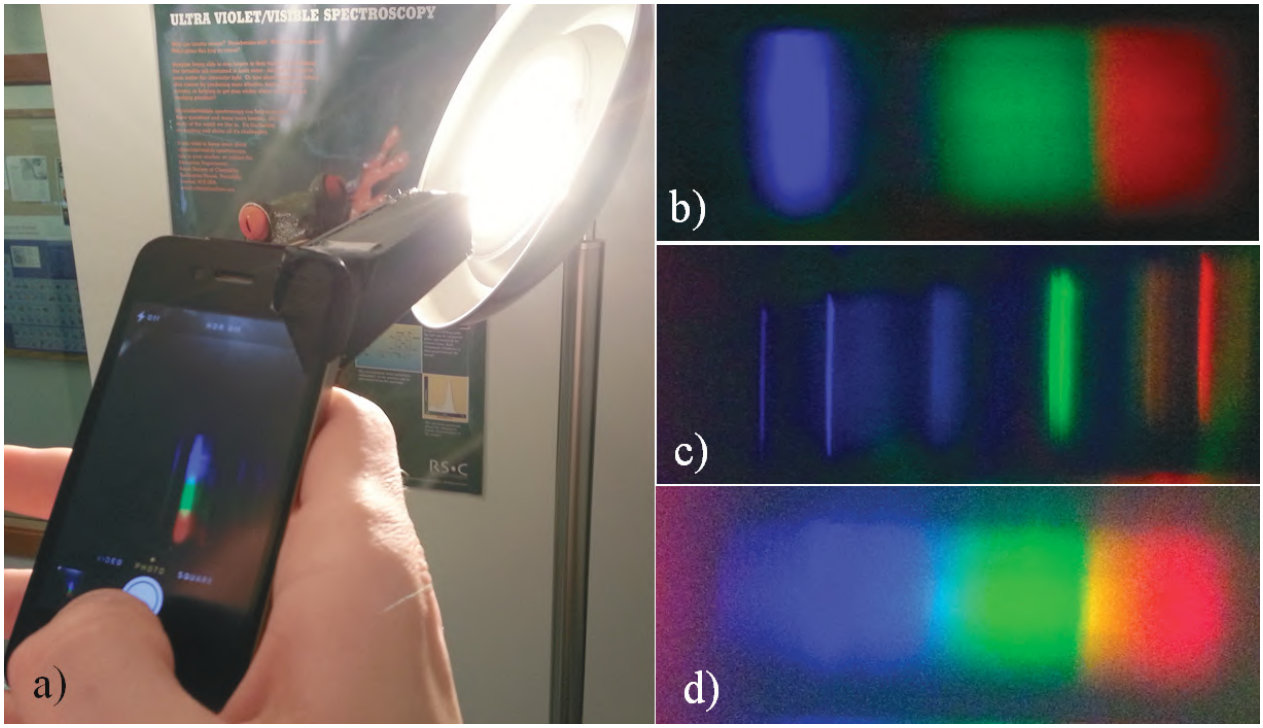

Fig. 4. Collection of spectra using the 3D printed spectrograph and an Apple iPhone. (a) Collecting a spectrum from an incandescent bulb. (b) Spectrum from a "white" LED. (c) Line spectrum from fluorescent lamp. (d) Broadband spectrum from incandescent bulb.

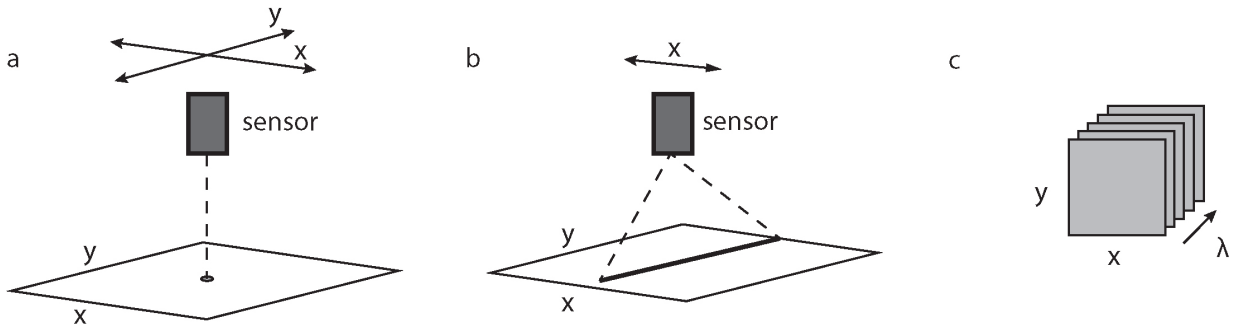

Fig. 5. (a) Diagram showing the operation of a whisk-broom hyperspectral imager. (b) Diagram showing the operation of a push-broom (line-scan) spectral imager. (c) Schematic representation of an image cube.

object of interest (Fig. 5a) (ii) push-broom (or line-scan), where a complete spectrum is measured at many positions along a line (say, the y-axis), then the position is scanned along the x axis (Fig. 5b) and (iii) frame devices, where standard grey-scale images are obtained at a range of wavelengths. All of these devices take time to build up a complete spatial-spectral image (the three-dimensional record of x spatial dimension – y spatial dimension – spectral dimension is called an image cube, Fig. 5c), which can cause problems if objects in the images are changing and/or moving unpredictably. There are alternative imager designs that can obtain all the information in an image cube in a single exposure.[24, 25] The School of Chemical Sciences at the University of Auckland has whisk-broom imaging capability for characterising small objects in the infrared spectral region and for imaging Raman spectroscopy. Most visible imaging spectrophotometers, however, use the push-broom or frame approach. A push-broom imager is particularly useful where there is uniform relative motion of the camera relative to the scene – for example satellite and airborne imaging of the earth and monitoring of items moving along a conveyer belt. Frame imaging devices allow ready adaptation of standard cameras, and do not require a method to scan the imager relative to the scene. Selection of spectral regions for frame images could be by using a series of narrow band filters which are sequentially placed in front of the camera or by using an electronically-controlled device such as a liquid-crystal tunable filter (LCTF) or acousto-optical tunable filter (AOTF). These latter devices cost in excess of $10 000 NZD, but allow selection of (say) 10 nm portions of both the visible and near-infrared spectrum.

A relatively cheap line-scan imaging spectrophotometer can be constructed using a benchtop spectroscope such as that sold by Paton Hawksley Education Ltd. (http://www.patonhawksley.co.uk/spectroscope.html) This design was first reported by Sigernes,[26-28] and we have constructed one and now use it for scientific imaging,[29] while a related low-cost design has been reported recently.[30] The Sigernes design is similar to the spectrophotometers described in the previous section, except an additional lens assembly is used to focus the scene onto the entrance slit to the spectroscope. The camera with a lens to focus the spectral information is placed at the exit of

the spectroscope. An optical arrangement slightly more complex than a simple diffraction grating is required to obtain a suitable image, and the Paton Hawksley spectroscope has a plano-convex collimation lens and a grism - a combination of grating and prism – within its body. The dispersion of light from this spectroscope is almost linear with wavelength. The complete device provides very good line scan hyperspectral images, with the main disadvantage being that it has low light throughput, so that bright illumination or long exposure times are required. For some applications this imager provides more useful information than the much more expensive LCTF-based devices in our laboratory, since it has a spectral resolution on the order of 2 nm so can, for example measure interference spectra that would be averaged out by the wider (10 nm) bandpass of our LCTF. While low-cost hyperspectral imagers are now available, they need the development of readily available, user-friendly software before they become more widely used. They also require calibration for wavelength, brightness and distance and can generate very large data files.

Imaging spectrophotometry in amateur astronomy

Simple diffraction systems and consumer cameras have also been revolutionising amateur astronomy and, in particular, astrophotography. Comparatively low-cost transmission gratings are allowing hobbyists to make spectral measurements of stars, planets and galaxies, and there is also low-cost software that automates spectral interpretation. Since stars are point sources, spectral information can frequently be acquired with simple diffraction gratings without the requirement for slits or pinholes. Three representative websites are given to provide an idea of the activity in this area: http://www.skyandtelescope.com/get-involved/pro-am-collaboration/the-revival-of-amateur-spectroscopy/, http://mo-astro.com/Spectroscopy.aspx, http://www.rspec-astro.com/star-analyser/.

Citizen science and real-world applications

The Whitesides group has championed the idea of using simple chemical analysis devices together with camera phones to perform telemedicine, where results could be relayed to a remote expert.[31] Their papers include the concept of μPADs (microfluidic paper-based analytical devices) – making low-cost chemical diagnostic devices that could then be imaged and interpreted.[32] These papers have generated a large amount of interest in the scientific community, with the initial paper cited over 400 times.

An example of the next step beyond individual imaging devices is the iSpex device from the Netherlands, which is designed as a citizen science project to monitor dust in the atmosphere via polarisation methods.[33] The iSpex adaptor slides over the iPhone camera, and then images are taken of different points in the sky. At each point in the sky, spectral / polarisation information is obtained. The smart phone is able to record both the position and orientation of the camera when each image is taken, and this information is then relayed back to the researchers so that they can evaluate which part of the sky has just been imaged, when in the day (to determine the relative position of the sun) and from which direction. The data from all the iSpex users can be combined to create a map of atmospheric dust.

There are further examples of citizen science. The Gulf of Mexico oil spill resulted in the formation of an online community who developed simple fluorimeters to monitor oil and NDVI imagers to monitor plant health, and who now provide designs for several instruments on the Public Lab website.[10, 20] Aircasting (aircasting.org) has published instructions allowing interested members of the public to build an air quality monitoring system (analysing for NO_2, CO, and particulates) for a few hundred dollars, with the information being mapped using the GPS capability of a linked smartphone. An alternative model to these citizen-initiated approaches is the development of a smartphone-based monitoring program for threat agents (such as chemical or biological agents), where the smartphone would have a built in sensor and could automatically report the presence of a threat agent to a central authority. The US Department of Homeland Security investigated such a possibility in the Cell-All program in 2010-2012,[34] although it should be noted that some authors have criticised this approach to smartphone-based sensing.[35]

Possibilities for the future

We are not convinced that it is appropriate to take the expensive smartphone that students will be texting on while eating lunch, and couple it into an experimental device where they might be analysing chemical or biological materials. In that respect, the introduction of personal smartphones into the traditional laboratory as components of individual instruments needs careful thought. Scheeline's approach has been to use the cell phone spectrophotometer as a device to teach students about spectroscopy and data analysis, which does not require significant exposure of the smartphone to hazardous substances.[9,18] Outside of the laboratory, smartphone-based imaging devices should revolutionise field measurements such as monitoring stream water quality, and such initiatives are already underway. Plug-in pH analysers are available (e.g. from Sensorex, www.sensorex.com), as an alternative to photographing pH or other test strips (e.g. using the App from Colorimetrix, www.colorimetrix.com). Other research groups are developing electrochemical sensors that could be controlled by a smartphone and could be linked with electrochemiluminescence measurements,[36] while thermal imaging accessories for smartphones are commercially available (http://flir.com/flirone/explore.cfm). All of these developments increase the potential uses of smartphones as scientific instruments.

One possibility for laboratory use is to make greater use of Bluetooth-enabled or IP connected cameras separate from the smartphone, so that the familiarity, computing power and intercommunication capability of the smartphone is retained but the smartphone is spatially separated from the biological material or chemical reagents. A current problem with this approach is that separate cameras are more of a specialty item and so are com-

paratively expensive compared to the camera already present on a student's smartphone. This may change if remotely connected cameras continue to gain market share in applications such as car reversing cameras, or baby and pet monitors.

Smartphone-based spectrophotometers are now at the stage where they could readily be constructed and used for science fair projects, in classrooms, and for NCEA extended practical investigations. Imaging spectrophotometers are more challenging to construct and use at this time, but two low-cost approaches have been reported. The applications of spectrophotometers and other devices mentioned in this article for monitoring water quality, air quality, plant health, and preventative health monitoring are being actively investigated, and it is clear that they also offer potential solutions to New Zealand-focussed issues.

Acknowledgements

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References

1. Anon., http://chdk.wikia.com/wiki/CHDK (accessed 8 Nov 2014).
2. Russ, J.C. *The Image Processing Handbook*, 6th edn., CRC Press, Boca Raton, 2011.
3. Sumner, R., Processing RAW images in MATLAB, 2013, http://users.soe.ucsc.edu/~rcsumner/rawguide/index.html (accessed Nov 8 2014).
4. Anderson, M.R.; Baughn. J.W. *J. Heat Transfer* **2005**, *127*, 588-596.
5. Wiberg R.; Lior. N. *Rev. Sci. Instrum.* **2004**, *75*, 2985-2994.
6. Ariza-Avidad, M.; Nieto, A.; Salinas-Castillo, A.; Capitan-Vallvey, L.F.; Miskelly, G.M.; Sailor, M.J. *Nanoscale Res. Lett.* **2014**, *9*, 410.
7. Zamora, L.L.; López, P.A.; Fos, G.M.A.; Algarra, R.M.; Romero, A.M.M.; Calatayud, J.M. *Talanta* **2011**, *83*, 1575-1579.
8. Choodum, A.; Kanatharana, P.; Wongniramaikul, W.; Daeid, N.N. *Talanta* **2013**, *115*, 143-149.
9. Scheeline, A. *Appl. Spectrosc.* **2010**, *64*, 256A-268A.
10. Anon., Infragram, http://www.publiclab.org/wiki/infragram (accessed Nov 8 2014).
11. Ulman, U.; Janky, J.M. Cell Phone NVDI Sensor, *USA Pat.* 13/749,587, 2012.
12. Hsieh K.-T.; Urban, P.L. *RSC Advances* **2014**, *4*, 31094-31100.
13. Wagner, J; Miskelly, G. *J. Forens. Sci.* **2003**, *48*, 593-602.
14. Wagner, J; Miskelly, G. *J. Forens. Sci.* **2003**, *48*, 604-613.
15. Miskelly, G.; Wagner, J. *Forens. Sci. Int.* **2005**, *155*, 112-118.
16. Miskelly G.; Wagner, J. Image and Vision Computing New Zealand 2006, Great Barrier Island, NZ, 2006.
17. Wagner, J. PhD thesis, University of Auckland, 2008.
18. Scheeline, A.; Kelley, K. in http://www.asdlib.org/onlineArticles/elabware/Scheeline_Kelly_Spectrophotometer/Cell Phone Spectrometer Paper.pdf (accessed Nov 8 2014).
19. Smith, Z.J.; Chu, K.; Espenson, A.R.; Rahimzadeh, M.; Gryshuk, A.; Molinaro, M.; Dwyre, D.M.; Lane, S.; Matthews D.; Wachsmann-Hogiu, S. *PLoS ONE* **2011**, *6*, e17150.
20. Anon., Spectrometer, http://publiclab.org/wiki/spectrometer (accessed 8 Nov 2014).
21. Scheeline, A.; Thu, B.A.; Energy Dispersive Device, *USA Pat.* US 2013/0093936, 2012.
22. Gallegos, D.; Long, K.D.; Yu, H.; Clark, P.P.; Lin, Y.; George, S.; Nath P.; Cunningham, B.T. *Lab Chip* **2013**, *13*, 2124-2132.
23. Anon., RSpec-Explorer real-time classroom spectroscopy, http://www.fieldtestedsystems.com (accessed Nov 8 2014).
24. Wong, G. *J Phys: Conf. Series* **2009**, *178*, 012048.
25. Muhammed, H.H. *Sensor Rev.* **2014**, *33*, 257-266.
26. Sigernes, F.; Holmes, J.M.; Dyrland, M.; Lorentzen, D.A.; Svenøe, T.; Heia, K.; Aso, T.; Chernouss S.; Deehr, C.S. *Opt. Express* **2008**, *16*, 15623-15632.
27. Sigernes, F.; Lorentzen, D.A.; Heia, K.; Svenøe, T. *Appl. Optics*, **2000**, *39*, 3143-3153.
28. Volent, Z.; Johnsen G.; Sigernes, F. *Appl. Optics* **2009**, *48*, 4170-4176.
29. Leacock-Johnson, A.; Garcia Sega, A.; Sharief, A.; Sailor M.J.; Miskelly, G.M. *Sensor Actuat., A: Phys.* **2013**, *203*, 154-159.
30. Habel, R.; Kudenov, M.; Wimmer, M. *Eurographics* **2012**, *31*, 449-458.
31. Martinez, A.W.; Phillips, S.T.; Carrilho, E.; Thomas, S.W.; Sindi, H.; Whitesides, G.M. *Anal. Chem.* **2008**, *80*, 3699-3707.
32. Martinez, A.W.; Phillips, S.T.; Whitesides, G.M. *Anal. Chem.* **2010**, *82*, 3-10.
33. Anon., iSpex, http://ispex.nl/en/ (accessed Nov 10 2014).
34. Anon., Cell-All: super smartphones sniff out suspicious substances, 2012, http://www.dhs.gov/cell-all-super-smartphones-sniff-out-suspicious-substances (accessed Nov 10 2014).
35. Monahan, T.; Mokos, J.T. *Geoforum* **2013**, *49*, 279-288.
36. Doeven, E.H.; Barbant, G.J.; Kerr, E.; Hogan, C.F.; Endler J.A.; Francis, P. *Anal. Chem.* **2014**, *86*, 2727-2732.

Continued from page 21

10. Dogra, M.; Palmer, B.D.; Bashiri, G.; Tingle, M.D.; Shinde, S.; Anderson, R.F.; O'Toole, R.; Baker, E.N.; Denny, W.A.; Helsby, N.A. *Br. J. Pharmacol*., **2011**, *162*, 226-236.
11. Palmer B.D.; Thompson A.M.; Sutherland H.S.; Blaser, B.; Kmentova, I.; Franzblau, S.G.; Wan, B.; Wang, Y,; Ma, Z.; Denny, W.A. *J. Med. Chem*. **2010**, *53*, 282-294.
12. Blaser, A.; Palmer, B.D.; Sutherland, H.S.; Kmentova, I.; Franzblau, S.G.; Wan, B.; Wang, Y.; Ma, Z.; Thompson, A.M.; Denny, W.A. *J. Med. Chem*., **2012**, *55*, 312-326.
13. Thompson, A.M.; Sutherland, H.S.; Palmer, B.D.; Kmentova, I., Blaser A.; Franzblau, S.G.; Wan, B.; Wang, Y.; Ma, Z.; Denny, W.A. *J. Med. Chem*. **2011**, *54*, 6563-6585.
14. Sutherland, H.S.; Blaser, B.; Kmentova, I.; Franzblau, S.G.; Wan, B.; Wang, Y,; Ma, Z.; Palmer, B.D.; Denny, W.A.; Thompson, A.M. *J. Med. Chem*., **2010**, *53*, 855-866.
15. Kmentova, I.; Sutherland, H.S.; Blaser, A.; Franzblau, S.G.; Wan, B.; Wang, Y.; Ma, Z.; Denny, W.A.; Palmer, B.D.; Thompson, A.M. *J. Med. Chem*., **2010**, *53*, 8421-8439.
16. Cellitti S.E.; Shaffer, J.; Jones, D.H.; Mukherjee, T.; Gurumurthy, M.; Bursulaya, B.; Boshoff, H.I.; Choi, I.; Nayyar, A.; Lee Y.S;, Cherian, J.; Niyomrattanakit, P.; Dick, T.; Manjunatha, U.H.; Barry, C.E;, Spraggon, G.; Geierstanger, B.H. *Structure*, **2012**, *20*, 101-112.
17. Franzblau, S. G.; Cho, S.; Kim, Y.; Wang, Y.; Lu, Y.; Wang, B.; Xu, J.; Mdluli, K.; Upton, A.M.; Ma, Z. Poster F-834, 52nd Interscience Conference on Antimicrobial Agents & Chemotherapy, November 2012, San Francisco.

Article

The nature of science: teaching the next generation

Reece N. Oosterbeek[1], Cristina Cochrane[2], Robert James[3], Sandra Jackson[4] and M. Cather Simpson[1*]

[1] Photon Factory, School of Chemical Sciences and Department of Physics, The MacDiarmid Institute for Advanced Materials and Nanotechnology, The University of Auckland, Private Bag 92019 Auckland 1142, New Zealand (email: *c.simpson@auckland.ac.nz)*

[2] Christ the King School, 288 Richardson Rd, Mt Roskill 1041, Auckland, New Zealand

[3] Waimauku School, 2 Muriwai Rd, Waimauku, Auckland 0812, New Zealand

[4] Kings School, 258 Remuera Road, Remuera, Auckland 1541, New Zealand

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Abstract

The Science Teaching Leadership Programme is an initiative administered by the Royal Society of New Zealand and funded by the Ministry of Business, Innovation and Employment. It is a professional development course that places science teachers in scientific research institutions, with the aims of improving their understanding of science, developing their leadership skills, and enhancing their science teaching when they return to their schools. The Photon Factory has hosted several Teacher Fellows; here we evaluate these experiences. The research projects carried out by Teacher Fellows in the Photon Factory include laser microsurgery of bone, and the development of both paper and polymer-based microfluidics for primary and secondary school level learning. Teacher Fellow feedback indicates that the programme is very effective at improving teachers' leadership skills and understanding of the nature of science. Teacher Fellows also return to their schools eager to improve science teaching as a result of this programme, and are finding strong support for their new ideas and initiatives from other teachers and school management. Challenges that the Teacher Fellows encounter to full implementation of their new ideas include their day-to-day time commitments and the reluctance of some of their colleagues to change long held teaching practices.

Introduction

The Science Teaching Leadership Programme was initiated in 2014; it replaced the Primary Science Teacher Fellowships and Endeavour Teacher Fellowships administered by the Royal Society of New Zealand.[1] These programmes support the Science in Society strategic plan launched by the Ministry of Business, Innovation and Employment and Ministry of Education.[2] They provide the opportunity for teachers of years 1 – 10 to be hosted in a working scientific research environment, with the stated goals that the teacher will:[1]

- gain an understanding of the Nature of Science curriculum strand through workshops and working in a scientific organisation for two terms;
- develop their leadership skills through participating in leadership training; and
- facilitate improvement of science teaching and student learning school-wide, working alongside their principal and/or head of department to enhance the school's science programme and vision for science.

Approximately 400 of these fellowships have been awarded over the past 8 years,[1] including three to teachers who performed their research in the Photon Factory at the University of Auckland. Cristina Cochrane (Christ the King School; decile 3) and Robert James (Waimauku School; decile 10) completed their fellowships in 2013 and 2014, respectively. Sandra Jackson (King's School; decile 10) is a current Teacher Fellow. Here we will discuss their experiences, from the points of view of both parties involved – the Teacher Fellow and the host institution.

The Photon Factory opened in 2010 as an advanced, multi-user pulsed laser facility in the Faculty of Science at The University of Auckland. Our high-tech, ultrafast laser pulses are used for everything from discovering fundamental knowledge to advancing high-tech manufacturing on a microscopic scale. The Photon Factory is also committed to outreach and education with school students and teachers, and hosting Teacher Fellows is one important mechanism for us to achieve our goals. To date, two Teacher Fellows have completed their fellowships at the Photon Factory, with a third underway.[3]

Evaluating the programme

The nature of science

Understanding the nature of science is one of the core strands in the New Zealand curriculum, and is required for all students up to Year 10. Achieving a greater understanding of the nature of science is one of the central goals of the programme, and is facilitated by immersion in a working scientific environment, as well as numerous workshops undertaken through the Science Teaching Leadership Programme. In the Photon Factory, we actively encouraged this new understanding by linking the Teacher Fellows into ongoing research projects, some at the very forefront of discovery. In our view, it is important for the teachers to experience how scientific questions are asked and answered first-hand. We also want them to feel both the frustration of failure and the satisfaction of success in learning something entirely new in science, or in understanding some "known" science for the first time.

To evaluate the effectiveness of these methods, teachers were asked to rate their understanding of the nature of

science before and after the programme. Both completed Teacher Fellows rated themselves 2/5 before, and 5/5 after the programme, indicating that they felt their understanding of science was greatly advanced by the programme.[4, 5] Feedback from Teacher Fellows also provides insight into the new understanding gained over this time:

> Teachers are 'cultural brokers' that pass on important messages to the students. We must move beyond the belief that teaching science involves passing on a set of facts to students…
>
> Robert James [5]

> …science is a comprehensible idea and not a body of knowledge…
>
> Cristina Cochrane [4]

These comments reveal an increased appreciation for the nature of science, not as a set of facts to be learned by rote, but as an idea and a way of looking at the world.

One observation commonly noted by Teacher Fellows is the collaborative nature of practising scientists. The stereotypical view of a scientist is often the loner who comes up with breakthroughs on their own; however this is not usually how science actually works. Collaborating and working in teams is often far more effective, as it allows researchers to draw upon a broader base of expertise to solve complex problems. This, too, is an important facet of the nature of science and scientific discovery.

Leadership skills

Improving the leadership skills of science teachers is another core goal of the Science Teaching Leadership Programme, with the aim of equipping teachers to more effectively model science investigation in their classrooms, as well as successfully lead curriculum innovations in science and technology at their schools. The hosting of teachers at scientific institutions goes some way to achieving this goal by improving teachers' knowledge of science as described above, but cannot equip teachers with all the required skills. Feedback from past Teacher Fellows has noted that the leadership training and curriculum development courses were of particular importance in developing these skills.

In the Photon Factory, the Teacher Fellows are given "ownership" of some or all of their projects. They work in a team, but they have each been responsible for driving some aspect of the research forward. Initially, this can be challenging for both the Teacher Fellows and the Photon Factory team. However, by the end of the fellowship term, all of our Teacher Fellows have clearly become more proactive and assertive about their projects.

The combination of the experience in the Photon Factory and the leadership training in the Science Teaching Leadership Programme clearly has led to positive outcomes. When asked to evaluate their confidence and ability to teach and lead science at school, these teachers averaged 2.3/5 before the programme and 5/5 afterwards, indicating that the combination of training and experience has been effective in achieving the stated goal of improved leadership skills.

Improvement of science teaching

Arguably the most important goal of the Science Teaching Leadership Programme is for the teacher to "facilitate improvement of science teaching." when they return to their schools. This target represents the culmination of the additional goals of understanding the nature of science and improving leadership skills – by achieving these it is anticipated that teachers can effectively lead changes within their school to improve the quality of science education.

Without a thorough review of schools nationwide it not possible to draw firm conclusions about how far science teaching is being improved as a result of this initiative. However, we can present some recurring responses from teachers as to the challenges and opportunities faced in translating what they have learned in their fellowships into practice in their schools.

Opportunities

- Many teachers are supportive and eager to improve science teaching.
- A large number of teachers have completed these programmes already – greater collaboration between past Teacher Fellows and sharing resources/ ideas would be valuable.
- Links with science institutions provide opportunities for learning to take place outside the classroom.

Challenges

- Some teachers hold outdated beliefs about the nature of science and how to teach it, and are unwilling to change.
- Time commitments are an issue for teachers, as modifying the curriculum and creating new resources (and unit plans) requires significant time investment.
- It can be difficult to integrate out-of-classroom experiences into the teaching programme.

Although there are clear challenges to implementing the lessons learned from the Science Teaching Leadership Programme to improve science teaching in schools, there is strong support from school leadership. The 2012 ERO Science in the New Zealand Curriculum report[6] indicated that the priority given to science in the curriculum in many schools is lacking, and with support from management, certain schools are moving to rectify this.

Science capabilities

A recent development in science teaching in New Zealand is the introduction of five "science capabilities" to help implement aspects of the New Zealand Curriculum.[7, 8] A key goal of the New Zealand Curriculum is to ensure all students become "responsible citizens in a society in which science plays a significant role" – these capabilities are designed to help meet this target:

· Gather and interpret data

- Use evidence
- Critique evidence
- Interpret representations
- Engage with science

Focusing science education in these areas is intended to allow learners to become scientifically literate – an important skill even if they do not go on to a career in science. Involvement in the Science Teaching Leadership Programme requires teachers to not only observe these capabilities being demonstrated by scientists, but allows them to develop and apply them themselves in their research projects. This in turn assists teachers in passing these skills on to their students.

These capabilities are often ones that Teacher Fellows mention as a new skill learned during the course of the programme – systematically gathering data, thinking critically about your own and others' results, and drawing appropriate conclusions. This indicates that the Science Teaching Leadership Programme is working successfully to support teachers adopting these science capabilities.

Teaching Fellow projects

A major component of the Science Teaching Leadership Programme is the hosting of Teacher Fellows in a scientific institution, where they are able to gain an understanding of how science is practised in the real world. This is implemented in the Photon Factory by integrating Teacher Fellows into ongoing research projects, sometimes quite completely and sometimes with a quasi-independent side-project. It is imperative that this research is of the highest quality, to ensure that teachers have an accurate experience of the nature of science. This means that some of this research can be published in the peer-reviewed literature, a beneficial though not necessary outcome.

Laser microsurgery of bone – C. Cochrane

Cristina Cochrane (Christ the King) joined a small project team that consisted of a physics MSs student (Simon Ashforth), and a biomedical engineering student (Jason Ng), to explore the benefits and limitations of using femtosecond laser pulses for microsurgery of bone (Fig. 1). The project had already begun when she joined the group, and is part of a larger initiative funded by the Ministry of Business, Innovation and Employment (UOAX1202), with support from a US company (Intuitive Surgical, Inc.).

Almost from the time they were invented, lasers have shown great promise for surgical applications because they can cut and cauterize simultaneously. Unfortunately, traditional laser methods lead to charring and necrosis when applied to bone.

Femtosecond laser pulses, however, interact with materials through a process that minimizes thermal and mechanical effects, and in biomaterials leads to reduced tissue damage.[9] Thus femtosecond laser pulses are an excellent laser option for implementation in surgical procedures for bone.[9, 10] The use of femtosecond lasers for orthopaedic surgical applications also has potential

Fig. 1. Teacher Fellow Cristina Cochrane (right) with Simon Ashforth (left) and Jason Ng (middle) work together to apply the Photon Factory's femtosecond laser pulses to the microsurgery of bovine pastern bone.

advantages over the mechanical oscillating drills, saws and diamond discs that are conventionally used.[11] These mechanical tools generate excessive friction and high temperatures that destroy vital bone cells, impede bone regeneration and healing, and complicate post-operative care.[12-14] Because of their "cold cutting" ability, femtosecond laser pulses offer a significant improvement over traditional methods.

Once Cristina became familiar with the overall project, she took leadership over testing a particular hypothesis: the efficiency of bone removal with the femtosecond pulses in the Photon Factory is dependent upon the focal depth of the laser beam relative to the surface of the bone. Bovine pastern bone, with soft tissue removed, was machined using a femtosecond laser micromachining system (Mantis and Legend Elite, Coherent Inc., USA). The 800 nm 110 fs pulses (repetition rate 500Hz), were directed to a JPSA IX-100 micromachining stage, where the bone sample was placed for machining. The sample was translated across the beam at a constant rate to write lines. The position of the focal point relative to the surface of the bone was altered by moving the sample vertically. After machining, the ablation depth was measured using optical coherence tomography.

As the focal point moved deeper into the cortical bone sample, the efficiency of removal (ablation depth per pulse) of the tissue initially increased linearly; the maximum was observed at about 2300 μm below the surface (Fig. 2). Further translation of the focal spot into the sample led to linear decrease in the efficiency. The maximum ablation efficiency was observed at a distance approximately equal to the Rayleigh range, defined by:

$$Z_R = \frac{\pi \omega_0^2}{\lambda}$$

where λ is the laser wavelength and ω_o is the beam waist. This result is similar to that observed by Jiang *et al.*,[15] in which similar behaviour was observed for Nd:YAG laser pulses focussed 1-2 mm below the surface of both aluminium and low carbon steel.

The results from Cristina's project have been incorporated into a paper submitted for publication.

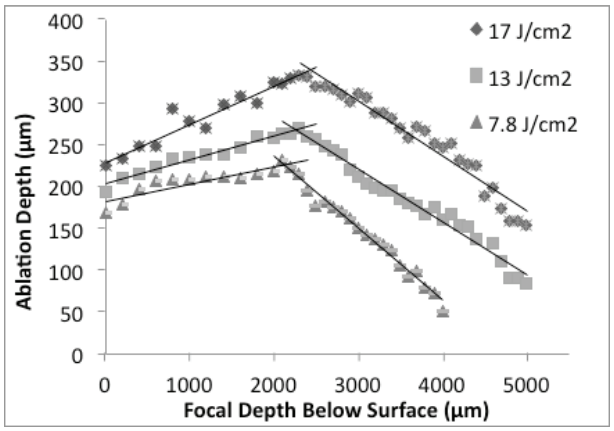

Fig. 2. The ablation depth (a measure of tissue removal efficiency) as a function of laser focal point position relative to the surface of the sample for bovine cortical bone (pastern). Three laser fluences were tested (blue circles 17 J cm^{-2}; green squares 13 J cm^{-2}; red diamonds 7.8 J cm^{-2}). The maximum efficiency is observed when the laser focal point is approximately 2300 µm below the surface.

Paper microfluidics – R. James

When Robert James (Waimauku School) joined the Photon Factory, he chose to work on a project associated with our group's burgeoning research thrust in microfluidic device development. Robert merged the fundamental research and our joint interest in public engagement with science (Fig. 3). The project goals focused on the exploration and development of paper microfluidic devices, and their use as an initial platform for a new interactive science education website for teachers and students to get "hands on" experience with microfluidics remotely.

Microfluidic devices are fascinating examples of how science concepts such as laminar flow, turbulence, shear stress, and viscosity can be taught through the construction of state-of-the-art, high-tech devices. Using microfluidics as a platform for science education can lead to improved attitudes towards science and nanotechnology.[16] Unfortunately, the high cost of the associated equipment needed for traditional microfluidic devices (pumps, microscopes etc.) has limited their uptake. Paper-based microfluidics offers an excellent alternative.

Paper microfluidics is a rapidly developing field that uses a variety of different methods to produce low-cost, equipment-free microfluidic testing devices that has found particular utility as analytical devices in the developing world.[17-19] Robert's microfluidic project complements other recent work to exploit these advantages of paper as a microfluidic substrate in the high school classroom, to provide valuable exposure for students to cutting-edge science.[20]

Developing a microfluidic device that is useful for teaching in a primary school setting is more challenging – students this young are initially unfamiliar with and sometimes not ready to comprehend many of the basic concepts of fluid flow, much less the details of the microscopic and macroscopic behaviour. Robert and the paper microfluidic team in the Photon Factory were nonetheless successful at developing low-cost paper microfluidic devices for primary school classrooms that illustrate the basics of microfluidics and other scientific principles in an engaging fashion.

To make his devices, Robert laser micromachined channels of varying shapes, widths, and depths in a wide variety of paper types, testing hypotheses about the effects of the structure of the paper, the shape of the channel and the characteristics of the fluid upon the resultant flow. He used the KrF excimer laser (Coherent Xantos XS). The 248 nm, 5 ns pulses (repetition rate 500Hz) were directed to the JPSA IX-100 micromachining stage, where the paper sample was placed for machining. A scanning electron microscope (SEM) image of one of these channels is shown in Fig. 4, where the paper fibres as well as the 200 mm channel can be observed.

Using this fabrication technique, microfluidic devices were made using a combination of channels and wells, to demonstrate capillary action and colour theory with inexpensive, hands-on devices that both appeal to and address the curricular goals for primary school aged children. Some examples of these devices are shown in Fig. 5.

Robert's project also involved working with Photon Factory staff and a computer science programmer to develop an interactive website. The goal of this part of the project is to make the laser micromachining and nature of science experience of the Photon Factory available to all schools and teachers in New Zealand. Once the website is complete, classes from anywhere in NZ will be able to log in and submit their hypotheses and designs for microfluidic devices. The Photon Factory staff will machine them into paper and send them to the students by post. The students can test them in their own classrooms, and then upload their results to the website. The website is nearing completion, and can be accessed at www.lasermaze.org.

Water quality microfluidics – S. Jackson

Sandra Jackson (Kings School) is a current Teacher Fellow in the Photon Factory. She has started a project to develop inexpensive, reusable microfluidic devices that will allow school students and teachers to analyse water quality in the field. This builds upon the previous work in the lab, including Robert's, on paper microfluidics and focuses further on using research to develop teaching tools. The project also links in with other microfluidic analysis research in the Photon Factory, and Sandra has been working closely with the laser machining team, the centrifugal microfluidic team and the sperm sorting team to achieve her project goals (Fig. 6).

As previously discussed, microfluidic devices have been seen to be an effective teaching tool for illustrating cutting edge science and the theory behind it. Conventional polymer and glass based microfluidics can also be used in school settings to enhance educational outcomes,[21, 22] where the existing knowledge about these techniques provides a broad base of expertise to draw upon, and where gravity or manual pump flow is suitable. This conventional approach can be enhanced by the addition of disposable paper microfluidic components.

Fig. 3. Teacher Fellow Robert James (right) demonstrates a vibrating membrane reflector device of his own construction at the MOTAT Science Street Fair. Robert's keen interest in science outside the classroom was a key driver in his fellowship project, and is well aligned with the Photon Factory's overarching goals.

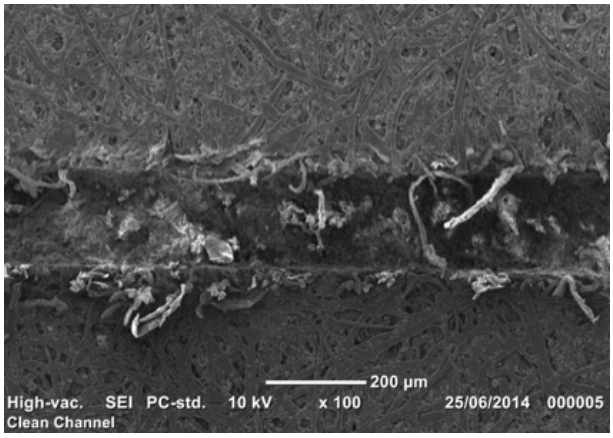

Fig. 4. Scanning electron microscope (SEM) image of a microfluidic channel machined in paper using an ultraviolet (248 nm), nanosecond pulsed laser. The paper fibres are evident as well as the machined channel in the centre. Different types of paper exhibit different microscopic structural properties that affect the details of the results from laser micromachining.

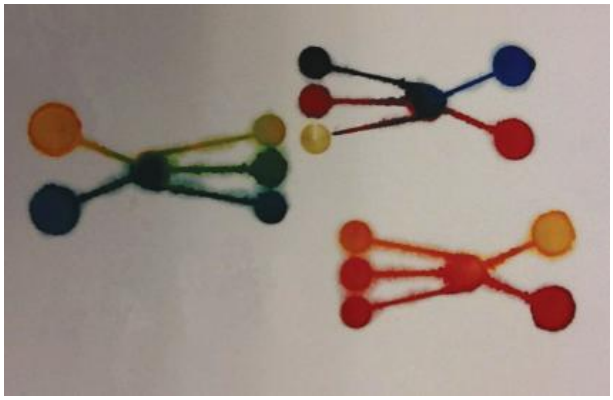

Fig. 5. Examples of paper microfluidic mixing devices created by Robert and machined in the Photon Factory, and designed to illustrate the combination of colours to primary school students. The base colours are placed in the side with two channels (e.g. blue and yellow in the device on the left). The microfluidic flow (mixing primarily by diffusion, although the roughness of the channels seen in Fig. 4 also produces turbulence) generates a gradient of final colour (here, in three output channels).

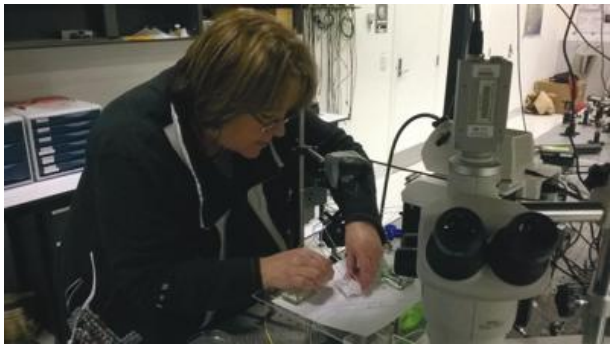

Fig. 6. Teacher Fellow Sandy Jackson aligns a microfluidic mixing device for microscopic analysis in the Photon Factory.

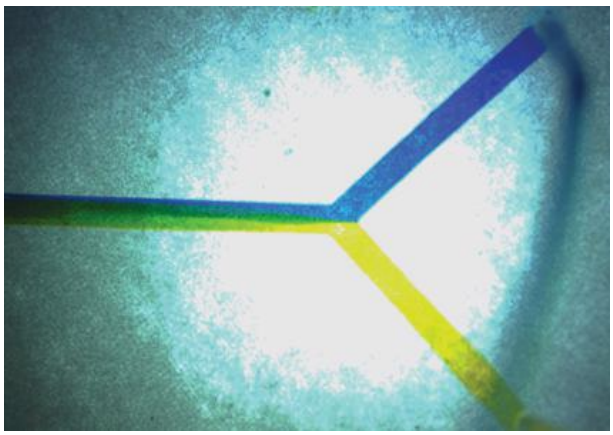

Fig. 7. Microscope image of a microfluidic mixing device mixing blue and yellow dyes. The laminar flow leads to mixing by diffusion, as can be seen in the colour separation of the two streams as they merge. The flow is from left to right in this image.

Sandra's target student cohort is slightly older than Robert's. Her project will lead to microfluidic devices that demonstrate the details of how fluid moves in microfluidic channels, how it is different from macroscopic (turbulent) fluid flow, and explores how to present these ideas to a class in an accessible and exciting, engaging way. These goals are achieved by a device that she is designing and constructing that can be used to analyse water quality, incorporating tests such as pH and heavy metal testing.

Sandra's initial efforts have resulted in production of a microfluidic mixing device (Fig. 7) to mix different dyes together, and show the effects of diffusion and laminar versus turbulent flow. Recently, she was part of a team that won one of the "top three videos" commendations for their movie of a related device, submitted to an international microfluidic conference (MicroTAS 2014, San Antonio, TX).[23] The video shows some of the ways in which Sandra will be using her devices and her high-tech experience to teach both the scientific content and the nature of science, when she returns to Kings School.

Evaluating the projects

The value of Teacher Fellows completing research projects is undeniable – they provide an opportunity for teachers to learn new skills, and understand more clearly how science is practised. From the Photon Factory's perspective, they provide critical experience needed to help us understand better how to reach students and teach-

ers. These projects are not without their challenges however, and we have identified several routes to improvement.

Perhaps the most significant challenge for both teachers and Photon Factory members is communication. School teachers can be years out of their degrees, while university students and staff are immersed in jargon and scientific detail. Conversely, while everyone in the Photon Factory attended primary school at some point, their anecdotal memories or incidental experiences since then do not make them qualified primary school educators. We approach these mismatches in background and immediate experience by explicit conversations – early and often – of what we have to offer each other. The Teacher Fellows help make the Photon Factory outreach more relevant to New Zealand schools and curricular goals, and the Photon Factory helps the Teacher Fellow achieve the programme goals.

One example of a difficulty encountered during these projects is the issue of confidentiality. The Photon Factory performs a significant number of industrially-focused projects, and all of the Teacher Fellows participate to some degree. Teachers are accustomed to working in a very collaborative environment, where their very purpose is to disseminate knowledge. Cristina's laser bone surgery research (*vide supra*) was very commercially relevant; drawing the boundaries of confidentiality so that there was no ambiguity was quite difficult. Cristina struggled with discerning between sensitive and public information, and we struggled with articulating these and providing clear guidelines. In the end, we reached understanding but getting to that point involved many, many discussions.

One unanticipated adjustment that the Teacher Scholars had to make was to the unstructured workflow of the research environment. A teacher's regular day is heavily regimented by the schedule of the school day, with classes and breaks at set times. Research in the Photon Factory is the opposite. Our researchers have the freedom to set their own schedule and tasks, and the focus is on the results. In addition, research is not predictable – often one cannot predict tomorrow's activities until today's results are analysed. The goals and objectives of research projects can often change when interesting results are seen, diverting the project course away from the original plan. This can be problematic for teachers, who are skilled and experienced in preparing and executing long-term plans. This adjustment has become easier with each Teacher Fellow, as the Photon Factory team learned how to adapt better and prepare the Teacher Fellow's expectations.

Conclusions

In our experience, the Science Teaching Leadership Programme, an initiative administered by the Royal Society of New Zealand as part of the Science in Society strategic plan launched by the Ministry of Business, Innovation and Employment and Ministry of Education, has been very effective at improving teachers' perceptions of the nature of science and equipping them with the necessary skills to teach and lead science education at their schools. The three Teacher Fellows who have participated in the programme in the Photon Factory at the University of Auckland have found their projects engaging and their experiences positive. In return, the Photon Factory students, staff and director have found the perspective and insight provided by the Teacher Scholars invaluable for improving our outreach and education outcomes. In the Photon Factory, these Teacher Fellows perform publication-quality scientific research as part of a team of students and staff, often critically enhanced by the teacher's passion for education and outreach. Although Teacher Fellows may encounter some barriers to implementing their innovative changes when they return to their schools, the teachers with whom we have worked have been eager to implement changes to science education in schools and have strong support from their school management to do so.

References

1. The Royal Society of New Zealand 2014. *Science Teaching Leadership Programme*. See http://www.royalsociety.org.nz/teaching-learning/science-teaching-leadership-programme/ (accessed 30/10/2014).
2. Joyce, S.; H. Parata, *A Nation of Curious Minds - He Whenua Hihiri i te Mahara - A National Strategic Plan for Science in Society*, 2014, Ministry of Business, Innovation and Employment, Ministry of Education: http://www.msi.govt.nz/assets/MSI/Update-me/Science-in-society-project/science-in-society-plan.pdf (accessed 30/10/2014).
3. The three Teacher Fellows in the Photon Factory have been part of the now superseded Primary Science Teacher Fellowships, that has the same goals as the new Science Teaching Leadership Programme. In this article, when the Science Teaching Leadership Programme is discussed, this refers to both the new programme and the superseded Primary Science Teacher Fellowships and Endeavour Teacher Fellowships.
4. Cochrane, C., *Primary Science Teacher Fellowship Final Fellowship Report*, 2013, The Royal Society of New Zealand: New Zealand Science, Mathematics and Technology Teacher Fellowship Scheme.
5. James, R., *Primary Science Teacher Fellowship Final Fellowship Report*, 2014, The Royal Society of New Zealand: New Zealand Science, Mathematics and Technology Teacher Fellowship Scheme.
6. Education Review Office 2012. *Science in the New Zealand Curriculum: Years 5 to 8*. http://www.ero.govt.nz/National-Reports/Science-in-The-New-Zealand-Curriculum-Years-5-to-8-May-2012 (accessed 4/11/2014).
7. Ministry of Education 2014. *Introducing five science capabilities*. Te Kete Ipurangi. See http://scienceonline.tki.org.nz/Introducing-five-science-capabilities (accessed 4/11/2014).
8. Hipkins, R. *Unlocking the idea of 'Capabilities' in science*. New Zealand Science Teacher 2014. Available from: http://www.nzscienceteacher.co.nz/curriculum-literacy/key-competencies-capabilities/unlocking-the-idea-of-capabilities-in-science/ (accessed 4/11/2014).
9. Smith, G.; Kalli, K.; Sugden, K. *Advances in Femtosecond Micromachining and Inscription of Micro and Nano Photonic Devices*. Frontiers in Guided Wave Optics and Optoelectronics 2010.
10. Lubatschowski, H.; Heisterkamp, A.; Will, F.; Singh, A.I.; Serbin, J.; Ostendorf, A.; Kermani, O.; Heermann, R.; Welling, H.; Ertmer, W. *RIKEN Review* **2003**, *50*, 113-118.
11. Emigh, B.J.; Hayward, J.E.; An, R.; Hsu, E.M.; Crawford, T.H.; Haugen, H.K.; Wohl, G.R.; Fang, Q. *J. Biomed. Optics*, **2012**, *17(2),* 0280011-0280016.

Continued page 41

Article

Alumina microstructure and its properties as an adsorbate: an example of research at the Light Metals Research Centre

Grant J. McIntosh*, Gordon E. K. Agbenyegah and James B. Metson

Light Metals Research Centre, University of Auckland, Private Bag 92019, Auckland 1142 (email: *g.mcintosh@auckland.ac.nz)*

Keywords: *volatiles capture, pore structure, adsorbate-adsorbent, specific surface area*

Introduction

Aluminium is ubiquitous in our modern world, with its global importance and utility reflected in the 50 metric megatonnes of primary metal produced worldwide during 2013,[1] and at least that quantity again produced through recycling. Primary metal is produced exclusively by the Hall-Héroult process in which alumina (Al_2O_3) is electrolytically reduced after dissolution in molten cryolite (Na_3AlF_6). To feed this demand, approximately 107 metric megatonnes of alumina were produced[2] worldwide during 2013 with the vast majority (~94 %) used in primary metal production.

Al_2O_3 plays an interesting dual role in the Hall-Héroult process; it is used not only as the feedstock, but as an adsorbate in dry-scrubbing systems for the capture of volatile fluorides, including the extremely toxic compound HF which is generated during electrolysis. This reacted alumina is ultimately fed into the electrolysis cells, providing an effective means of recycling fluoride, thereby dramatically reducing one of the industry's major feedstocks. However, with rising pressures on the industry, particularly concerning energy consumption (more than 2 % of the world's electric power is consumed by the Hall-Héroult process), increasing metal production by way of higher amperages has led to challenges in maintaining the fluoride balance in some smelters. With excess fluoride (concentrations of AlF_3 in excess of that expected in strictly stoichiometric cryolite) being intimately related to, and indeed used specifically to control, cell temperatures and ultimately process efficiency, and with problems associated with maintaining fluoride emissions below government mandated thresholds, the adsorption properties of alumina are becoming increasingly important to the industry as a whole. Understanding the mechanism of HF adsorption and subsequent reaction on the alumina has therefore been of considerable interest.

Complicating matters for studies relevant to the aluminium industry, smelter grade aluminas (SGAs) span a wide range of particle morphologies and crystallographic phases, which influence (amongst other properties), the pore characteristics of the final material.

The Light Metals Research Centre (LMRC) at the University of Auckland has long had an interest in this area. In this paper we discuss two examples of recent research we have undertaken regarding the impacts of alumina properties, particularly regarding its role as an adsorbent, on significant problems in the aluminium industry. These examples are the application of laboratory-based approaches to explore the fundamentals of the fluoride adsorption capacity of alumina, and working with industrial partners to understand the impacts of these phenomena on the smelter fluoride cycle, a large scale real-world problem.

Light Metals Research Centre (LMRC)

Founded in 2002 based on the research histories of Professors Barry Welch, John Chen, Margaret Hyland and Jim Metson, and Academic Director Mark Taylor, the LMRC at the University of Auckland has established an international reputation for world-leading expertise in the alumina refining and primary aluminium smelting industries. LMRC focusses on providing independent research and development capabilities, consulting services as well as industry-relevant training programmes such as the successful Postgraduate Certificate in Light Metals Reduction Technology from the University of Auckland. Since its inception, LMRC has seen the founding academic staff more involved in leading and guiding research more fundamental in nature, while still maintaining strong ties to the other centre activities. Indeed, LMRC has co-hosted a number of postgraduate students in areas of fundamental research such as alumina properties, gas adsorption and electrolyte chemistry, supervised within the Departments of Chemical and Materials Engineering and the School of Chemical Sciences. The centre is currently overseen by its Director, Mark Dorreen, with managers Pretesh Patel looking after all projects in Europe and the Gulf regions, Yashuang Gao responsible for those in China, and Ron Etzion for modelling and fundamental research.

LMRC is also involved in the development and commercialisation of technologies within the centre and with partner companies. One example is Shell Heat Exchanger (SHE) technology, currently undergoing extended performance trials on a group of pots in an operating smelter in Germany. Originally designed for efficient air-driven cooling of the reduction cell sidewall, essential for operation at increased amperage and metal production, it is now also being trialled for heat retention during periods of decreased amperage to allow stable operation while accommodating deep power modulation. Similarly, we are currently commercializing a comprehensive smelter operation, control and management supervisory software package, Gen3. This suite is designed to address a wide range of smelter management issues, provide early detection of abnormalities, improved smelter efficiency, reduction of emissions, increase pot lifetimes, and optimise staff performance and utilisation. In performance trials Gen3has brought improvements of +1% current efficiency and -100kWhr/kg Al.

October of 2014 saw LMRC relocate its facilities from the city campus to the University's newly-opened Newmar-

ket campus. Located at the former site of Lion Breweries, the new campus accommodates staff and research students spanning a range of engineering and science disciplines, with LMRC amongst the first groups to relocate. This has provided LMRC with generous new laboratory space including a general wet chemistry laboratory, a dedicated HF laboratory for testing the kinetics and capacity of the adsorption of HF by alumina (Fig. 1), a designated area for a suite of furnaces and high temperature research equipment such as a full sized sidewall rig for SHE testing, an analytical laboratory including XRD, LECO oxygen analyser, FT-IR, and N_2 physisorption capabilities, and a dedicated workshop.

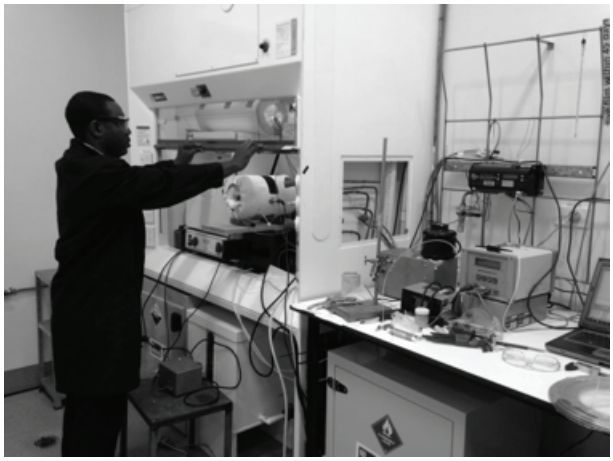

Fig. 1. The new HF adsorption facility

Smelter grade aluminas (SGA): materials properties and pore structure

The properties of the SGAs trace from those of the aluminium hydroxide from which they are derived. The hydroxide, gibbsite, is produced by the Bayer process in which bauxite is dissolved in heated NaOH solution, with $Al(OH)_3$ subsequently crystallised from a purified sodium aluminate solution. SGA growth is dominated by particle aggregation (being considerably faster than direct crystal growth), with strategies concerning the crystal seeding and control of the precipitation conditions dictating, amongst other properties, particle size. This ultimately impacts the phase composition of the final material following calcination. Alumina during the middle stages of calcination can span a wide range of largely defect spinel structures, collectively termed the transition aluminas, with γ-, γ'-, δ-, and θ-Al_2O_3 structures particularly common in the SGAs. The fully calcined hexagonal α-phase (corundum) typically constitutes only a few percent of the final product. The phases listed are in order of decreasing residual hydroxide content, with the phase distribution dictated by calcination conditions, primarily temperature and time. Extremes of phases are associated with negative impacts on the smelting process: the relatively under-calcined γ-Al_2O_3 has been associated with increased HF generation; [3,4] on the other hand, the over-calcined α-Al_2O_3 is the least soluble polymorph leading to undissolved alumina settling out onto the cathode of the reduction cell, with the ultimate consequence being significant energy losses due to increased electrical resistance.

Industrial stationary calciners, the biggest of which range in capacity from 3 to 4,000 T/day, strive for high throughput and low energy consumption, which has the potential for under- or over-calcination of the gibbsite (particularly the fine material). However, heat transfer into the cores of the finer particles is obviously much more rapid than in larger grains, and these materials can therefore be converted almost entirely to α-Al_2O_3. Environmental scanning electron microscopy (ESEM) is a powerful tool for visualising the relationship between phase and particle size. Using charge contrast techniques,[5,6] for example, readily charging α-Al_2O_3 can be easily identified as bright white particles providing immediate visual evidence that, indeed, it is typically only the smallest particles (<50 μm in diameter) that tend to be dominated by this phase (Fig. 2). As a consequence of the range of particle sizes, and hence phases, that may be adopted, SGAs are often very complex, multifaceted materials.

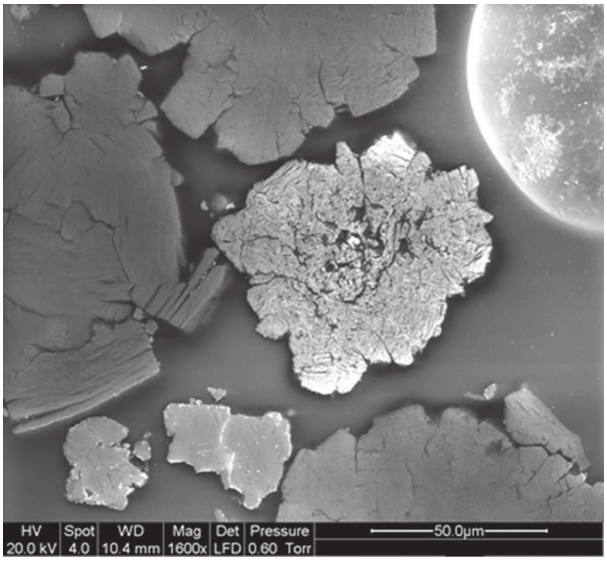

Fig. 2. ESEM image of α-Al_2O_3 grain (white)

The phase distribution has far-reaching impacts on other particle properties, as each phase has associated with it unique average pore size and surface area characteristics. From under- to over-calcined alumina, specific surface areas (SSAs) drop whilst average pore diameter increases.[4] In terms of an adsorbent/dry scrubbing agent, a shift toward under-calcined materials such as γ-Al_2O_3, with a BET (Brunauer-Emmett-Teller) SSA of ~300 $m^2\ g^{-1}$, should ostensibly be favoured (industrial SGAs typically possess SSAs of 70-80 $m^2\ g^{-1}$). Indeed, high BET surface area for increased adsorbate capture is a desired quality for general adsorbents. However, in the particular case of alumina, the residual hydroxide makes these phases a potent source of HF[3,4]. It might be thought that the increase in HF generated may be off-set by the increased SSA/scrubbing capacity. However, there has been growing evidence that the smallest pores may be inaccessible in industrial scrubbers due to kinetic limitations.[7,8] Where the balance lies, given the role of alumina both in generating and recycling fluorides, is therefore an important question to the industry.

HF adsorption

Some insight into the role of kinetically restricted access to the pores should be obtained by consideration of the mechanism of the HF-surface interaction; these insights might also be expected to be of wider relevance to general adsorbate-adsorbent systems. Such systems are generally assumed to interact by the formation of adsorbent mono- and multilayer(s) and the Al_2O_3-HF system is no exception.[9-11] Indeed, the initial adsorption interaction is followed rapidly by an annealing reaction, irreversibly capturing the HF on the alumina surface. This should therefore be observed in a characteristic perturbation to the pore structure of scrubbed aluminas. Pore size distributions (PSDs) have been obtained by application of the Barrett-Joyner-Halenda (BJH) method[12] during N_2 physisorption measurements on unreacted (primary) SGAs, or prim-Al_2O_3. This approach starts by measuring the liquid volumes lost from an N_2-saturated adsorbent at a given pressure, which is being incrementally reduced, with large pores losing their N_2 adsorbate at higher pressures than smaller ones. Assuming pores are cylindrical, the pore diameter of the smallest empty pore is obtained solely from the current pressure (by way of the modified Rayleigh equation). Then, with the adsorbate volume lost in a given pressure decrement equated with the volume of the emptied pore, it is trivial to deduce an effective length.[13] Consequently, one can extract the complete geometries of a discrete set of representative cylindrical pores.

Owing to an irreversible reaction with HF,[14] these measurements may also be performed on the scrubbed (secondary) aluminas, sec-Al_2O_3. This allows adsorption models to be directly tested; a fortuitous circumstance as a general adsorbate-adsorbent system may not survive the sample pretreatment conditions needed prior to measurement. For example, consider monolayer formation (Fig. 3a). A pore of diameter D in prim-Al_2O_3 shrinks by twice the monolayer thickness, $2t_m$, after scrubbing; this has an easily reconstructable effect on pore geometry. Applying these perturbations to the pores of pre-dosed materials, we can derive the PSD expected for materials following treatment with HF, and compare these directly to measurement.

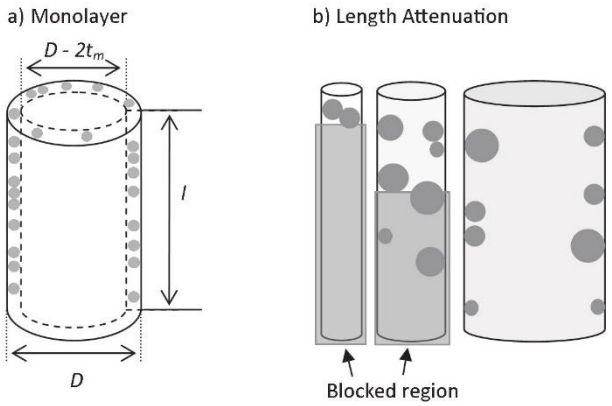

Fig. 3. Models of HF adsorption on alumina.

To test this, we first require a dosed sec-Al_2O_3. These are readily synthesized in the HF dosing rig pictured in Fig. 1. Briefly, several grams of alumina are placed in a heated reaction vessel (inside the oven, in the fume-hood), and anhydrous HF passed through the chamber. A Boreal laser detection system measures HF in the flue gas; experiments are said to have reached break-through when non-zero HF concentrations are detected, and saturation when concentrations reach that of the inlet gas, i.e. no appreciable scrubbing is occurring. A great deal regarding kinetics and scrubbing capacity can be learnt from experiments where aluminas are exposed to varying quantities of HF (particularly as a function of time); it should be noted that the PSDs shown in this article apply to materials treated to saturation loadings of HF.

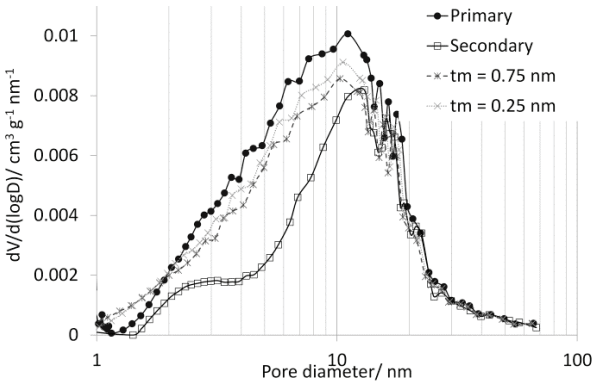

Fig. 4. Monolayer model results for HF adsorption impacts on pore size distributions.

The PSDs of typical SGAs, and the results of several monolayer models (with various estimates of t_m) are presented in Fig. 4. It is clear that monolayer models are inadequate to describe adsorption. In particular, increasing monolayer thickness cannot explain the emergence of a knee observed in the secondary material around 3-4 nm. This indicates that scrubbing slows, and therefore the PSD changes little from the original, in pores of this approximate size, and provides the first direct evidence of kinetically inaccessible pores.[15,16] Extending models to include kinetically restricted access to the pores, one can create two subsets of pore lengths, $L_p(D)$, for accessed and restricted pores (larger or smaller than some threshold pore diameter, D_{thresh}), respectively. We chose the following model for this partitioning:

$$L_p\left(D \geq D_{thresh}\right) = \frac{L_p(D)}{2}\left[1 + erf\left(\frac{D - D_{thresh}}{\sqrt{2}\sigma}\right)\right] \qquad 1$$

$$L_p\left(D \leq D_{thresh}\right) = L_p(D) - L_p\left(D \geq D_{thresh}\right) \qquad 2$$

Pores larger than D_{thresh} (eqtn (1)) have the monolayer model applied, the remainder left unmodified; following which the modified pores are then rebinned into a single distribution – see Fig. 5 for a schematic description of this partitioning process. The term D_{thresh} is a fitted term, expected to be ~3 nm – the position of the knee in Fig. 4; however, even with this rather contrived device, it was still found that the PSDs of secondary aluminas could not be adequately modelled.[15]

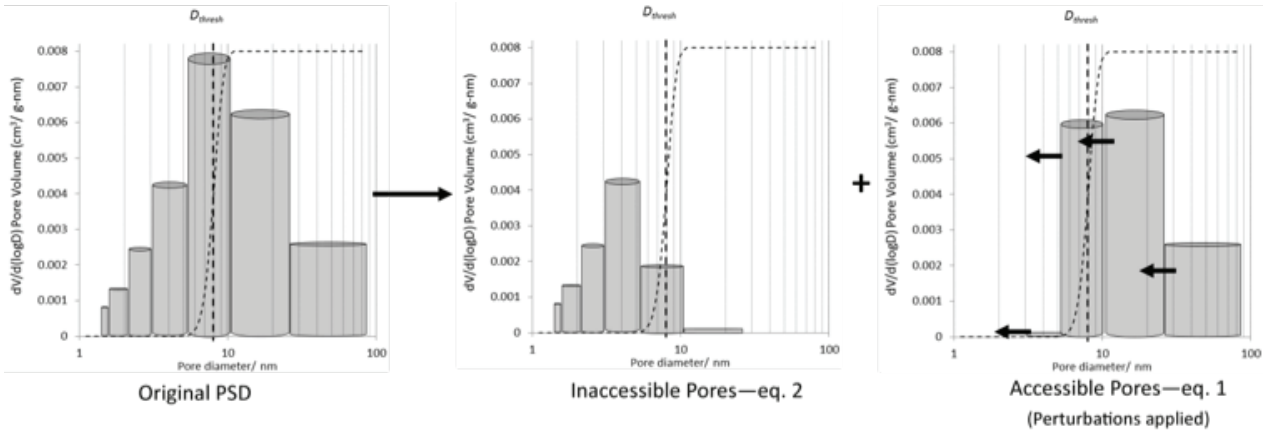

Fig.5. Schematic representation of pore partitioning – see equations 1 and 2.

A more sophisticated model was subsequently developed considering instead pore blocking and length attenuation as the primary loss of pore volume/surface area (Fig. 3b). Assuming some normally-distributed variability in adsorbate thickness (t_m), which may include variability in pore diameter itself, a more rigorous probabilistic model was constructed[15] based on the random doping of surface sites. When two sites on opposing sides of a pore wall were within $2t_m$ apart, the pore is potentially blocked and, assuming closed pores, any pore length below the blocking point was lost. For example, it was possible to show that pore lengths in a kinetically accessible region were attenuated as:[15]

$$L_{\text{sec}}(D) = A([\text{HF}])L_{prim}(D)\left[1 + erf\left(\frac{2t_m - D}{\sqrt{2}\sigma}\right)\right] \qquad 3$$

A([HF]) is an as-yet unspecified function of HF concentration whose value increases with either concentration or exposure time (i.e. pore lengths shorten more with increased HF exposure), and σ is the standard deviation in adsorbate thickness. The functions for dividing pores into accessible and inaccessible regions, eqtns (1) and (2), were used again, but within this model their mathematical forms could be rigorously justified.[15] As can be seen in Fig. 6 this model very faithfully reproduces the PSDs, indicating pore attenuation and not monolayer formation limits the scrubbing capacity of aluminas. Further, adsorbate thickness could be extracted after fitting the model form to the experimental data; modelling several aluminas (including industrial materials) a layer thickness estimate of (0.69 ± 0.24) nm was obtained, in excellent agreement with previous estimates obtained by very different procedures at (0.65 – 0.83) nm.[10] The position of the knee, where the transition from accessible to inaccessible pores occurs, is found to be 2.7 – 2.8 nm based on model fitting results.[15] As the models make no assumptions specific to the HF-Al_2O_3 system, these are very likely general phenomenon in adsorbate-adsorbent systems.

Fluoride recycling

The HF-Al_2O_3 system also provides a powerful example of how the mechanism of interaction in adsorbate-adsorbent systems can have important consequences on application; namely through the recycling of fluoride in

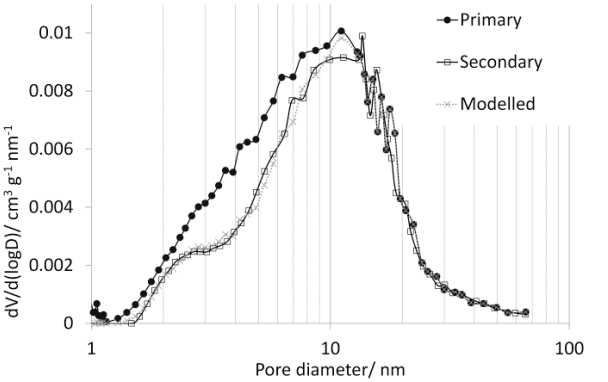

Fig. 6. Attenuation model results for HF adsorption impacts on pore size distributions.

the aluminium smelter, which plays a crucial role in energy consumption and materials feeds. As noted earlier, aluminium reduction is undertaken in a Na_3AlF_6 electrolyte; however, feeds of AlF_3 are commonly added to depress the liquidus temperature (freezing point) of the electrolyte and limit aluminium solubility. This allows a cell to be run at lower temperatures, and given the energy consumption intrinsic to the process, such savings are vital. However, a change in the fluoride concentration has a number of important negative impacts on the cell. A decrease in AlF_3 content increases the liquidus, which ultimately increases the cell operating temperature; this in turn makes the metal produced (which separates from the electrolyte when formed) more soluble in the electrolyte and susceptible to re-oxidation. On the other hand, too great an AlF_3 content reduces the solubility of Al_2O_3, which can settle on the cathode and (being an insulator) increases the cell resistance (and temperature) and therefore energy consumption. The balance is clearly very important, but is becoming extremely difficult to maintain, given the current drive to run higher amperages to produce more metal. Cell temperatures and dissolved AlF_3 concentration are intimately balanced; the cell walls have adhered a ledge of frozen (almost pure) cryolite, with liquidus and temperature changes leading to ledge freezing/melting, and therefore AlF_3 concentration/dilution. Clearly, the loss of volatile fluorides in the flue gases will therefore have a significant impact on AlF_3 content, and its incomplete return by way of adsorbate on the alumina makes maintaining the important fluoride balance extremely challenging.

To better understand these properties, given the number of interacting parameters involved, lab-based studies clearly have limitations. An extensive sampling campaign was therefore undertaken in Germany with the support of industrial partners Trimet Aluminium SE and Outotec GmbH. A range of aluminas (produced by differing calciner technologies and therefore possessing unique phase/pore size distributions) were sampled and a large number of smelter-recorded parameters (cell temperatures, alumina/AlF_3 feed quantities, applied voltages, metrics of cell stability, concentrations of HF in the flue gases) were collected. Integrating these parameters over 60 cells each, and over 24 hour periods over approximately 20 months, plant data were obtained which could be correlated against various alumina properties as determined by XRD and N_2 physisorption measurements, for example. In particular, several measures of SSA were examined to best assess the adsorption characteristics of alumina.

Extracting the influence of alumina properties on key performance measures has required multiple regression analyses. Several regression models of bath acidity (the concentration of excess AlF_3 in the electrolyte) were constructed,[17] ultimately employing all cell parameters listed, the concentration of α-Al_2O_3, and an SSA parameter as independent variables. The significance of each variable was assessed by its *P*-value, computed during the regression analysis; any variable with $P > 0.05$ (i.e. adopting a 95 % confidence level) was deemed insignificant, and therefore removed. This process of modelling followed by variable removal was iterated until all remaining variables were deemed significant.

Particularly interesting for the adsorbate-adsorbent interaction is the role of surface area metrics in these models. The BET method[18] is arguably the most widely employed model for determining surface areas of powdered materials. This model is an extension of the Langmuir approach to accommodate multilayer formation, in which the number of physisorbed probe molecules required to cover the surface, and the cross-sectional area of each probe, allows the total adsorbent surface area to be deduced.[13] The BET method does not allow one to distinguish the contributions of pores of different sizes, with any pore large enough to accommodate the probe molecule measured. However, the BJH method also allows for the determination of surface areas; with the diameters and lengths of the pores known, the surface area of each pore is easily derived, with total surface area obtained by summing over the pores. Careful choice of this summation range therefore allows the role of fine pores to be investigated.

To investigate the importance of the adsorbate-adsorbent interaction, models inclusive of all cell parameters, but focusing on surface area as the sole alumina property, were constructed. BET surface areas were used, as were various BJH estimates where the lower–bound of the summed pore size (x – see Fig. 7) was allowed to vary from the 1.7 nm typically employed. That is, BJH(x – 300) represents the total BJH surface area of pores between x and 300 nm in diameter. In particular, we allowed x to increase, to explore removing the contribution of the smallest pores, suggested to be kinetically prohibited from reacting by PSD modelling results, from the surface area estimates. The *P*-value for each predictor, modelled in turn, is plotted as a function of x (the smallest pore diameter included in the surface area estimate) in Fig. 7.

Clearly, the BET areas are statistically insignificant, i.e. there is no correlation between BET surface area and the concentration of AlF_3 in the electrolyte. However, BJH-based surface areas all demonstrate statistical significance as these measurements explicitly remove the contribution of fine pores which, as we demonstrated in the preceding section, should be inaccessible to the adsorbate. Further, a lower bound on the pore size giving the most significant predictor lies between 3 – 3.5 nm, corresponding almost exactly with the knee in the sec-Al_2O_3 PSD of Fig. 6 (representing the boundary between the accessible and kinetically inaccessible porosity) and in very good agreement with our model results. This strongly indicates that including porosity below this limit simply constitutes noise in the model, obscuring the importance of the alumina in carrying fluoride back to the reduction cell. This is demonstrated by the BET-based models, where differences in surface area/adsorbate carrying capacity of different aluminas is found to have no significant influence on the AlF_3 concentration in the electrolyte as these surface area estimates are heavily dominated by the contribution of fine (micro)pores. More generally, this provides independent verification for the role of transport kinetics and pore blocking (rather than simple availability of adsorption sites) in the activity of adsorbents, and the significant impacts this can have on real world processes.

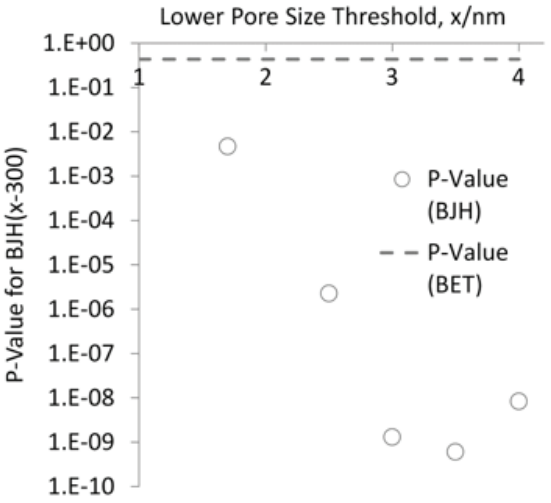

Fig. 7. *P*-value of SSA predictors in AlF_3 regression models.

Conclusions

In addition to its role as a feedstock in the aluminium industry, alumina plays a crucial role as an adsorbent in dry-scrubbing cell gases. This system, while of considerable practical importance to the smelter, also provides a useful test bed to examine important features of adsorbate-adsorbent systems. A fundamental laboratory-based approach has shown that a simple monolayer-based model of capture on adsorbate surfaces is not always the most realistic approach; issues of surface accessibility, either

by kinetic restrictions or pore blocking, can also manifest in specific effects, and these are observed in the HF-Al_2O_3 system.

The return of fluorides to the electrolysis cell by the alumina adsorbate is found to have a clear relationship with surface area measurements that specifically remove pores shown in the lab-based studies to be inaccessible on kinetic grounds. This ultimately has significant impacts on the smelting process in terms of the consumption of materials and energy, which imposes significant monetary costs. This provides an example of the impacts of subtle fundamental processes at the molecular level on chemistry performed in industry on extremely large scales.

Acknowledgements

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References

1. International Aluminium Institute; see: http://www.world-aluminium.org/statistics/primary-aluminium-production/#map (accessed 4 November 2014).
2. International Alumnium Institute; see: http://www.world-aluminium.org/statistics/alumina-production/#map (accessed 4 November 2014).
3. Hyland, M.; Patterson, E.; Welch, B. In *Essential Readings in Light Metals*; John Wiley & Sons, Inc., 2013; pp. 936-941.
4. Perander, L. M. PhD Thesis, The University of Auckland, 2010.
5. Roach, G. I. D.; Cornell, J. B.; Griffen, B. J. In *Light Metals*: Warrendale, PA, 1998; pp. 153-158.
6. Baroni, T. C.; Griffin, B. J.; Browne, J. R.; Lincoln, F. J. *Microscopy Microanal.* **2000,** *6*, 49-58.
7. Perander, L. M.; Zujovic, Z. D.; Kemp, T. F.; Smith, M. E.; Metson, J. B. *JOM* **2009,** *61*, 33-39.
8. Perander, L. M.; Stam, M. A.; Hyland, M. M.; Metson, J. B. In *Light Metals 2011*; John Wiley & Sons, Inc., 2011; pp. 285-290.
9. Cochran, C. N. *Env. Sci. Technol.* **1974,** *8*, 63-66.
10. Lamb, W. D. In *Essential Readings in Light Metals*; John Wiley & Sons, Inc., 2013; pp. 879-888.
11. Coyne, J. F.; Wong, P. J.; Wainwright, M. S.; Brungs, M. P. *Light Metals* **1989**, 113-118.
12. Barrett, E. P.; Joyner, L. G.; Halenda, P. P. *J. Am. Chem. Soc.* **1951,** *73*, 373-380.
13. Lowell, S.; Shields, J. E.; Thomas, M. A.; Thommes, M. *Characterization of Porous Solids and Powders: Surface Area, Pore Size and Density*; Springer Netherlands, 2004; Vol. 16.
14. Gillespie, A. R.; Hyland, M. M.; Metson, J. B. *JOM* **1999,** *51*, 30-32.
15. McIntosh, G. J.; Agbenyegah, G. E. K.; Metson, J. B.; Hyland., M.: Manuscript in Preparation, 2014.
16. Agbenyegah, G. E. K.; McIntosh, G. J.; Hyland, M. M.; Metson, J. B. "Changes to the Pore Size Distribution of Smelter Grade Alumina during HF Scrubbing"; Australasian Aluminium Smelting Technology Conference, 2014, Dubai, United Arab Emirates.
17. McIntosh, G. J.; Metson, J. B.; Niesenhaus, T.; Reek, T.; Perander, L. M. *JOM* **2014,** *66*, 2272-2281.
18. Brunauer, S.; Emmett, P. H.; Teller, E. *J. Am. Chem. Soc.* **1938,** *60*, 309-319.

Continued from page 35

12. Ionita, I.; Zamfirescu, M. *Femtosecond laser - the finest tool for hard tissue ablation*. In *Medical Laser Applications and Laser-Tissue Interactions V*, Munich, Optical Society of America, 2011.
13. Liu, X., Du, D.; Mourou, G. *J. IEEE Quantum Electronics* **1997**, *33(10)*, 1706-1716.
14. Wieger, V.; Zoppel, S.; Wintner, E. *Laser Physics* **2007**, *17(4)*, 438-442.
15. Jiang, C.Y.,; Lau, W.S.; Yue, T.M.; Chiang, L. *CIRP Annals - Manufacturing Technology* **1993**, *42(1)*, 223-226.
16. Tandon, V.; Peck, W. *Methods Molecular Biol.* **2013**, *949*, 41-54.
17. Li, X.; Ballerini, D.R.; Shen, W. *Biomicrofluidics* **2012**, *6(1)*, 011301.
18. Lisowski, P.; Zarzycki, P. *Chromatographia* **2013**, *76(19-20)*, 1201-1214.
19. Martinez, A.W.; Phillips, S.T.; Whitesides, G.M.; Carrilho, E. *Anal. Chem.* **2009**, *82(1)*, 3-10.
20. Hemling, M.; Crooks, J.A.; Oliver, P.M.; Brenner, K.; Gilbertson, J.; Lisensky, G.C.; Weibel, D.B. *J. Chem. Ed.* **2013**, *91(1),* 112-115.
21. Davis, T.A.; Athey, S.L.; Vandevender, M.L.; Crihfield C.L.; Kolanko, C.C.E.; Shao, S.; Ellington, M.C.G.; Dicks, J.K.; Carver, J.S.; Holland, L.A. *J. Chem. Ed.* **2014** (In Press).
22. Fonash, S. *J. Nanoparticle Res.* **2001**, *3(1)*, 79-82.
23. Information about this competition can be found at http://www.microtas2014.org/authors/video_overview.html. The video will be displayed on the Photon Factory website photonfactory.auckland.ac.nz once the conference organizers post it themselves. The video can be seen at http://youtu.be/CKn0WiIjQyg

Article

NMR spectroscopy – a simple yet powerful tool in chemical biology

Ivanhoe K.H. Leung

School of Chemical Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand. (email: *i.leung@auckland.ac.nz*)

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Introduction

Molecular recognition events between proteins and ligands play essential roles in almost all biological processes in cells, ranging from transport to signalling, metabolism to biosynthesis. The ligands involved in these biological processes can be small molecules, peptides, proteins, metal ions, nucleic acids or other biomolecules. Studies of these binding events at the molecular and atomic levels can therefore lead to deeper understandings of their corresponding biological processes. In addition, modern drug discovery programmes often involve the development of small molecule compounds that bind specifically to a target protein receptor.[1–3] The ability to measure, monitor, study and characterise protein-ligand interactions and complexes are therefore of paramount importance in the fields of chemical biology, medicinal chemistry and drug discovery.

Amongst the many biophysical methods that are available to study protein-ligand interactions,[4,5] nuclear magnetic resonance (NMR) is unique as it can provide information about almost all aspects of protein-ligand interactions. It has found diverse applications including ligand screenings, binding constant (K_D) measurements, structure and conformation determinations, and dynamics studies of both proteins and ligands.[6,7] Many NMR experiments are available, which can be broadly divided into two approaches. One approach is called "ligand-observed NMR", which involves the observation of ligand resonances. The other approach is called "protein NMR", which involves the monitoring of isotopically labelled protein resonances.

A number of excellent reviews have already been published focusing on the technical and practical aspects of both ligand-observed and protein-observed NMR experiments.[8-19] The aim of this article is to provide researchers, especially those who work at the interface between chemistry and biology but who may not necessarily be familiar with NMR, overview descriptions of some of the most popular NMR techniques in the studies of protein-ligand interactions.

Ligand-observed NMR

Ligand-observed NMR methods are widely used for the studies of protein-ligand interactions in both academia and industry. For example, it is used extensively as a screening tool in the area of fragment-based drug discovery.[20–23] There are several reasons for the popularity of ligand-observed experiments (as opposed to protein NMR). Firstly, they do not require isotopically labelled protein. Secondly, it is possible to screen mixtures of compounds in a single experiment provided there are no overlaps in chemical shifts. Thirdly, the applicability of ligand-based NMR experiments is not limited by the size of the protein.

There are three main types of ligand-observed NMR experiments. One involves observing changes of the ligand resonances in the presence and absence of a protein receptor. Another involves the use of a reporter ligand, which is in competition with the ligand-of-interest for the same binding site. A third type relies on the nuclear Overhauser effect (NOE). It involves monitoring the signals of the free ligand that is in exchange with the bound ligand.

Direct ligand observation

Direct ligand observation is the simplest form of ligand-observed NMR experiments (Fig. 1a). Ligand binding can be indicated by comparing changes in the NMR parameters of the ligand in the absence and presence of the receptor protein. When a ligand molecule is bound to a protein, it experiences different chemical environments and rotational correlation times. The observed NMR parameters will therefore reflect the population weighted average of the free and bound forms of the ligand provided the exchange between the two forms is fast. Binding constants (K_D) can also be obtained by following changes in the ligand NMR parameters at different protein or ligand concentrations through titration experiments.[24,25]

Any measurable NMR parameters may be monitored. Changes in chemical shift, linewidth and peak intensity are the most common as they can be readily followed using simple 1D spectra. The differences in ligand linewidth and peak intensity can be further enhanced by using relaxation-edited experiments such as the Carr-Purcell-Meiboom-Gill (CPMG) sequence by exploiting the differences in longitudinal (T_1) and transverse (T_2) relaxation time constants between the ligand free and protein-bound forms.[26] The most common nuclei for direct observation are ^{1}H [27,28] and ^{19}F [28–31] although other spin ½ nuclei including ^{13}C,[29] ^{15}N [32] and ^{31}P [33] have also been used. Nuclei with a large chemical shift range (such as ^{19}F and ^{31}P) have an additional advantage because they possess large chemical shift anisotropy (CSA). In such cases, even weak binding interactions may lead to line broadening in the ^{19}F or ^{31}P spectra owing to the strong T_2 dependent line broadening pathway.[33,34]

Generally, for a fast exchange system, a slight excess of ligand (usually around 10 fold over protein concentration) is used in order to increase the population of the protein-ligand complex. Whilst this is optimal for medium-affin-

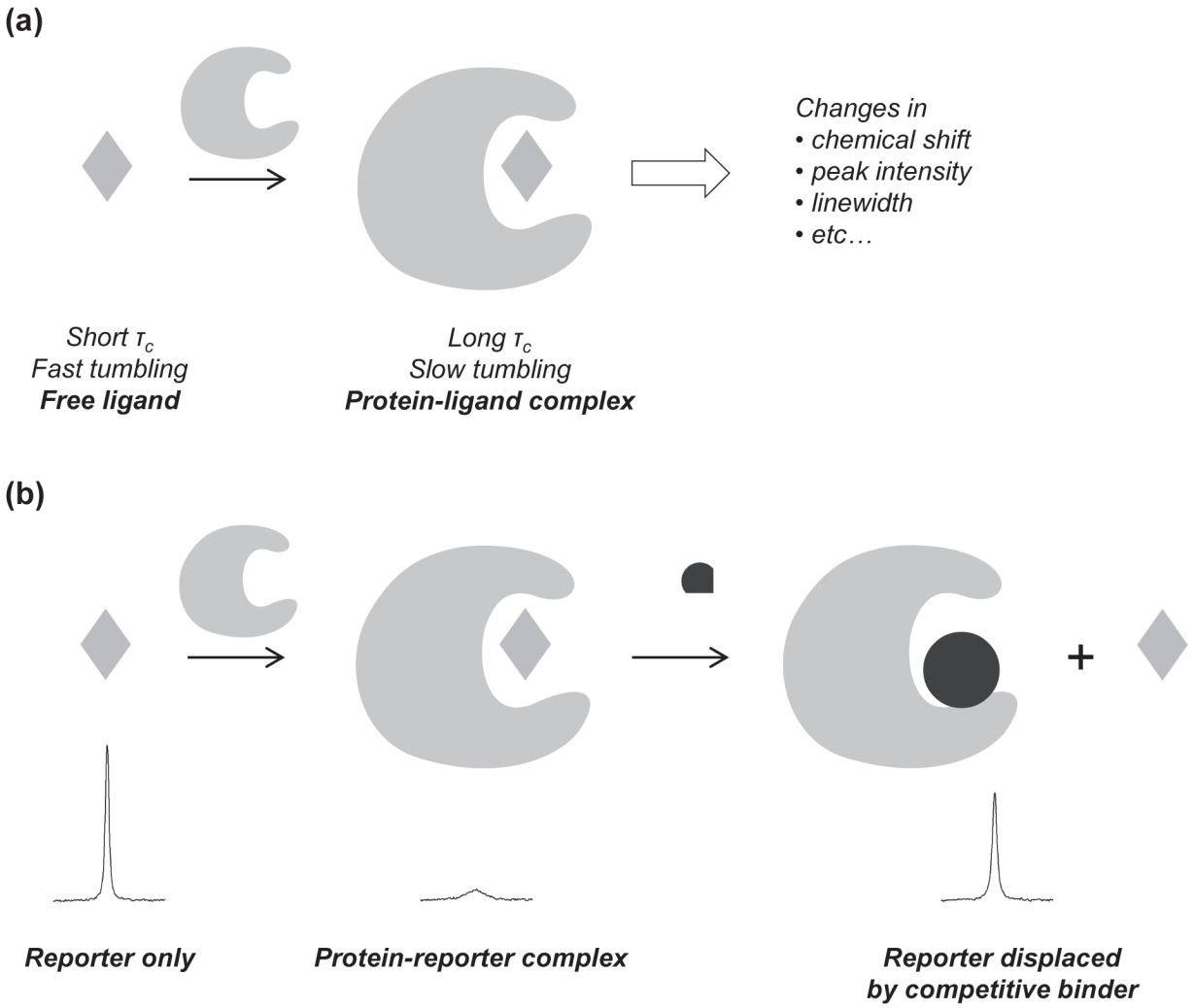


Fig. 1. (a) Scheme illustrating the principle of direct ligand observation in NMR screening. (b) Scheme illustrating the principle of reporter ligand displacement method in NMR screening.

ity protein-ligand systems, this setup may lead to false negatives for high-affinity ligands. This is because the dissociation rate (k_{off}) of high-affinity ligands from their protein-ligand complexes is usually slow. Under a slow exchange regime, the observed NMR signals no longer reflect the weighted populations of the free ligand and protein-ligand complex, and instead, they only reflect the free ligand population. Therefore, it may be difficult to detect slight decreases in peak intensity (as a result of ligand binding) as the spectrum is dominated by a large excess of free ligands. In such cases, a ~1:1 ratio of protein to ligand concentration can be used.

A recent example of applying direct ligand observation in ligand screening is reported by Manzenrieder *et al*. (Fig. 2).[33] As a proof-of-principle experiment, a library of five phosphorylated compounds was screened against the protein thermolysin, and binding was monitored by proton decoupled ^{31}P (^{31}P{^{1}H}) experiments. Upon addition of the protein, the ^{31}P signal of one of the five compounds disappeared, indicating binding of that particular compound to thermolysin. In order to test the binding specificity, a high-affinity known binder was then added to the mixture, which led to the reappearance of the vanished signal. This indicates the two compounds were competing for the same binding site. The authors also tested the lower limit of protein concentration that is required to detect binding. At 500 μM ligand concentration, they found that binding can be observed with as little as 3 μM protein owing to the strong CSA effect of ^{31}P.

Reporter displacement method

The reporter displacement method is an extension of the direct ligand observation method. It is a competition-based experiment, in which changes in the NMR parameters of a reporter ligand in the presence and absence of the ligand-of-interest are being monitored (Fig. 1b).[33,35–40]

There are two prerequisites for this method. Firstly, the ligand-of-interest and the reporter should compete for the same binding site, which otherwise may lead to false negative results. Secondly, the availability of a good reporter ligand is crucial: the k_{off} of the reporter should be sufficiently fast, and there should be no chemical shift overlap between the reporter and the ligands-of-interest. Binding constant of the ligands-of-interest can also be obtained by following the recovery of the reporter signal at different ligand concentrations, provided the K_D of the reporter to the target protein is known.

There are several advantages of using a reporter to follow ligand binding over direct ligand observation. Firstly, it

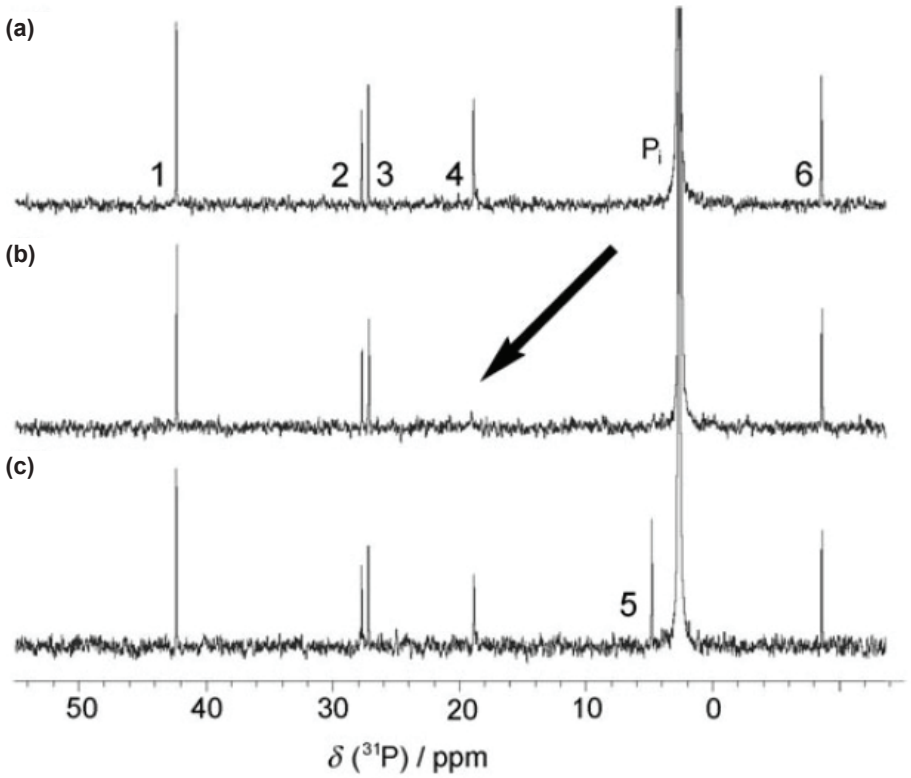


Fig. 2. Manzenrieder *et al*. applied $^{31}P\{^1H\}$ NMR to screen a mixture of five phosphorylated compounds to the protein thermolysin. (a) Library of five phosphorylated compounds (**1**, **2**, **3**, **4**, **6**; 0.5 mM each). (b) The signal of compound **4** disappeared upon addition of 0.25 mM thermolysin. (c) Addition of 0.5 mM compound **5**, a high-affinity binder of thermolysin, led to the recovery of the signal of compound **4**. Reprinted with permission from *Angew. Chem. Int. Ed.* **2008**, *47*, 2608–2611. Copyright 2008 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

provides site-specific binding information and therefore false positives due to non-specific binding can be minimised. Secondly, this method can be used to detect high-affinity ligands. This is because the experiment does not rely on the exchange between free and protein-bound forms of the ligand-of-interest, therefore it does not suffer from false negative results arising from slow ligand k_{off} as in the case of direct ligand observation.

We have recently applied the reporter displacement method to study ligand binding to prolyl hydroxylase domain 2 (PHD2), an enzyme that is involved in human oxygen sensing (Fig. 3).[38] 2-Oxoglutarate (2OG), the co-substrate of the enzyme, was used as the reporter ligand. As most PHD2 inhibitors to date are designed as 2OG competitor, binders can be readily identified and ranked according to their binding strengths. The simplicity of this method allows it to be applied routinely to screen and quantify novel binders for PHD2 and other oxygenases that utilise 2OG as a cosubstrate.

Nuclear Overhauser effect (NOE)-based methods

Another approach to study protein-ligand interactions is to utilise the nuclear Overhauser effect (NOE). Several techniques were developed based on this concept, the two most common techniques are saturation transfer difference NMR (STD-NMR)[41] and the water-ligand observation with gradient spectroscopy (waterLOGSY) method.[42]

STD-NMR

The STD-NMR method is based on the NOE between proteins and ligands (Fig. 4).[41] It is a combination of two experiments. In the first "on-resonance" experiment, radiofrequency pulses are applied to selected protein resonances for a defined length of time. Upon irradiation, all protein resonances become rapidly saturated by spin-diffusion. Magnetisation can also spread by the same process in an intermolecular fashion onto the bound ligands, which will lead to (partial) saturation of ligand resonances. If the ligand dissociates sufficiently fast, the saturation can be detected as a reduction in signal intensity in the spectrum. An "off-resonance" reference spectrum, which is essentially a normal ^1H spectrum, is also recorded without protein saturation in otherwise the same experimental conditions. Subtraction of the two spectra will lead to a "difference spectrum" in which only signals experiencing saturation are visible.

It is important to select a region of the protein that is far away from any ligand resonances for the selective on-resonance irradiation of the protein in order to avoid false positive results. The amount of time for the selective irradiation (saturation time) is typically between 1 and 5 seconds. A ligand excess of around 100 fold is usually used to ensure all the proteins are saturated with ligand molecules.

STD effects can be quantified by the STD factor, which is the fractional saturation of the on-resonance spectrum relative to the off-resonance spectrum. When comparing samples of different ligand excess, the STD amplification factor can be used. The STD amplification factor is the multiple of the STD factor and ligand excess. A mathematical representation is given below:

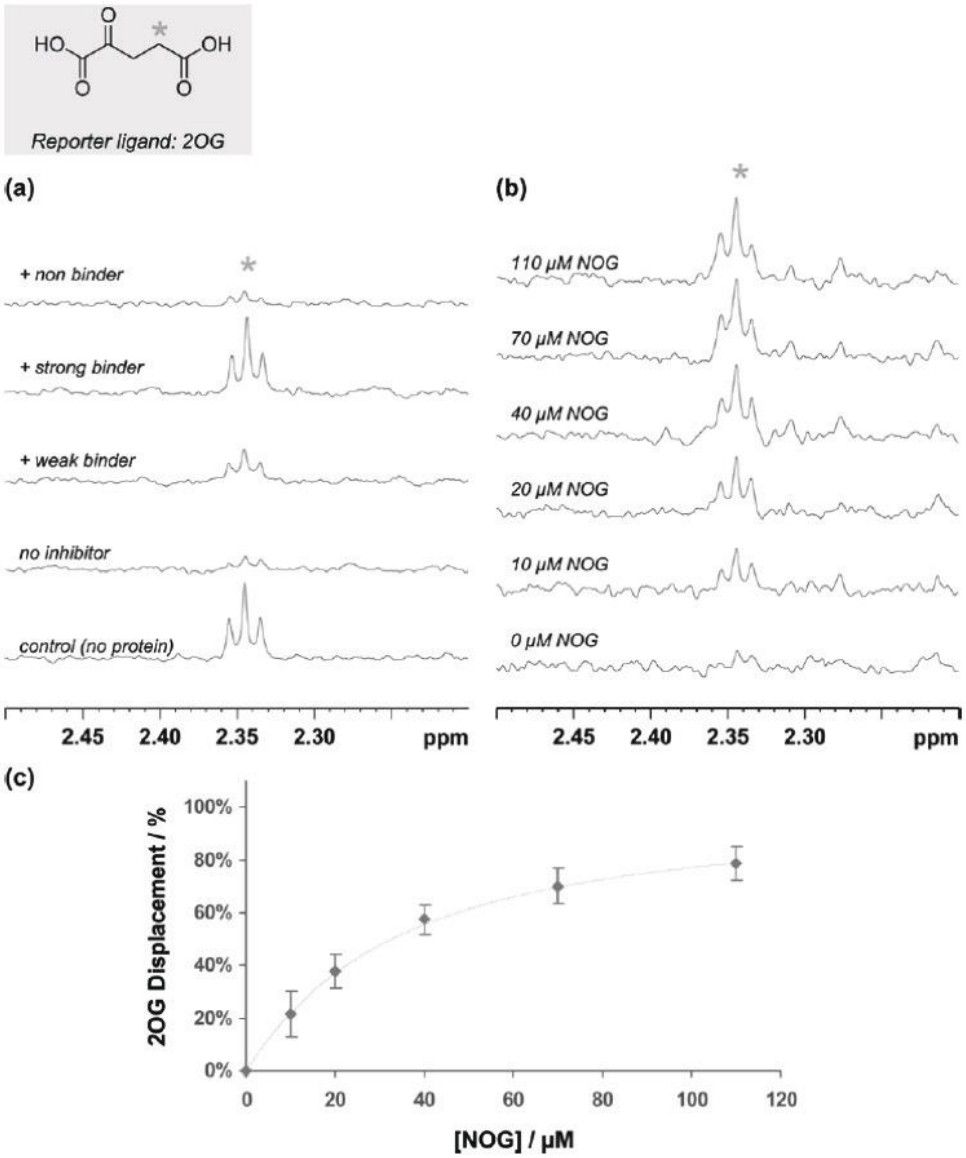


Fig. 3. Reporter ligand screening method. (a) Screening of PHD2 binders by monitoring the recovery of the reporter (2OG) signal. (b) Titration experiment monitoring reporter signal recovery at different concentrations of the ligand-of-interest (NOG). (c) Corresponding plot of the titration data. Reprinted with permission from *J. Med. Chem.* **2013**, *56*, 547–555. Copyright 2013 American Chemical Society.

$$\text{STD factor} = \frac{I_0 - I_{sat}}{I_0}$$

$$\text{STD amplification factor} = \frac{I_0 - I_{sat}}{I_0} \text{ x Ligand excess}$$

In which I_0 is the intensity of one signal in the off-resonance spectrum, I_{sat} is the intensity of the corresponding signal in the on-resonance spectrum, and $I_0 - I_{sat}$ represents the intensity of the STD spectrum.

As STD-NMR relies on fast ligand exchange between the free and protein-bound states, it cannot detect high-affinity protein-ligand systems due to slow ligand k_{off}. STD-NMR may not also detect ligands with very low affinity because the residence time of the ligand inside the protein binding site is too short for the transfer of magnetisation from the protein to the bound ligand.

The binding constant may be obtained by STD-NMR by observing changes in the STD amplification factor at different ligand concentrations.[43] However, its accuracy may be complicated by ligand rebinding, ligand relaxation time and protein saturation time. Firstly, even at modest saturation time (*e.g.* 2 seconds), the size of the observed STD signals is (partially) ordered by the ligand longitudinal relaxation time constant (T_1).[44] Secondly, ligand molecules may bind and then dissociate from the protein multiple times during the saturation time period.[43] These factors combine and contribute to an overestimation of K_D values.[43] Whilst in theory these influences may be minimised by using short protein saturation time, practically there will be problem with signal-to-noise ratio. Also, there may not be sufficient time for magnetisation to spread throughout the protein by spin-diffusion with short saturation time. In order to solve this problem, Angulo *et al.* proposed the construction binding curves using the initial growth rates of the STD amplification factors.[43] Although the protocol allows the accurate determination of K_D values, it is extremely time consuming as multiple STD spectra have to be recorded at different saturation times for each ligand concentration, and therefore the

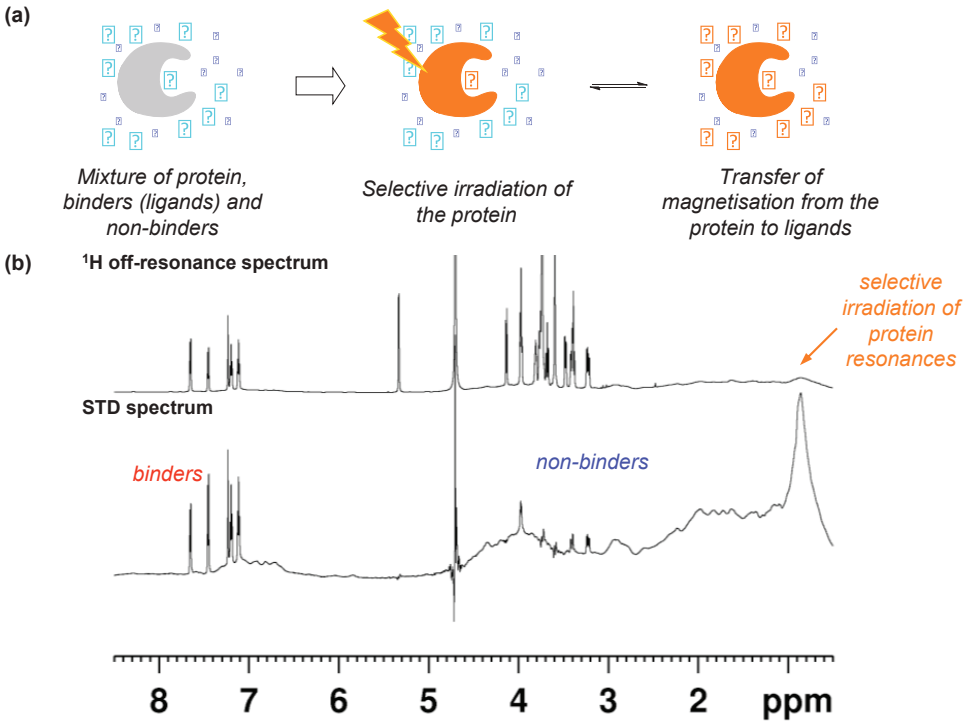


Fig. 4. (a) Scheme illustrating the principle of STD-NMR. (b) A typical STD-NMR spectrum. The mixture contained 100 μM bovine serum albumin (BSA), 10 mM tryptophan (binder) and 10 mM sucrose (non-binder). The saturation time was 2 seconds.

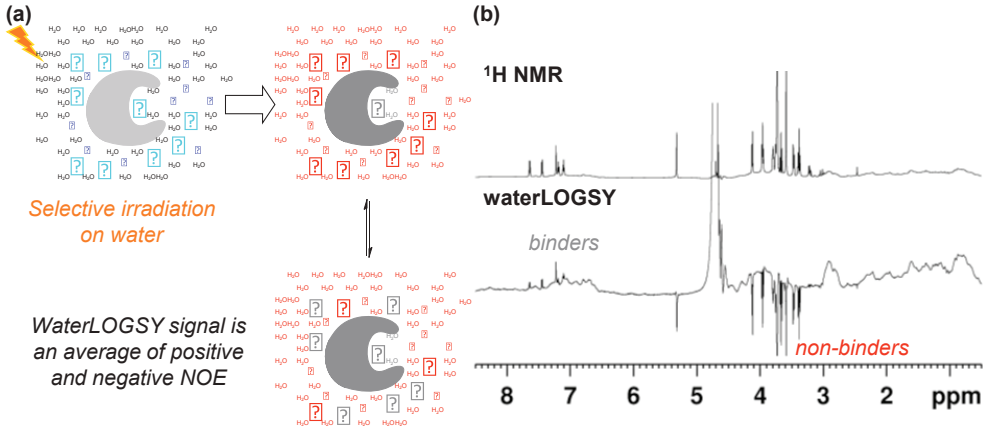


Fig. 5. (a) Scheme illustrating the principle of waterLOGSY. Red indicates positive NOE whilst grey indicates negative NOE. (b) A typical waterLOGSY spectrum. The mixture contained 100 μM bovine serum albumin (BSA), 2 mM tryptophan (binder) and 2 mM sucrose (non-binder) in 90% H_2O and 10% D_2O. The mixing time was 1 second.

use of STD-NMR to measure K_D is not widely applied.

Perhaps the most famous application of STD-NMR is the mapping of ligand binding epitope inside the protein binding site. Epitope mapping is achieved by the fact that the size of the observed STD signals generally correlate with the distance between the protein and ligand inside the binding site. However, as previously discussed, even at modest saturation time, the epitope map will be ordered by ligand T_1s rather than protein-ligand distances. Krishna and Jayalakshmi proposed the use of a complete relaxation and conformational exchange matrix analysis (CORCEMA-ST) to tackle this problem,[45] however, the method is time-consuming and require additional information such as the structural model of the protein for the full analysis. In order to simplify the analyses, Kemper *et al.* proposed the measurement of STD-NMR at saturation conditions (saturation time ~15 seconds), and then divided the observed STD enhancement of each resonance by the free ligand T_1 value of the same resonance.[46] This method thus allows one to define an accurate ligand binding epitope map from STD data without any requirement for knowledge of the protein structure.

WaterLOGSY

The waterLOGSY method is based on NOE between bulk water molecules, ligands and proteins (Fig. 5).[42] The bulk water is selectively saturated. Magnetisation then spreads in an intermolecular manner to free ligands, bound ligands and proteins, with subsequent magnetisation transfer from the protein to bound ligands. Due to differences in rotational correlation times between free and bound components of the mixture (water molecules, ligands and proteins) and hence opposite signs of their intermolecular NOEs, binders and non-binders can usually be distinguished as opposite phased resonances in the waterLOGSY spectrum.

As the bulk water is used for the transfer of magnetisation, experiments are usually conducted in 90% H_2O and

10% D_2O mixture. Typically, a NOE mixing time of 0.8 to 1 second is used for waterLOGSY experiments. A ligand excess of around 50 fold is used. This is because if the ligand excess is too large, the resulting waterLOGSY spectrum will be dominated by free ligand NOEs, whilst if the ligand excess is too small, the bound ligand concentration will be too low. Similar to STD-NMR, waterLOGSY generally does not work for very strong or very weak ligand systems, as it relies on fast exchange between free and bound ligands.

WaterLOGSY is widely used as a primary screening tool.[47] It has been shown to be a much more sensitive method than STD-NMR. The measurement of the binding constant by waterLOGSY has also been proposed, although Fielding *et al.* have shown that the accuracy may be influenced by protein concentration, although the exact reason is currently not known.[48]

Protein NMR

^{1}H-^{15}N heteronuclear single quantum correlation

The most common method to study protein-ligand interactions by protein-observed NMR is by chemical shift perturbation of backbone amide protons.[49] Analyses are usually conducted using ^{1}H-^{15}N heteronuclear single quantum correlation (HSQC) experiments. Each resonance on the HSQC spectrum represents a single amino acid (except for proline which has no NH). Side chain NH and NH_2 groups may also be present in the spectrum. Amide chemical shifts are highly sensitive to perturbations in the environment. The mapping of ligand binding sites on the protein can be readily obtained by comparing amide chemical shifts with and without the ligand. Such information is particularly useful, for instance, in establishing structural activity relationships (SAR-by-NMR) across a series of binders and ligands.[50] Provided the exchange between the ligand free and protein-bound forms is fast on the NMR time scale, it is also possible to measure K_D by following amide chemical shift changes at different ligand concentrations.[24,25]

^{1}H-^{15}N HSQC experiments usually require uniformly ^{15}N-labelled proteins, although other selective labelling schemes are also available.[51–53] For large proteins such as those with molecular weight >25 kDa,[54] ^{2}H,^{15}N-double labelled proteins may be required in order to slow down the transverse relaxation rates of the amide protons.[55] It has also been shown that at relatively high protein concentration (~1 mM), ligand binding can be monitored with unlabelled protein at natural abundance using the band-selective optimised flip-angle short-transient HMQC (SOFAST-HMQC) experiment.[56] Because amide

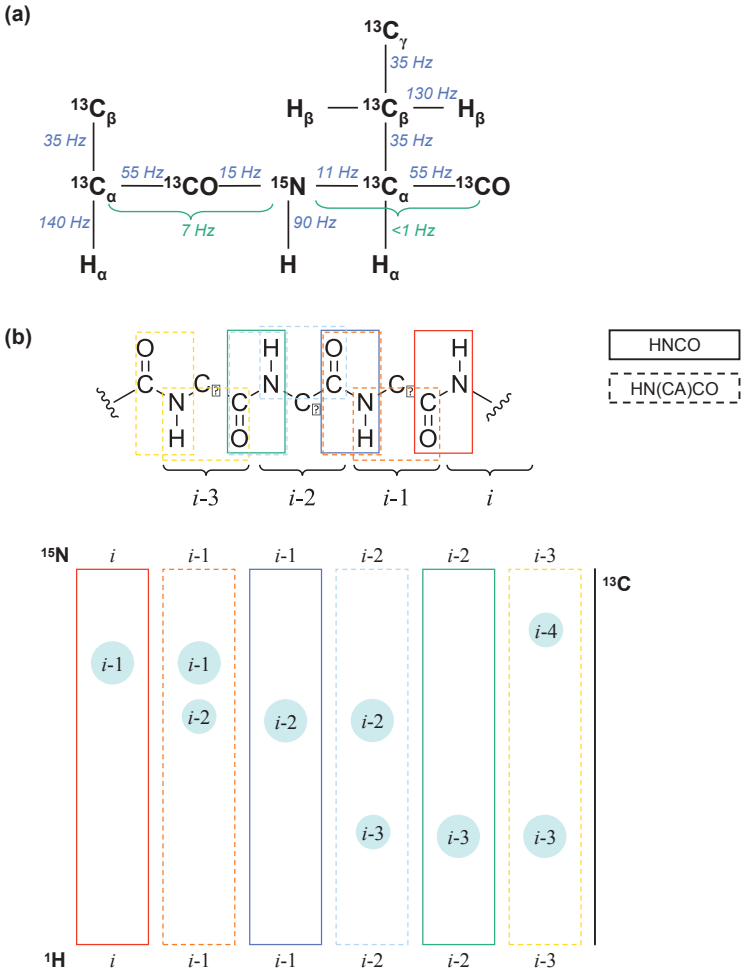


Fig. 6. (a) Typical $^1J/^2J$ coupling constants in a protein backbone spin system.[59] The blue numbers are ^1J and the green numbers are ^2J coupling constants respectively. (b) An illustration of a sequential walk along the ^{1}H-^{13}C plane of the HNCO (solid line) and NH(CA)CO (dotted line) experiments. HNCO shows correlation between the amide resonance of the current residue (*i*) and the CO resonance of the previous residue (*i*-1), whilst HN(CA)CO shows correlations between the amide resonance of the current residue (*i*) and the CO resonances of both the current (*i*) and the previous residues (*i*-1).

signals are being observed, ^{1}H-^{15}N HSQC experiments are usually conducted in 90% H_2O and 10% D_2O mixture, with a slightly acidic pH at around 6.5.

Protein backbone assignment

The bottleneck of protein NMR experiments is protein backbone assignment. For small proteins (MW < 10 kDa), the sequential assignment strategy may be used.[57] The first step involves the recording and analyses of 3D heteronuclear-edited correlation spectra (such as TOCSY-^{1}H-^{15}N HSQC) to identify amino acid spin systems by tracing through-bond scalar interactions along the amino acid side chain. The next step involves the recording and analyses of through-space dipolar interactions, usually using 3D heteronuclear-edited experiments such as the NOESY-^{1}H-^{15}N HSQC, to allow sequential NOE analysis along the protein sequence.

For larger proteins, the triple resonance assignment strategy can be used.[58,59] The minimum labelling requirement for this strategy is ^{13}C and ^{15}N. For proteins with a molecular weight of 25 kDa or above, triple labelling (with ^{2}H, ^{13}C and ^{15}N) is required.[55] Triple resonance experiments rely on the relatively large ^{1}J (and in some cases ^{2}J) couplings between ^{1}H, ^{15}N and ^{13}C in the protein backbone spin system (Fig. 6A). The first step usually involves the recording of at least one set of the triple resonance experiments, such as HN(CO)CACB, which gives correlation information between $^{1}H_i$, $^{15}N_i$, $^{13}C\alpha_{i-1}$ and $^{13}C\beta_{i-1}$, and HNCACB, which gives correlation information between $^{1}H_i$, $^{15}N_i$, $^{13}C\alpha_i$, $^{13}C\beta_i$, $^{13}C\alpha_{i-1}$ and $^{13}C\beta_{i-1}$. This allows sequential linking of the amide protons (Fig. 6B). Amino acid types can then be identified by the ^{13}C chemical shifts of α and β carbons.

Protein conformational and dynamic studies

Proteins are not rigid, and ligand binding may induce changes in the solution structure or dynamics of the protein. Protein-observed NMR can be applied to study these protein conformational changes upon ligand binding. For example, Bleijlevens *et al.* showed a conformational switch of AlkB, an enzyme that is involved in repairing damaged DNA, upon binding its cosubstrate 2OG and its coproduct succinate (Fig. 7).[60,61] ^{1}H-^{15}N HSQC shows that AlkB is unstructured in its *apo*-form, as indicated by the poor dispersion of the amide chemical shifts and resonance overlap. Upon addition of the coproduct succinate, the enzyme became slightly more folded as shown by the ^{1}H-^{15}N HSQC spectrum. Remarkably, AlkB became fully folded upon addition of the cosubstrate 2OG. This data provides a plausible mechanism for the release of succinate and replenishment of 2OG at the end of the catalytic cycle.

In addition to conformational change, protein NMR can also be applied to measure the overall and internal backbone dynamics of proteins in the nanosecond to picosecond timescale.[62,63] ^{15}N relaxation (T_1, T_2 and heteronuclear NOE) is a useful probe to characterise these dynamics because ^{15}N relaxation mainly reflects the reorientational motion of the N-H bond vector, which moves at a timescale (ns–ps) faster than the overall rotational correlation time (tens of ns). In a recent example, Ravindranathan *et al.* applied ^{15}N relaxation studies to study the influence of RNA binding to the backbone dynamics of the sterile alpha motif (SAM) domain of VTS1p, which is a posttranscriptional gene regulator in yeast.[64] The data suggests that the binding interface between the VTS1p-SAM domain and RNA became more rigid upon RNA binding. In contrast, the flexibility of the other regions on the protein domain was increased upon binding of the RNA. These experiments show that molecular dynamics could play a crucial role in modulating binding affinity and ligand recognition.

Conclusions and perspectives

In this article we have covered several NMR techniques that are commonly applied to study protein-ligand interactions, including both ligand-observed and protein-observed methods. We have described the information that these methods can provide, and also their advantages and limitations. This article is not intended to be a comprehensive review, and many emerging methods and their applications are not covered. In fact, the main focus of this article is to introduce to researchers who work at the interface between chemistry and biology, such as synthetic chemists and medicinal chemists, a flavour of

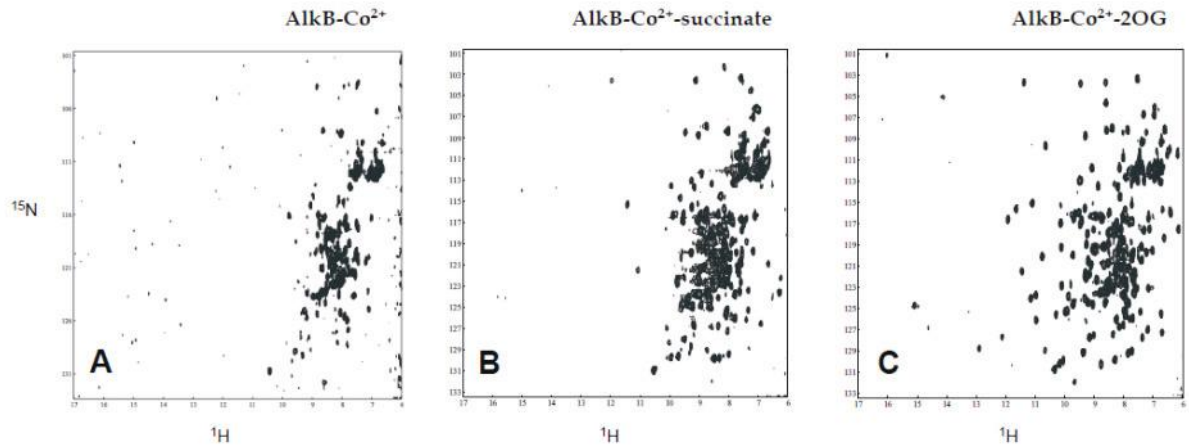


Fig. 7. ^{1}H-^{15}N HSQC spectra of AlkB. The catalytic Fe(II) is substituted by Co(II) to stop cosubstrate turnover. (a) AlkB is unstructured in the absence of its cosubstrate (2OG) or coproduct (succinate). (b) AlkB is partially structured in the presence of its coproduct succinate. (c) AlkB is fully structured in the presence of its cosubstrate 2OG. Reprinted with permission from *EMBO Rep.* **2008**, *9*, 872-877. Copyright 2008 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

what NMR can provide in the areas of inhibitor discovery and protein-ligand interactions. Given the prevalence of NMR applications in chemical biology presented in other reviews and conferences, it is conceivable that NMR will become an even more essential tool for studying proteins, enzymes, and their interactions with ligands and inhibitors in the future.

References

1. Bleicher, K. H.; Böhm, H.-J.; Müller, K.; Alanine, A. I. A guide to drug discovery: Hit and lead generation: beyond high-throughput screening. Nat. Rev. Drug Discov. **2003,** 2, 369–378.
2. Arkin, M. R.; Wells, J. A. Small-molecule inhibitors of protein–protein interactions: progressing towards the dream. Nat. Rev. Drug Discov. **2004,** 3, 301–317.
3. Congreve, M.; Murray, C. W.; Blundell, T. L. Keynote review: Structural biology and drug discovery. Drug Discov. Today **2005,** 10, 895–907.
4. Protein-ligand interactions: structure and spectroscopy; Harding, S. E., Chowdhry, B. Z., Eds.; Oxford University Press: Oxford, 2001.
5. Protein-ligand interactions: hydrodynamics and calorimetry; Harding, S. E., Chowdhry, B. Z., Eds.; Oxford University Press: Oxford, 2001.
6. Jahnke, W. Perspectives of biomolecular NMR in drug discovery: the blessing and curse of versatility. J. Biomol. NMR **2007,** 39, 87–90.
7. Pellecchia, M.; Bertini, I.; Cowburn, D.; Dalvit, C.; Giralt, E.; Jahnke, W.; James, T. L.; Homans, S. W.; Kessler, H.; Luchinat, C.; Meyer, B.; Oschkinat, H.; Peng, J.; Schwalbe, H.; Siegal, G. Perspectives on NMR in drug discovery: a technique comes of age. Nat. Rev. Drug Discov. **2008,** 7, 738–745.
8. Lepre, C. A.; Moore, J. M.; Peng, J. W. Theory and applications of NMR-based screening in pharmaceutical research. Chem. Rev. **2004,** 104, 3641–3675.
9. Otting, G. Experimental NMR techniques for studies of protein-ligand interactions. Curr. Opin. Struct. Biol. **1993,** 3, 760–768.
10. Jahnke, W.; Widmer, H. Protein NMR in biomedical research. Cell. Mol. Life Sci. **2004,** 61, 580–599.
11. Heller, M.; Kessler, H. NMR spectroscopy in drug design. Pure Appl. Chem. **2001**, 73, 1429–1436.
12. Powers, R. Advances in nuclear magnetic resonance for drug discovery. Exp. Opin. Drug Discov. **2009,** 4, 1077–1098.
13. Blommers, M. J. J.; Flörsheimer, A.; Jahnke, W. Strategies for drug discovery using NMR. In BioNMR in drug research. Methods and principle in medicinal chemistry; Zerbe, O., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2002; Chapter 20, pp 439–457.
14. Marchioro, C.; Davalli, S.; Provera, S.; Heller, M.; Ross, A.; Senn, H. Experiments in NMR-based screening. In BioNMR in drug research. Methods and principle in medicinal chemistry; Zerbe, O., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2002; Chapter 14, pp 321–340.
15. NMR of biomolecules. Towards mechanistic systems biology; Bertini, I., McGreevy, K. S., Parigi, G., Eds.; Wiley-VCH Verlag & Co.: Weinheim, 2012.
16. Meyer, B.; Peters, T. NMR spectroscopy techniques for screening and identifying ligand binding to protein receptors. Angew. Chem. Int. Ed. **2003,** 42, 864–890.
17. Ludwig, C.; Guenther, U. L. Ligand based NMR methods for drug discovery. Front. Biosci. **2009,** 14, 4565–4574.
18. Mercier, K. A.; Shortridge, M. D.; Powers, R. A multi-step NMR screen for the identification and evalution of chemical leads for drug discovery. Comb. Chem. High Throughput Screen. **2009,** 12, 285–295.
19. Hajduk, P. J.; Meadows, R. P.; Fesik, S. W. NMR-based screening in drug discovery. Quart. Rev. Biophys. **1999,** 32, 211–240.
20. Congreve, M.; Chessari, G.; Tisi, D.; Woodhead, A. J. Recent developments in fragment-based drug discovery. J. Med. Chem. **2008,** 51, 3661–3680.
21. Jhoti, H.; Cleasby, A.; Verdonk, M.; Williams, G. Fragment-based screening using X-ray crystallography and NMR spectroscopy. Curr. Opin. Chem. Biol. **2007,** 11, 485–493.
22. Dalvit, C. NMR methods in fragment screening: theory and a comparison with other biophysical techniques. Drug Discov. Today **2009,** 14, 1051–1057.
23. Murray, C. W.; Rees, D. C. The rise of fragment-based drug discovery. Nat. Chem. **2009,** 1, 187–192.
24. Fielding, L. NMR Methods for the determination of protein-ligand dissociation constants. Curr. Top. Med. Chem. **2003,** 3, 39–53.
25. Fielding, L. NMR methods for the determination of protein–ligand dissociation constants. Prog. Nucl. Magn. Reson. Spectrosc. **2007,** 51, 219–242.
26. Hajduk, P. J.; Olejniczak, E. T.; Fesik, S. W. One-dimensional relaxation- and diffusion-edited NMR methods for screening compounds that bind to macromolecules. J. Am. Chem. Soc. **1997,** 119, 12257–12261.
27. Jardetzky, O.; Wade, N. G.; Fischer, J. J. Proton magnetic resonance investigation of enzyme-coenzyme complexes. Nature **1963,** 197, 183–184.
28. Dalvit, C.; Gossert, A. D.; Coutant, J.; Piotto, M. Rapid acquisition of ^{1}H and ^{19}F NMR experiments for direct and competition ligand-based screening. Magn. Reson. Chem. **2011,** 49, 199–202.
29. Krishna Sastry, M. V.; Swamy, M. J.; Surolia, A. Analysis of dynamics and mechanism of ligand binding to Artocarpus integrifolia agglutinin. A ^{13}C and ^{19}F NMR study. J. Biol. Chem. **1988,** 263, 14826–14831.
30. Dalvit, C.; Flocco, M.; Veronesi, M.; Stockman, B. J. Fluorine-NMR competition binding experiments for high-throughput screening of large compound mixtures. Comb. Chem. High Throughput Screen. **2002,** 5, 605–611.
31. Tengel, T.; Fex, T.; Emtenäs, H.; Almqvist, F.; Sethson, I.; Kihlberg, J. Use of 19F NMR spectroscopy to screen chemical libraries for ligands that bind to proteins. Org. Biomol. Chem. **2004,** 2, 725–731.
32. Werbeck, N. D.; Kirkpatrick, J.; Reinstein, J.; Hansen, D. F. Using 15N-ammonium to characterise and map potassium binding sites in proteins by NMR spectroscopy. ChemBioChem **2014,** 15, 543–548.
33. Manzenrieder, F.; Frank, A. O.; Kessler, H. Phosphorus NMR spectroscopy as a versatile tool for compound library screening. Angew. Chem. Int. Ed. **2008,** 47, 2608–2611.
34. Dalvit, C.; Fagerness, P. E.; Hadden, D. T. A.; Sarver, R. W.; Stockman, B. J. Fluorine-NMR experiments for high-throughput screening: theoretical aspects, practical considerations, and range of applicability. J. Am. Chem. Soc. **2003,** 125, 7696-7703.
35. Jahnke, W.; Floersheim, P.; Ostermeier, C.; Zhang, X.; Hemmig, R.; Hurth, K.; Uzunov, D. P. NMR reporter screening for the detection of high-affinity ligands. Angew. Chem. Int. Ed. **2002,** 41, 3420–3423.
36. Dalvit, C.; Flocco, M.; Knapp, S.; Mostardini, M.; Perego, R.; Stockman, B. J.; Veronesi, M.; Varasi, M. High-throughput NMR-based screening with competition binding experiments. J. Am. Chem. Soc. **2002,** 124, 7702–7709.
37. Dalvit, C.; Flocco, M.; Stockman, B. J.; Veronesi, M. Competition binding experiments for rapidly ranking lead molecules for their binding affinity to human serum albumin. Comb. Chem. High Throughput Screen. **2002,** 5, 645–650.
38. Leung, I. K. H.; Demetriades, M.; Hardy, A. P.; Lejeune, C.; Smart, T. J.; Szöllössi, A.; Kawamura, A.; Schofield, C. J.; Claridge, T. D. W. Reporter ligand NMR screening method for 2-oxoglutarate oxygenase inhibitors. J. Med. Chem. **2013,** 56, 547–555.
39. Araç, D.; Murphy, T.; Rizo, J. Facile detection of protein-protein interactions by one-dimensional NMR spectroscopy. Biochemistry **2003,** 42, 2774–2780.

40. Dalvit, C.; Mongelli, N.; Papeo, G.; Giordano, P.; Veronesi, M.; Moskau, D.; Kümmerle, R. Sensitivity improvement in ^{19}F NMR-based screening experiments: theoretical considerations and experimental applications. J. Am. Chem. Soc. **2005,** 127, 13380–13385.
41. Mayer, M.; Meyer, B. Characterization of ligand binding by saturation transfer difference NMR spectroscopy. Angew. Chem. Int. Ed. **1999,** 38, 1784–1788.
42. Dalvit, C.; Pevarello, P.; Tató, M.; Veronesi, M.; Vulpetti, A.; Sundström, M. Identification of compounds with binding affinity to proteins via magnetization transfer from bulk water. J. Biomol. NMR **2000,** 18, 65–68.
43. Angulo, J.; Enríquez-Navas, P. M.; Nieto, P. M. Ligand–receptor binding affinities from saturation transfer difference (STD) NMR spectroscopy: the binding isotherm of STD initial growth rates. Chem. Eur. J. **2010,** 16, 7803–7812.
44. Yan, J.; Kline, A. D.; Mo, H.; Shapiro, M. J.; Zartler, E. R. The effect of relaxation on the epitope mapping by saturation transfer difference NMR. J. Magn. Reson. **2003,** 163, 270–276.
45. Jayalakshmi, V.; Rama Krishna, N. Complete relaxation and conformational exchange matrix (CORCEMA) analysis of intermolecular saturation transfer effects in reversibly forming ligand-receptor complexes. J. Magn. Reson. **2002,** 155, 106–118.
46. Kemper, S.; Patel, M. K.; Errey, J. C.; Davis, B. G.; Jones, J. A.; Claridge, T. D. W. Group epitope mapping considering relaxation of the ligand (GEM-CRL): including longitudinal relaxation rates in the analysis of saturation transfer difference (STD) experiments. J. Magn. Reson. **2010,** 203, 1–10.
47. Dalvit, C.; Fogliatto, G.; Stewart, A.; Veronesi, M.; Stockman, B. WaterLOGSY as a method for primary NMR screening: Practical aspects and range of applicability. J. Biomol. NMR **2001,** 21, 349–359.
48. Fielding, L.; Rutherford, S.; Fletcher, D. Determination of protein-ligand binding affinity by NMR: observations from serum albumin model systems. Magn. Reson. Chem. **2005,** 43, 463–470.
49. Williamson, M. P. Using chemical shift perturbation to characterise ligand binding. Prog. Nucl. Magn. Reson. Spectrosc. **2013,** 73, 1–16.
50. Shuker, S. B.; Hajduk, P. J.; Meadows, R. P.; Fesik, S. W. Discovering high-affinity ligands for proteins: SAR by NMR. Science **1996,** 274, 1531–1534.
51. Kainosho, M. Isotope labelling of macromolecules for structural determinations. Nat. Struct. Biol. **1997,** 4, 858–861.
52. Patzelt, H.; Goto, N.; Iwai, H.; Lundstrom, K.; Fernholz, E. Modern methods for the expression of proteins in isotopically enriched form. In BioNMR in drug research; Zerbe, O., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2003; Chapter 1, pp 1–38.
53. Ohki, S.-y.; Kainosho, M. Stable isotope labeling methods for protein NMR spectroscopy. Prog. Nucl. Magn. Reson. Spectrosc. **2008,** 53, 208–226.
54. Kay, L. E.; Gardner, K. H. Solution NMR spectroscopy beyond 25 kDa. Curr. Opin. Struct. Biol. **1997**, 7, 722–731.
55. Gardner, K. H.; Kay, L. E. The use of 2H, 13C, 15N multidimensional NMR to study the structure and dynamics of proteins. Annu. Rev. Biophys. Biomol. Struct. **1998**, 27, 357-406.
56. Quinternet, M.; Starck, J. P.; Delsuc, M. A.; Kieffer, B. Unraveling complex small-molecule binding mechanisms by using simple NMR spectroscopy. Chem. Eur. J. **2012,** 18, 3969–3974.
57. Wüthrich, K. NMR of proteins and nucleic acids; John Wiley and Sons, Inc.: New York, 1986; pp 130–161.
58. Ikura, M.; Kay, L. E.; Bax, A. A novel approach for sequential assignment of 1H, 13C, and 15N spectra of larger proteins: heteronuclear triple-resonance three-dimensional NMR spectroscopy. Application to calmodulin. Biochemistry **1990,** 29, 4659–4667.
59. Sattler, M.; Schleucher, J.; Griesinger, C. Heteronuclear multidimensional NMR experiments for the structure determination of proteins in solution employing pulsed field gradients. Prog. Nucl. Magn. Reson. Spectrosc. **1999,** 34, 93–158.
60. Bleijlevens, B.; Shivarattan, T.; Flashman, E.; Yang, Y.; Simpson, P. J.; Koivisto, P.; Sedgwick, B.; Schofield, C. J.; Matthews, S. J. Dynamic states of the DNA repair enzyme AlkB regulate product release. EMBO Rep. **2008,** 9, 872–877.
61. Bleijlevens, B.; Shivarattan, T.; van den Boom, K. S.; de Haan, A.; van der Zwan, G.; Simpson, P. J.; Matthews, S. J. Changes in protein dynamics of the DNA repair dioxygenase AlkB upon binding of Fe2+ and 2-oxoglutarate. Biochemistry **2012,** 51, 3334–3341.
62. Kleckner, I. R.; Foster, M. P. An introduction to NMR-based approaches for measuring protein dynamics. Biochim. Biophys. Acta. **2011,** 1814, 942–968.
63. Kempf, J. G.; Loria, J. P. Protein dynamics from solution NMR: theory and applications. Cell Biochem. Biophys. **2003,** 37, 187–211.
64. Ravindranathan, S.; Oberstrass, F. C.; Allain, F. H.-T. Increase in backbone mobility of the VTS1p-SAM domain on binding to SRE–RNA. J. Mol. Biol. **2010,** 396, 732–746.

Some unremembered chemists

A series of articles that explores the lives and work of selected chemists who have made a significant contribution to the advancement of the discipline, the profession and well-being of mankind, yet who are little remembered.

Philip Wilfred Robertson (1884-1969)

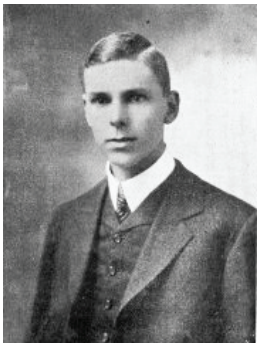
Brian Halton

School of Chemical & Physical Sciences, Victoria University, PO Box 600, Wellington 6140
(email: *brian.halton@vuw.ac.nz*)

Philip Wilfred Robertson was born in Ponsonby, Auckland, on September 22nd, 1884 the son of Donald Robertson, a postal clerk who was to become public service commissioner in Wellington, and his wife Edith Martin.[1] PW, as he was referred to by most (but Robbie by his friends[2]) was educated at Ponsonby School in Auckland and The Terrace School, on Fitzherbert Terrace in Wellington. His secondary education was gained at Wellington College where he was school dux in 1900. This was followed by entry to Victoria College to study the sciences. He took the introductory programme in chemistry taught by Professor T.H. Easterfield in the second year that it was offered. At that time the college had no permanent building of its own and science classes were held in the upstairs rooms of the Wellington Technical School on Victoria Street.[3,4] After an outstanding undergraduate career, PW graduated MA with first-class honours in chemistry, conferred on the 29th of June in 1905, and an MSc in 1906 by which time he had published some nine papers alone in the journals of the Chemical Society (UK). Easterfield promulgated the concept of research from the earliest time of study, but even so, this level of publication by a student in his first years is truly amazing. PW also had papers read by Easterfield before members of the New Zealand Institute, the forerunner of the Royal Society of New Zealand, and published in their proceedings; one paper was published jointly with Easterfield.

As the leading student in his class PW gained a Sir George Grey Scholarship, a Senior Scholarship, and the Jacob Joseph Scholarship. His senior scholarship was the second for Victoria College. These achievements, coupled with his prowess at hockey and tennis, secured for him Victoria College's first Rhodes scholarship and the second offered in New Zealand. He proceeded to Trinity College, Oxford in October 1905 and won an open science scholarship there with a value of GBP 80. This scholarship was considered by the Oxfordians to require a greater scholastic feat than the winning of a Rhodes scholarship.[5] As PW was receiving the stipends of a Rhodes scholar he was entitled only to the honour and glory of the open science scholarship apart from certain privileges attached to the title of *Scholar of Trinity*. Nonetheless, the college authorities chose to give him the benefit of the scholarship by allowing him to pursue his studies abroad for a year at the close of his Oxford course.

Robertson gained first-class honours in natural sciences after two years and spent a year pursuing other chemical interests that led to further publications. Then, in



P.W. Robertson, Rhodes Scholar 1905 (from *The Spike* or *Victoria College Review*, June 1905, p. 54; with permission).

May 1908, he registered at the University of Leipzig to take his PhD with Professor Arthur R. Hanszch. Hantzsch is the well-known heterocyclic chemist whose pyridine and pyrrole syntheses were each named after him. PW was a competent linguist having studied German under von Zedlitz at Victoria College and, it is reputed, was so fluent that he easily passed for a native in Germany and Austria. His research in Leipzig involved the salts and hydrates of hydroxyazo compounds and copper ammonia complexes. He gained three publications with his supervisor in *Berichte der Deutschen Chemischen Gesellschaft*, one in 1909 and two in 1910. His PhD was completed in June 1909 with the title (in German) *Optical Studies of I Copper ammonia complexes, II Yellow and red salts of oxyazobenzenes*. In those days formal application for doctoral examination was required and PW applied for his on June 9, 1909, as shown. It was followed by a letter asking if the likely date of examination was known. It actually took place on June 22 when PW was deemed to be an outstanding first class candidate.[6] Among the courses that he took during his PhD were those on the photochemistry of organic compounds, mineralogy, salts and complexes, and theoretical and technical electrochemistry, all from the Chemistry Department staff, Böttger, Le Blanc, Ley, Stobbe and Zirkel.

Arthur .R. Hantzsch

Sekt.: III Prokanz.: Köster

№ 126

Um die philosophische Doktorwürde bewirbt sich

Herr Philip Robertson aus Auckland (Neuseeland)

(Leipzig, Tal. Rhode-Str. 7 II)

Die von dem Bewerber eingereichte Abhandlung

Optische Studien über:

I. Kupferammoniakkomplexe.

II. Gelbe und rote Salze aus p-Oxyazobenzolen.

nebst Curriculum vitae, Erklärung, und 3 Zeugnissen folgt hierbei.

Um Begutachtung der Abhandlung werden zunächst die Herren

Kollegen Hantzsch u. Beckmann ersucht.

Die Gebühren sind dem Fakultätsdiener eingehändigt.

Leipzig, den 9 Juni 1909

d. Z. Prokanzellar. Köster

Prädikate der Dissertation: I = egregia; II = admodum laudabilis; III = laudabilis; IV = illaud.

Fächer der mündlichen Prüfung: Chemie (Hantzsch), Mineralogie, Physik (Des Coudres)

Sonstige Bemerkungen:

Zeugnis über die Ostern Semester wird nachgeliefert.

The application by P.W. Robertson for doctoral examination, June 1909 (courtesy Leipzig University archive)

Following his doctoral completion in Leipzig, Robertson accepted appointment as professor of chemistry at Government College, Rangoon, in Burma. Prior to 1904 this was Rangoon College but that year its name changed to Government College and stayed as such until 1920 when it became University College ahead of merging that same year with the Baptist-affiliated Judson College. By 1880, Arts and Science intermediate level courses at Rangoon College were given by staff members of the College who were recognized by London University. Robertson became one of these. His decision to take a position in Burma was to enable him to study Buddhism first-hand as he has described in his autobiography.[7] The sojourn in the tropics was less than two full years, but during his time there he contracted malaria and, although he recovered, its effects never completely left him to the extent that he was often cold, muffled in a thick scarf and overcoat even on the warmest of days, and he rarely went out in the evenings.[8]

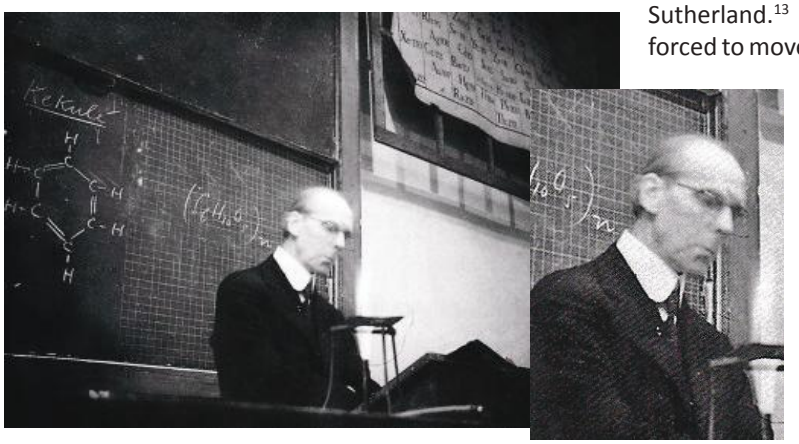
From Rangoon, PW returned to England in 1911 to a lectureship at Imperial College London. His time there generated six further publications with the research students that he supervised. It was after his return in 1912 that PW married Florence Elizabeth Graham, whom he met in London. Florence was a widow with a seven year old child Sybil, and it was only in 1917 that the couple had their own child, daughter Monica born on October 5th that year.[9]

When Thomas Easterfield, Victoria College's inaugural professor of chemistry, resigned to take up the Directorship of the newly established Cawthron Institute in Nelson, the selection of his successor seems to have been easy. P.W. Robertson had been an outstanding early student who had established himself in London and had just been awarded the 1919 Hector Medal by the New Zealand Institute; he was the second chemist (after Easterfield) to receive this award. It is not surprising, therefore, that P.W. Robertson was offered the chair in chemistry and his acceptance of it was announced[4] by the College Council on December 17, 1919 and reported in The Evening Post the day after.[10] As an aside, he became the fourth member of the College professorial board to hold a New Zealand university degree. The return to his *alma mater* was for the 1920 academic year and he arrived with his wife, step-daughter and daughter. The Robertson household was established in Talavera Terrace (below Weir House) and next door to Professor T. A. Hunter, Victoria's Professor of Philosophy. PW remained as Professor of Chemistry at Victoria for some 30 years.

Robertson's arrival in Wellington coincided with the expansion of the College's sole building, now known as the Hunter Building. Government had approved an expansion to the north to accommodate the library, but it was about the time of PW's arrival that the announcement for a science expansion of the south of the building was made.[4] Thus, his first three years at Victoria University College as it then was, was to the building expansions with the noise, dust and dirt that go with them. On arrival the only employee in chemistry was George Bagley, the Assistant and Demonstrator and a former Easterfield student. During his first year PW had A.D. (Bobby) Munro appointed to follow Bagley, a position that subsequently became permanent and to which Munro was appointed in 1928 as the second academic in chemistry - a lecturer. PW continued the previously set teaching programmes that included evening and Saturday lectures to which he added a tutorial after the Friday evening discourse. His impact on the College calendar was evident in 1922 as the course times and offerings became more regulated. By then research was performed for an MSc in the sciences and it was from the work of students from this pool that most of PW's subsequent New Zealand research was advanced. No PhD degree in chemistry was awarded in Wellington until the late 1940s despite a short trial period in the mid-late 1920s, but that saw no chemistry candidate.

Hunter Building 1927, Victoria University, Wellington. S P Andrew Ltd :Portrait negatives. Ref: 1/1-018906-F. Alexander Turnbull Library, Wellington, New Zealand. http://natlib.govt.nz/records/22559009

The extensions to the Hunter Building were completed in 1923 and formally opened on October 23. By then PW's textbook *Quantitative Analysis in Theory and Practise*, written in London with D.H. Burleigh, had been published and become a standard text in many universities.[11] As a lecturer, PW's impact on the student body has been recorded by a few of those who attended his classes from the late 1920s until the mid-1940s.[12] PW was reported as entering the lecture theatre though a door beside the bench at which time the buzz in the room stopped abruptly. He was tall and sparely built, always wearing his small, steel-rimmed glasses and, up to the time of his retirement, a brown suit with high, white, Edwardian stiff shirt collar and a paisley tie. He would approach the lectern and place his papers on it without looking at the students until he had seated himself on a tall laboratory stool behind the bench, folded his arms and cleared his throat. Only then did he glance briefly at the class before launched into his discourse. The first lecture of the year began with, *Chemistry consists of two main branches*.[3] He spoke, matter-of-factly, though quietly, pronouncing his words clearly. Occasionally he would rise to turn and write a new chemical term on the blackboard before returning to his perch, erect on the stool. Occasionally, when he was unwell from his malaria, his assistant would place a small table and chair for him and on cold days he would light the Bunsen burner, which was always on the bench, but never used for demonstration. The material of each lecture was painstakingly condensed, and frequently updated from the latest developments provided in the literature.



P.W. Robertson lecturing in Hunter C3 (by the late Des Hurley; with permission)

Underneath his controlled exterior PW had a whimsical sense of humour, very dry and not often apparent, but it could show itself unexpectedly as a funny remark in the middle of a lecture. Because he rarely changed his delivery style, the class frequently missed the point until several sentences later when someone would laugh belatedly, to be followed by the rest of the class. A thin smile would then pass across PW's face. When demonstrating in the laboratory, PW moved along the rows of students methodically, guiding each one in turn. He would perch on the student's stool, watch their manipulations and offer gentle correction when it was needed, often by way of outrageous analogy never to be forgotten by the student. For example, on one occasion a student used too much water to wash a precipitate free of contaminant and much of the needed precipitate was lost. PW had sat behind watching with folded arms. He said nothing until the procedure was finished and the female student was glumly observing the small quantity of material remaining. Without emotion, PW quietly remarked: *You know, it is easier to wash a baby with several thimblefuls of water than a bath-full*.[3]

PW - Unattributed (from *J. NZIC*, **1950**, *14*, 68)

Philip Robertson's wife, Florence, did not settle well to life in Wellington to the extent that in 1927 she took her two daughters and returned to England and had Monica educated at boarding school from 1930 to 1934. Apparently Florence returned to Wellington in 1930, but never for very long periods until after Monica completed secondary schooling. Her initial departure left PW an involuntary bachelor and he shared his home with philosophy lecturer (and subsequently noted psychologist) Ivan Sutherland.[13] However, with her 1930 return, Ivan was forced to move out.[13] After Florence and Monica returned to Wellington in 1934 Monica attended Victoria University College for a couple of years, presumably from the commencement of the 1935 academic year. However, PW dissuaded (even prevented her[9]) from completing her degree as he felt it inappropriate for women to be educated to that level![9] Monica and Florence returned to the UK permanently in 1937 or 1938 by which time Robertson's marriage had ended. Monica married Bill Williams, subsequently editor of the *Dictionary of National Biography*,[9] whom she had met in Wellington in 1938, but that did not last as he returned from a distinguished army career in WWII a different man. Monica subsequently recorded that Florence apparently did not care much for her husband.[8] Florence died in 1968, one year before PW.

Philip Robertson firmly established the ethos of research in the Chemistry Department at Victoria University College becoming one of the few New Zealand chemists of his generation to establish a lasting international reputation for his scientific work. It was achieved with minimal equipment and funding but with the research assistance of 102 MSc students. His work has been loosely described as encompassing the relationship between chemical constitution and chemical properties[14] and it was quite distinct from his doctoral studies in Leipzig. His under-

graduate researches and his studies in London provide the foundations of much of his later work. The late Brian Shorland,[3] a student of Robertson's from 1928, wrote of the works under five categories in a tribute to the man upon his retirement[14] and Peter de la Mare commented in his 1969 obituary in *Chemistry in Britain*.[15] In today's age the studies are best described as physical organic in nature, a classification that had not emerged in the era when Ingold and Hughes were advancing the concepts in the UK and Robertson doing the same in New Zealand, specifying it as kinetic in nature. It needs to be remembered that in the Robertson era supplies of chemicals and the equipment to carry out research were strictly limited to the extent that the favourite piece of equipment he had was a one half ounce bottle capped with a ground glass stopper.[14]

Thus, Robertson's studies can be described as involving analytical aspects which led to his elegant method of determining chlorine, bromine and carbon in organic compounds, the halogenation of phenols and the production of substituted aromatics, the physical properties of solutions (especially phenols), the melting characteristics of acid amides, and detailed halogenation studies.[14,15] Joan Cameron has described his achievements in chemistry as *'including substantial contributions to the basic understanding of the reactivity of certain carbon compounds, and how their properties such as boiling points were related to their chemical structure'*.[3] Studies by Robertson and his students extended the knowledge of melting point variations in homologous series of compounds to comparable variation in compound association thereby laying the foundation for structural differences and compound configuration. These conclusions were enhanced by observations in the amide series covering a wide range of compounds. The attention to detail that Robertson instilled in his charges was such that his tabulation of melting points appeared in an early text on the fatty acids and their derivatives.[16] It was the relationship of physical properties and compound composition that led PW to his major interest in organic reaction mechanisms.

The halogenation work of Robertson attracted most attention and led to some 28 publications. He added substance to Ingold's theory of electrophilic halogenation and provided rate data to substantiate the acceleration cause by the presence of electron donating alkyl substituents and the reduction by electron accepting groups. His students showed that as electron withdrawal increased the reaction became nucleophilic in nature and the rate then increased. They also demonstrated that the reaction profiles are not always simple with solvent effects and pH giving way to ter- and tetra-molecular processes. Their work expounded the mechanism of the reactions and in the latter case the presence of Br_4 was proposed[17] and HBr_3 in the nucleophilic reactions with HBr.[18] The area was nicely placed in perspective by the late Peter de la Mare during his tenure as assistant lecturer at University College in London.[19] Indeed, it was de la Mare's 1941 MSc studies with Robertson that continued through fruitful collaboration to mid-1953, which not simply held Robertson's attention but set de la Mare on the road to his distinguished career as a physical organic chemist and foremost authority on electrophilic substitution. Yet at the conclusion of his Victoria studies, de la Mare joined the Agricultural Research Laboratory to work with Brian Shorland. However, the enforced move of most of the laboratory staff to the Ruakura Research Station in Hamilton immediately post-WWII was not to his liking. Dissatisfaction with the new regime led Peter (among others[3]) to move to London for successful PhD studies with (Sir) Christopher Ingold and a remarkably successful future career.

Philip Robertson played a major role in developing science in New Zealand by training the number of chemists that he did. A remarkably high number of his MSc students went on to distinguished careers in science, many gaining a doctorate in overseas laboratories (dominantly the UK). Among those noted by Robertson himself in his 1949 review of science at Victoria College[20] were (MSc graduation year in parenthesis): Dr H.L. Richardson, adviser in soil conservation to the Chinese government (1925); Dr G. M. Richardson, noted for his chemistry of bacterial processes at the Dunedin Medical School (1925); Dr F. B. Shorland, head of the fats research division of DSIR who established the industry of extracting vitamin-rich fish oils and became a renowned nutritionist (1932);[3] and Dr P.B.D. de la Mare (1942), about whom Robertson in 1949 said '*at present lecturer at the University College, London, for whom a distinguished career in chemistry is confidently predicted*'. Peter de la Mare had gained a lectureship at University College London prior to the becoming Professor of Chemistry at Bedford College and before accepting the headship of chemistry at Auckland University in 1967. Others that now fully justify mention are O.H. Keys, inaugural editor of this journal (1931); T.A. Glendenning, tutor Wellington Technical College and second editor of this journal (1921); N.T. Clare, chief scientist Ruakura Animal Research Station who had been PW's lab boy (1934); B.E. Swedlund, a reader in chemistry at Auckland University (1944); E.P. White, the agricultural chemist who isolated, purified and structurally identified spirodesmyn (1938); I.K. Walker, a Director of the DSIR (1937); H.P. Rauthbaum, distinguished DSIR scientist (1947); W.E Dasent, lecturer, bursar and registrar at Victoria University (1950); and J.K. Hayes, Professor of Botany at Victoria University (1952). In addition to his students' achievements, PW was involved in the early planning of Victoria's new building to the south of the Biology Block projected for Chemistry and Geology – subsequently to be named the Easterfield Building – which gained priority in the developmental schemes of the College and became the first science building in the post-WWII era in New Zealand.

Unlike the vast majority of his scientific colleagues in New Zealand, Professor Robertson was a cultured individual who gained much recognition in literary circles.[2] He became friendly with the British artist Christopher Perkins and socialised with him and his family in their home at 151 Upland Road in Kelburn, and in his own. It was on his second meeting with Perkins that PW commissioned the artist to paint his portrait,[8] a painting that now hangs

close to the School of Chemical and Physical Sciences in Victoria University of Wellington. PW paid Perkins the sum of GBP 20 for the commission and subsequently had him also paint a portrait of Professor George William von Zedlitz, Victoria's first professor of modern languages. PW had used his time in Oxford to become widely read, well-travelled, and with an eloquent writing style. He believed that science should inform art, and art science as both were aspects of the whole.Thus he was to the fore with his literary writings, which included his early *A soul's progress: mezzotints in prose* (1920) that represented five periods in the history of the soul of an imaginary young scientist trying to escape a narrow intellectual view of the world. He wrote letters to the local newspapers complaining about the poor status of the arts, criticised the government's lack of skill not only in managing the economy but its lack of support for the country's cultural heritage, and he joined with other members of the professorial staff in public debates, in particular on the role of the university, freedom of thought and of the press.

The Perkin's portrait of P.W. Robertson; courtesy of VUW image services

P.W. Robertson was appointed emeritus professor following his retirement in late 1949 and returned to London shortly afterwards where he was closer to his daughter. He became a regular visitor to University College London. He died in London on May 7, 1969, aged 84.

References and Notes

1. Davis, B.R. *Robertson, Philip Wilfred*, *Dictionary of New Zealand Biography Te Ara - the Encyclopedia of New Zealand,* **1998**, *4*; updated 22-Jan-2014. See: www.TeAra.govt.nz/en/biographies/4r23/robertson-philip-wilfredand (accessed 18 July 2014).
2. Unattributed, *P.W. Robertson MA, MSc(NZ), MA(Oxon.), PhD (Leipzig), FRSNZ, J. NZIC,* **1950**, *14*, 68-71.
3. Cameron, J. *Brian Shorland: Doyen of New Zealand Science* (N.F Curtis and B. Halton eds.) New Zealand Association of Scientists: Wellington 2014.
4. Halton, B. *Chemistry at Victoria: The Wellington University*, 2nd. edn.; available for free download at: www.victoria.ac.nz/scps/about/attachments/ChemHist_second-edition_lowres.pdf.
5. PapersPast: The New Zealand Herald, Vol. XLIII, Issue 13088, 30 January 1906, p.5; see: http://paperspast.natlib.govt.nz/cgi-bin/paperspast?a=d&d=NZH19060130.2.34&cl=&srpos=0&e=-------10--1----0--&st=1.
6. I thank Petra Hesse of the University of Leipzig archive for providing this information. Unfortunately the thesis is no longer available.
7. Robertson, P. W. *Life and Beauty – a spiritual autobiography*, Edward Arnold: London, 1931, pp.173.
8. Garrett, J. *An Artists Daughter with Christopher Perkins in New Zealand*, Shoal Bay Press, Auckland, 1986.
9. I am grateful to John Milner, Monica's son and P.W. Robertson's grandson for this and other matters of family history. See also Nicholls, C.S. *Williams, Sir Edgar Trevor [Bill] (1912–1995*), *Oxford Dictionary of National Biography*, Oxford University Press, 2004; on-line edn, May 2011: www.oxforddnb.com/view/article/57959 comments on Monica's marriage to Trevor Williams (accessed 18 July 2014).
10. Paperspast: The Evening Post , Vol. XCVIII, Issue 146, 18 December 1919, p.5; see: http://paperspast.natlib.govt.nz/cgi-bin/paperspast?a=d&d=EP19191218.2.53&cl=CL2.1919.12.18&e=-------10--1----0--.
11. Robertson, P.W.; Burleigh, D.H. *Quantitative Analysis in Theory and Practise*, E. Arnold: London 1920, pp. 63.
12. I am indebted to the late Brian Shorland (see ref. 3), Joan Cameron and Bruce Cockburn for their comments.
13. Sutherland, O. *Paikea; The life of I.L.G. Sutherland*, Canterbury University Press, Christchurch, New Zealand, 2013, p.195.
14. Shorland, F.B. *The contributions of Professor P.W. Robertson to chemical research, J. NZIC,* **1950**, *14*, 71-78.
15. De la Mare, P.B.D. *Philip Wilfred Robertson*, *Chem. Brit*. **1969**, *5*, 525-526.
16. Ralston, A.W. *Fatty Acids and their Derivatives*, John Wiley & Son, New York, Chapman & Hall Ltd., London,1948.
17. de la Mare, P.B.D.; Robertson, P.W. *J. Chem. Soc.* **1948**, 100-106.
18. Morton, I. D.; Robertson, P. W. *J. Chem. Soc.* **1945**, 129-31; Swedlund, B. E.; Robertson, P. W. *J. Chem. Soc.* **1945**, 131-133.
19. de la Mare, P.B.D. *Qtr. Rev. Chem. Soc.* **1949**, ***3***, 126-145.
20. Robertson, P.W. *Science at Victoria College*, *The Spike or Victoria College Review*, May 1949, 26-28.

Book review

Book review: *Brian Shorland – Doyen of New Zealand Science*

Written by Joan Cameron and edited by Neil Curtis and Brian Halton

This book[1] traces the life of Brian Shorland from his boyhood in Island Bay, Wellington, through a professional life which starts as a cadet in agricultural science, while studying for a degree, progresses to a doctorate overseas, and to a professional scientist. Eventually he heads his own division of DSIR, and ultimately enters a fruitful retirement, during which he considers the broader implications of his scientific work.

The book's eighteen chapters portray not only Shorland's life, but also the milestones of the history of the development of the science of fats, and the changes in the culture of government funded science in New Zealand. This last feature is noted in the biography's foreword (p. v), and this book offers insights that are complementary to the more formal histories of New Zealand science, in particular that of DSIR.[2] The interplay of these three themes is shown in Fig.1.

Cameron's biography reveals Shorland's innovative thinking at an early stage of his career – choosing to undertake his own research into the prospect for energy production from geothermal fields in his own time while a cadet at the Agricultural Chemical Laboratory, undertaking his own field trip by motorcycle to collect samples at Wairakei. His two jointly authored papers on this topic preceded others' formal investigation of the idea by more than two decades.[3] On their own initiative, Shorland and a fellow cadet undertook research into oily eel meal after hours and in their spare time, incurring the wrath of their boss – Chief Agricultural Chemist, Barney Aston – when they sought to publish a paper about it in a scientific journal. Aston's anger at these upstarts' cheekiness subsided when the editor accepted the paper,[4] since Aston was himself frequently published in the same journal. This incident probably resonates with older scientists who will remember the expectations of deference to senior staff implicit in the hierarchical structure of government scientific organisations throughout much of the twentieth century. In any event, having a few papers under his belt and scholarships from his studies at Victoria University College, Shorland was well equipped academically – if apprehensive socially – to venture to Liverpool University and to obtain a doctorate.

The break in the flow of Shorland's life story at Chapter 5 to give a historic perspective on fats research seemed an intrusion at first reading. It was only in the penultimate chapter that it becomes apparent that Shorland himself was delighted at the inclusion of such perspectives, and clearly gave the biographer a mandate to structure the book in this rather unexpected format (see Fig. 1).

Chapter 6 describes Shorland's doctoral research in 1935-1937, and corresponds to a small spike in the annual number of his publications (Fig. 2). The next two chapters describe perhaps less fulfilling parts of Shorland's career. The first of these chapters describes his involvement with the Karitane Products Society, which established a fish-liver oil factory in Melrose, a Wellington suburb (Fig. 3), at which Cameron was employed while an undergraduate student.[5] The second of these chapters describes the

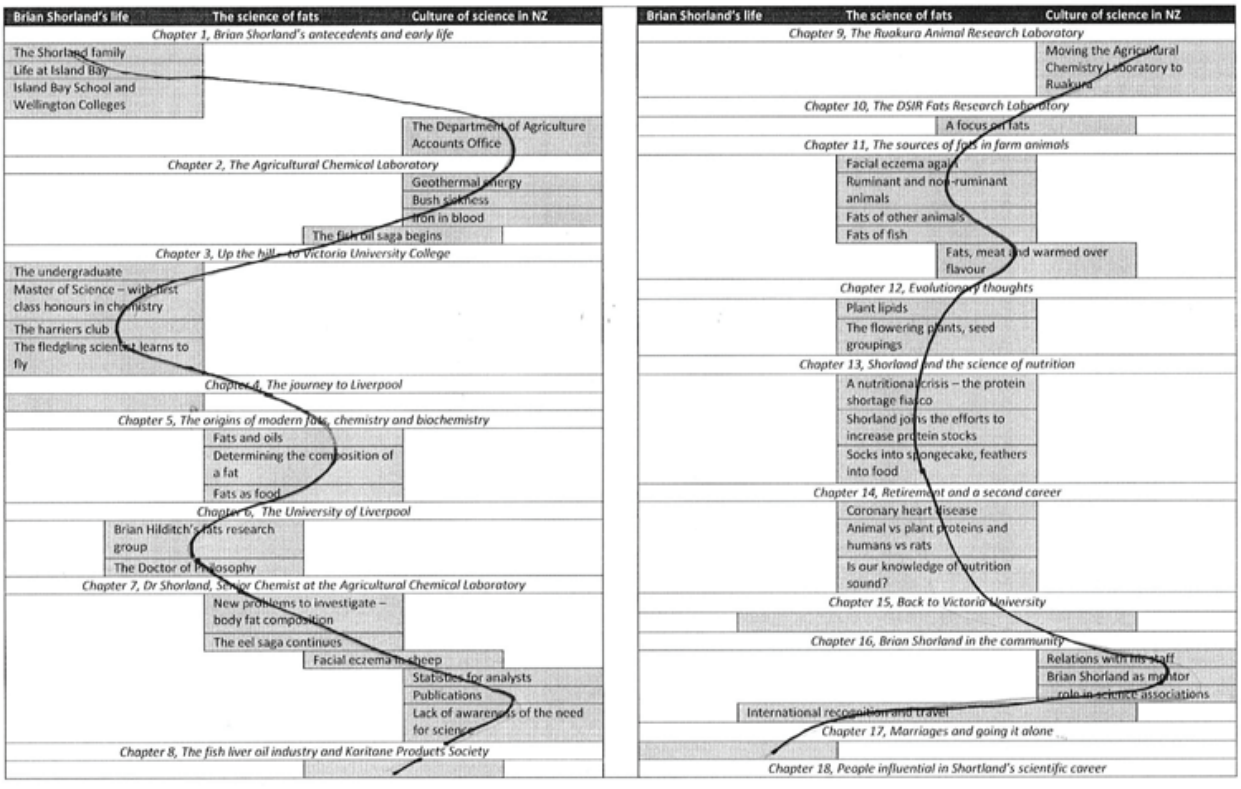


Fig.1. Variation of themes in Joan Cameron's biography of Brian Shorland

establishment of the Agricultural Chemistry Laboratory at Ruakura on the outskirts of Hamilton, and culminates in Shorland's decision not to transfer to the newly established facility. Of that point in Shorland's career, Cameron writes, "What to do next? Shorland was at a point of despair! He went to see Dr Ernest Marsden, Secretary of the DSIR, and asked what he should do – meaning what could Marsden do?" (p. 83). In fact, Marsden was already well informed of Shorland's work and responded by telling him to "go home and write out a proposal for establishing a Fats Research Unit, and to give it to him next morning" (p. 84).

And so, the Fats Research Laboratory, with Shorland as its head, came to be established in old houses in Wellington's Sydney Street West. The Laboratory was ultimately incorporated into DSIR's Food Chemistry Division (p. 94),[6] and was one of the last of a succession of government laboratories that occupied the initially impressive brick Dominion Laboratory building.[7] These years were highly productive for Shorland in terms of his research (Fig. 2), with a trend towards an increasing interest in the nutritional value of fats, a matter which was to occupy more of his thinking in retirement (Fig. 4). In addition, he became interested in the prospects of manufacturing food from apparently inedible sources of protein. In the book, this is addressed in a section delightfully entitled 'Socks into spongecakes, feathers into food'.

Shorland was always critical of research which, although undertaken on animals, foresaw nutritional benefits for humans. This resonates with the debate about the health benefits of coconut oil,[8] for which the testing has largely been done on animals,[9] which surfaced during the writing of this review.

Required to retire from DSIR at the age of 60 in 1969, Shorland was one of many scientists of his era who were still able to remain intellectually active by involvement with other organisations. For Shorland this included a review on coronary heart disease for the Royal Society of New Zealand (Chapter 14), an honorary research fellowship in biochemistry at Victoria University of Wellington (Chapter 15) and an enhancement of his earlier involvement in science associations, including the New Zealand Association of Scientists (the publishers of the biography) and the New Zealand Institute of Chemistry (chapter 16). Shorland's increasing preoccupation with nutrition and health is marked by his involvement with organisations such as the New Zealand Nutrition Society and the Wellington Medical Foundation; indeed his very last paper is simply entitled 'Food for New Zealanders'.[10] This period of his life also marks an excursion into somewhat eccentric self-sufficiency (pp. 150-152), Cameron's telling of which introduces a note of humour.

The last section of Chapter 17 – entitled 'Brian's last days' – is a personal reminiscence from his biographer, Joan Cameron. Here she recalls how the biography was commissioned: when she offered to write it, he pushed a pile of papers towards her, "saying dismissively 'Well, get on with it then'". She recalls the details of Brian's and her attendance at what was to be his final meeting as a mem-

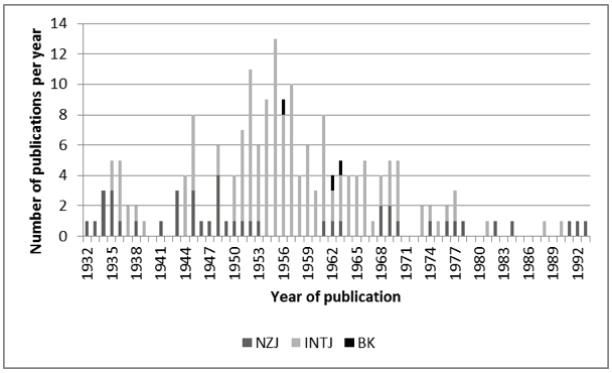


Fig. 2. Research productivity of Brian Shorland, 1932-1993, compiled from the biography's appendix (NZJ, Article published in a New Zealand journal; INTJ, Article published in an international journal; BK, Book.)

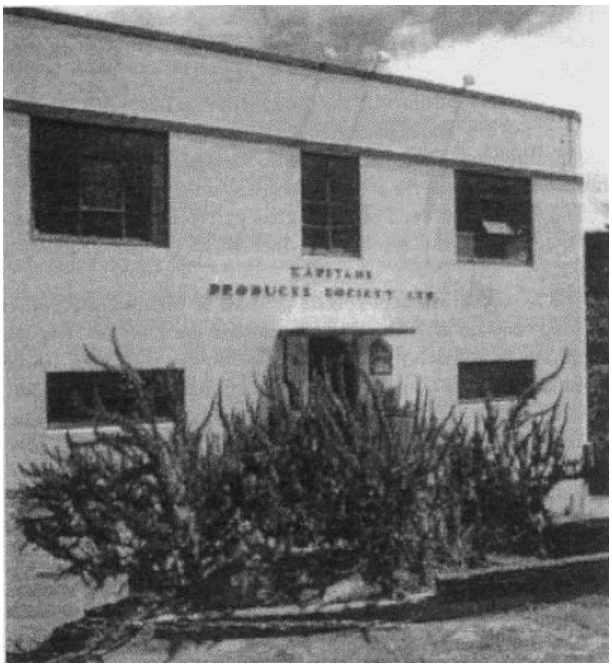


Fig. 3. The Karitane Products Factory in Melrose, Wellington, where during her employment as a laboratory assistant, Shorland's biographer probably first encountered Brian Shorland. The building, designed by prominent Wellington architect William Gray Young, is near the Karitane Hospital and Sir Truby King's residence. It has a category 1 rating on the NZ Heritage List and is currently used as residential accommodation. [Photo: http://nzetc.victoria.ac.nz/tm/scholarly/ChaStra-fig-ChaStra230a.html].For modern views of the building and its environs, see: http://www.heritage.org.nz/the-list/details/4431.

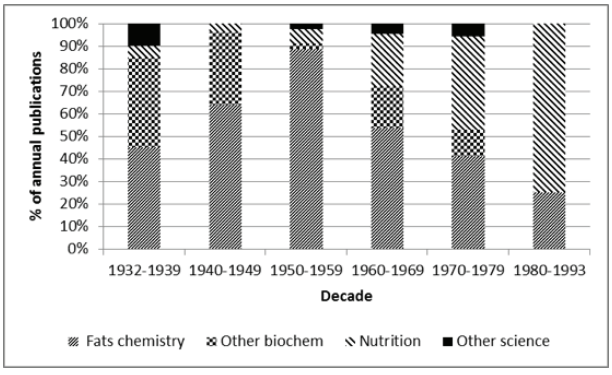


Fig. 4. Changing emphasis on research through Brian Shorland's career, compiled from the biography's appendix.

ber of the board of the Wellington Medical Foundation. Cameron must surely have been touched by the knowledge that her conversation with him during the evening two days later, in which he told her, 'You have put me in a far wider context than I had ever dreamed of. I think you're marvellous', was probably his last (p. 157).

While the end of Chapter 17 would have been a fitting point at which to close the book, Cameron (or perhaps her editors) chose to include as the book's final chapter biographies of twelve people who are purported to have influenced Shorland's scientific career. In fact, the most influential of these people are already mentioned in earlier chapters at the appropriate stages of Shorland's career, and so these biographies – if needed at all – might have been better as an appendix. Deletion of these pages might have made for a rather less cramped layout for the text, and perhaps the inclusion of additional photographs – all for the same cost of publication.

Nevertheless, the editors have produced from Cameron's work an interesting book about a twentieth century New Zealand scientist whose life and times deserve to be better known.

References

1. Cameron, J. *Brian Shorland – Doyen of New Zealand Science*. NZ Association of Scientists: Wellington, 2014.
2. Atkinson, J.D. *DSIR's First Fifty Years*. DSIR: Wellington, 1976.
3. Bruce, J.A.; Shorland, F.B. *NZ Journal of Agriculture* **1932**, *45*, 272; Bruce, J.A.; Shorland, F.B. *NZ Journal of Agriculture* **1933**, *46*, 29.
4. Denz, F.A.; Shorland, F.B. *NZ Journal of Science and Technology* **1934**, *15*, 327.
5. Mattingley, J.M. 'Fish-liver Oils: a Wartime Success Story', in Hogan, D.; Williamson, B. (eds) *New Zealand is Different: Chemical Milestones in New Zealand History*. NZ Institute of Chemistry: Christchurch, 1999.
6. Galbreath, R. *DSIR: Making Science Work for New Zealand*. Victoria University Press: Wellington, 1998.
7. Hodder, P. *Chemistry in New Zealand* **2014**, *78*(4), 158-163; Hodder, C.; Hodder, P. *A Forgotten Corner of Wellington – Sydney Street West*. HodderBalog: Wellington, 2015.
8. Shaw, D. 'Stop going nuts over coconut'. *New Zealand Herald*, 24 October 2014: http://www.nzherald.co.nz/opinion/news/article.cfm?c_id=466&objectid=11347584, (accessed 24 October 2014).
9. Nevin, K.G.; Rajamohan, T. *Food Chemistry* **2006**, *99*(2), 260; Sutter, F., *et al. Animal Nutrition* **2000**, *53*, 1.
10. Shorland, F.B. *NZ Medical Journal* **1993**, *106*, 436.

Peter Hodder

Victoria Business School

Victoria University of Wellington

and

HodderBalog Social and Scientific Research

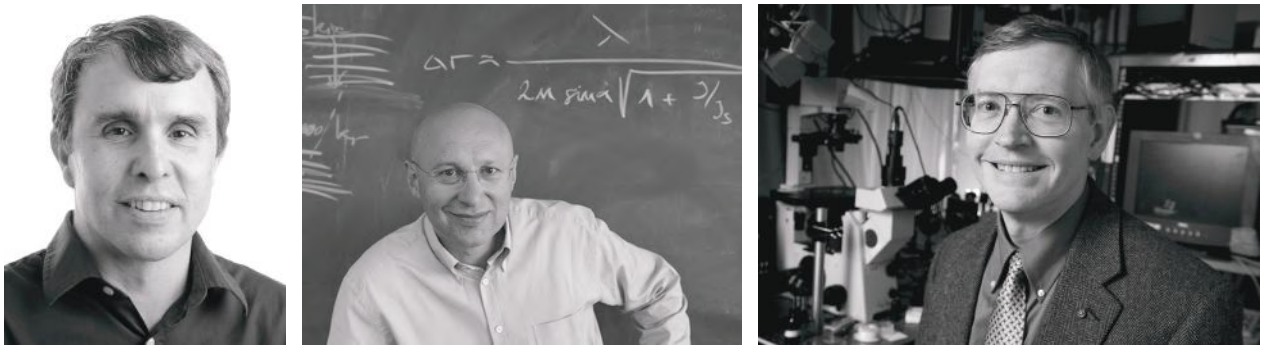
Wellington

The 2014 Nobel Prize in Chemistry

Brian Halton

School of Chemical & Physical Sciences, Victoria University, PO Box 600, Wellington
(email: *brian.halton@vuw.ac.nz*)

The Royal Swedish Academy of Sciences awarded the 2014 Nobel Prize in Chemistry to ***Eric Betzig***, ***Stefan W. Hell***, and ***William E. Moerner*** of the Janelia Farm Research Campus at the Howard Hughes Medical Institute in Ashburn, Virginia, the Max Planck Institute for Biophysical Chemistry in Göttingen and the German Cancer Research Center in Heidelberg, and the Chemistry Department at Stanford University in California, respectively, *for the development of super-resolved fluorescence microscopy*. The Nobel Prize-winning microscopy techniques have allowed scientists to visualize precise molecular mechanisms inside living cells, opening new windows to how life can be studied.

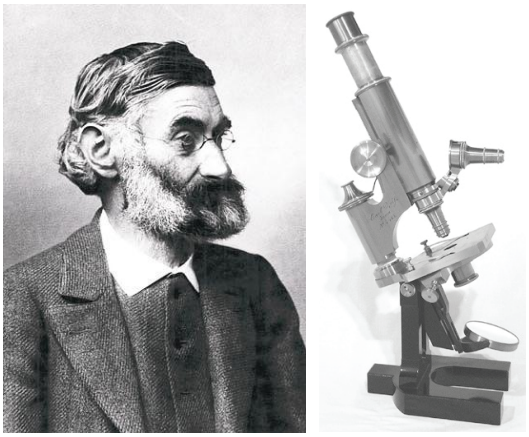


Left: Eric Betzig (courtesy Dr. Betzig); centre: Stefan W. Hell. © Max Planck Institute for Biophysical Chemistry, with permission; right: William E. Moerner (courtesy Stanford University)

Until recently, optical microscopy has been limited because it was presumed that it could give a resolution no better than to half the wavelength of light. The 2014 Nobel Laureates have ingeniously circumvented this limitation using fluorescent molecules in a new technique called super-resolved fluorescence microscopy and brought optical microscopy into the nano dimension by combining physics and molecular biology. Examples of the methods include photo-activated localisation microscopy (PALM) developed in 2006 by Eric Betzig and Harald Hess at Janelia and by Samuel Hess at the University of Maine; stochastic optical reconstruction microscopy (STORM) developed at the Howard Hughes Medical Institute; stimulated emission depletion (STED) microscopy by Stefan Hell at the Max Planck Institute in Göttingen; and saturated structured illumination microscopy (SSIM) at Janelia and the University of California, San Francisco.[1]

The work that has gained the 2014 Nobel recognition comes from a two-pronged ground-breaking approach that has taken optical microscopy into the nano dimension.[2] It marks the fifth time that the Nobel Prize has been awarded for an advance in microscopy and, in the view of this author, it could have gained either the chemistry or physics awards. Termed *nanoscopy*, this technique now allows scientists to visualise the pathways of individual molecules inside living cells by using fluorescent proteins. One can now see how molecules create synapses between nerve cells in the brain, track proteins involved in Parkinson's, Alzheimer's and Huntington's diseases as they aggregate, and follow individual proteins in fertilised eggs as these divide into embryos.

In 1873, Ernst Abbe defined the physical limit for the maximum resolution of traditional optical microscopy no better than around 0.2 μm for visible light. The ability to resolve objects with optical microscopy had been limited by the wavelength of light – anything smaller than about 0.5 μm appeared somewhat blurry because of diffraction effects. Despite electron microscopy and X-ray technologies going beyond this level of detail, those techniques kill any living cell in making the

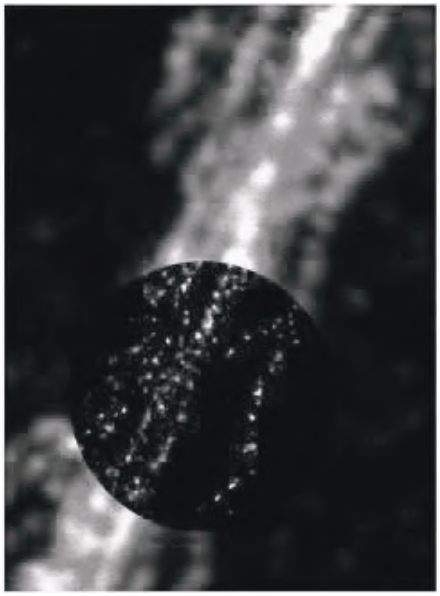


Left: Ernst Abbe; Right: 1879 Zeiss Microscope with optics by Ernst Abbe

observation and this same limit also applied to the diffraction fluorescence microscopy frequently used in biology and medicine. Betzig, Hell and Moerner were awarded their prize for having surpassed this limit and taken optical microscopy into the nano world to enable examination of living cells.

The developments are based on two separate principles. The first was developed by Stefan Hell, a 51-year-old physicist at the Max Planck Institute for Biophysical Chemistry. It radically overcame the resolution limit of

light microscopes with an entirely new concept. It was whilst at the University of Turku in Finland that Hell developed the principle for a new form of microscopy. Then, after transferring to the Max Planck Institute in 1997 to study sub-diffraction-resolution microscopy, he and his co-workers published the 1999 results obtained from his new microscope. These showed that he had translated his idea into an instrument which produced an image of a common bacterium with a resolution higher than the Abbe limit.[3] This 2000 paper named the technique STED microscopy. Hell's apparatus employs one laser beam to the fluorescent molecules in, for example, a cell nucleus, and another to blank out all the fluorescence except that occurring in a defined nano-size volume. Moving over the nucleus nanometer by nanometer, taking a snap at each stop, the microscope then produces an image of the nuclear cell molecules. The technique was not simply invented by Hell but also developed by him to application readiness. It was the first focused light microscopy method no longer limited by diffraction and allows up to ten times greater detailed observation in living cells than previously. It made structures visible that are much smaller than 200 nm.



STED microscopy (circular inset image) provides approximately ten times sharper details of filament structures within a nerve cell compared to a conventional light microscope (outer image); © G. Donnert, S. W. Hell, Max Planck Institute for Biophysical Chemistry, with permission.

In order to overcome the phenomenon of light diffraction, Hell and his team applied a donut-shaped STED beam to the focal spot of the fluorescence excitation beam. It switches off fluorophores at the spot periphery effectively confining them to the non-fluorescing ground state. In contrast, molecules at the donut centre in the fluorescence beam fluoresce freely. The resolution is typically improved by up to ten times compared with conventional microscopes. This means that labelled protein complexes with separation of only 20-50 nm can be discerned. As the brightness of the STED beam is increased, the spot in which molecules can fluoresce is further reduced in size and, in principle, the resolution of the system can be increased to molecular dimensions.

By developing special fast recording techniques for STED microscopy, Hell and the team further succeeded in recording fast movements within living cells. The exposure time for single images was reduced in such a dramatic way that they can film movements within living nerve cells in real-time and with a resolution of 65 to 70 nm - some three-to-four times better than conventional light microscopes.[3]

The second principle was established independently by Eric Betzig and William Moerner working separately. They arrived by a far more circuitous route at the other prize-winning technology now known as *single-molecule microscopy*. This method relies, in part, on the ability to turn the fluorescence of individual molecules on and off, a trick that Moerner had accomplished with green-fluorescing proteins in 1997 when at the University of California in San Diego. Betzig learned that other fluorescing proteins could be switched on and off at will. With that information, he realized that the Abbe limit could be exceeded by taking multiple images of the same area, allowing just a few interspersed molecules to fluoresce each time. By superimposing the images on each other a denser super-image is obtained, resolved at the nano level. This method was used for the first time by Eric Betzig in 2006. Today, nanoscopy is used worldwide and new knowledge of great benefit to mankind is produced daily.

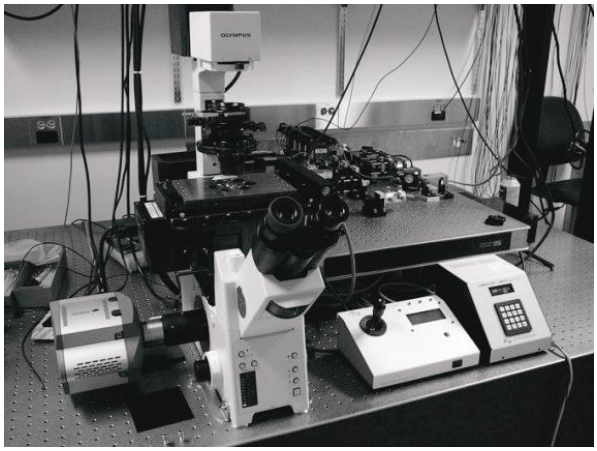
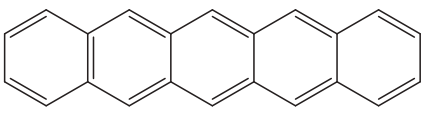


Photo-activated localisation microscope (PALM) developed by Eric Betzig and Harald Hess in 2006 (courtesy of Dr Betzig)

It is obvious that scientists need to study living cells in the smallest molecular detail and have the ability to dive deeper and deeper into human biology visualising the inner workings of cells at a molecular level. W.E. Moerner, the Harry S. Mosher Professor of Chemistry at Stanford, provided the ground-breaking work to observe molecules at the smallest scales, opening up new possibilities for discovery in areas ranging from disease management to drug development. From 1981 to 1995, he was a research staff member at IBM, and it was there that he made the first of two major discoveries key to his role in the Nobel-winning work. In 1989, he used laser-based techniques to allow the first visualisation of a single molecule, namely pentacene.



pentacene

"Prior to W.E.'s work, we all believed in molecules, but no one had ever seen one," said long-time colleague in the Stanford Chemistry Department, Richard Zare. "It opened up all sorts of new experiments in which you can see how cells divide, how the ribosomes can make proteins, and how the cells work" he said.[4] Moerner joined the chemistry faculty at the University of California-San Diego in 1995, and it was there that he made the second major discovery, albeit somewhat by accident. With colleague Robert Dickson he found that when looking at cells tagged with a green fluorescent protein, instead of staying brightly lit, the tags turned the fluorescence on and off (blink) at different wavelengths "like mini beacons, or flashlights, telling us where the structure is and in precise detail going far beyond the optical limit of diffraction" Moerner said.[4] This led to an entirely new way of looking at living cells as one can now go to factors of ten or more below the former level using fluorescence.

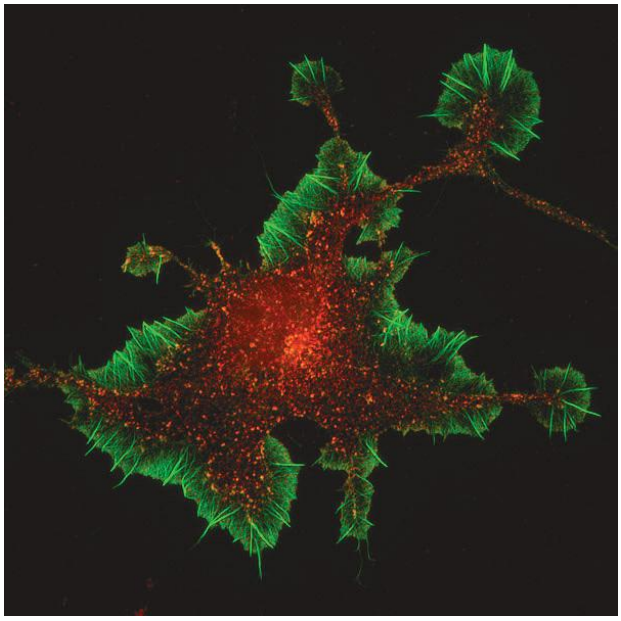


Image of a specialised brain cell captured using a structured illumination super-resolution microscope (Photo by Brad Zuchero and Andrew Olson, Stanford University School of Medicine; with permission)

In contrast to William Moerner, Eric Betzig is a physicist, inventor, and engineer. After two and a half years of theoretical research, he took his theories into the laboratory, where he applied them to the challenges of biological research aimed at developing a microscope that allows biologists to peer inside living cells with unprecedented resolution.[4] Trained as an experimental physicist, Betzig made waves in his field early on by helping to develop the technique now known as near-field microscopy that allows for the identification of nano-sized features with chemical contrast. It brought into focus structures that scientists had long considered too small to see with a light microscope. He made it more practical for biologists by allowing powerful imaging of dead cells.

The technique developed by Betzig and Moerner involves illuminating the sample with a weak laser pulse to ensure that only a tiny fraction of the fluorescent molecules will blink at a given time. Because of this it is extremely unlikely that any of these blinking molecules are separated by distances less than the diffraction limit. As each molecule emits a number of photons during a blink, they are detected as an intensity peak that has a normal distribution and a width that is limited by the diffraction limit. However, since the light comes from a single molecule, its location can be put at the centre of the normal distribution with high probability. Since the uncertainty in the location of the molecule falls as the inverse of the square root of the number of photons detected, an individual image can show only the locations of a few molecules. However, by repeating the process many times, a composite image of all the molecules can be created.[5]

Both prize-winning technologies are now used daily in biology and medicine worldwide for myriad purposes as noted at the outset. With the two technologies having given rise to nanoscopy, and in accord with earlier major innovations in scientific instruments, the field has blossomed. It now encompass other branches of research, generated improvements and variations, and stimulated a budding industry. All of this because Hell, Betzig, and Moerner circumvented the Abbe limit – in the accolade of the Nobel announcement: *ingeniously*.

References

1. See: http://www.hhmi.org/news/eric-betzig-wins-2014-nobel-prize-chemistry (accessed 21 October 2014).
2. See: http://www.nobelprize.org/nobel_prizes/chemistry (accessed 10 October 2014).
3. See: http://news.stanford.edu/news/2014/october/moerner-nobel-prize-100814.html (accessed 17 October 2014).
4. See: http://www.mpibpc.mpg.de/14734047/pr_1429 (accessed 21 October 2014).
5. Johnston, H. *Chemistry Nobel awarded for super-resolution microscopy*, Physics World, Institute of Physics, 8 October 2014; see: physicsworld.com (accessed 21 October 2014)

Dates of note

Sir ***Edward Frankland***, the English chemist who was one of the first investigators in the field of structural chemistry, invented the chemical bond, and became known as the father of valency and organometallic chemistry, was born on January 18, 1825. ***Adolf Friedrich Johann Butenandt***, the German biochemist who was the co-winner (with Ruzicka) of the 1939 Nobel Prize for Chemistry for pioneering work on sex hormones, died this day 20 years ago. January 19, 100 years ago, saw the issue of US Patent 1,125,476 to ***George Claude*** of Paris titled *A System of Illuminating by Luminescent Tubes*; it led to the neon sign in 1915. ***Alexandre-Emile Beguyer de Chancourtoi***, the French geologist who arranged the chemical elements in order of atomic weights for the first time in 1862, was born on January 20, 1820. ***Horace Wells***, the American dentist and pioneer in the use of surgical anaesthesia, was born on January 21, 1815. ***André-Marie Ampère*** was born on Jan 22, 1775, as was ***Louis Carl Heinrich Freidrich Paschen*** 150 years ago in 1865. Remembered for the Paschen Series of spectral lines of hydrogen, he was a German physicist and outstanding experimental spectroscopist who also showed the identical match to the spectral lines of helium found earlier in the solar spectrum to those of helium on earth and then newly discovered. ***Johann Wilhelm Ritter***, the German physicist who discovered the ultraviolet region of the electromagnetic spectrum, died on January, 23, 1810. ***Ernst Abbe***, the German physicist who established a technical and theoretical foundation for the design of optical instruments and is known to chemists for his refractometer, was born on January 23, 175 years ago in 1840. January 24, 1950 saw the original microwave oven patent issued to its inventor ***Percy LeBaron Spencer*** under the title *Method of Treating Food*. January 27, 1970 saw ***James M. Schlatter*** receive his US patent for *Peptide Sweetening Agents*, which eventually led to the marketing of aspartame under the name *NutraSweet*. The antibiotic *terramycin* was announced in *Science* this day in 1950. ***Doug Engelbart***, the man who invented the computer mouse, was born on January 30, 1925. The same day in 1995 saw the drug *hydroxyurea* announced as the first effective treatment for sickle-cell anaemia by the US National Heart, Lung, and Blood Institute in Washington. ***Henry Livingstone Sulman***, the British metallurgist who with H.F.K. Picard invented the froth flotation process for concentrating ores preliminary to the extraction of metal, died on January 31, 75 years ago.

Sidney Gilchrist Thomas, the British metallurgist who, in 1875 developed with his cousin Percy Gilchrist the Thomas-Gilchrist process that eliminated the phosphorus impurity of certain iron ores in the Bessemer converter, died on February 1, 1880. ***William H. Stein***, the American biochemist who (with Moore and Anfinsen) won the 1972 Nobel Prize for Chemistry for studies of the pancreatic enzyme ribonuclease, died on February 2, 1985. ***Paul Scherrer***, the Swiss physicist whose collaboration with Peter Debye produced a method for X-ray diffraction analysis, was born on February 3, 125 years ago. ***John Boyd Dunlop***, the pioneer of the pneumatic tyre, was born on February 5, 175 years ago. ***William Cullen***, the Scottish physician and chemist who in 1747 held the first independent university lectureship designated for chemistry in the British Isles at Glasgow University, died on February 5, 1790, 225 years ago; he was born on April 15, 1710. ***Friedlieb Ferdinand Runge***, the German chemist considered by some to be the originator of paper chromatography who identified caffeine, was born on February 8, 1795, the day in 1975 that Sir ***Robert Robinson***, the British chemist and recipient of the 1947 Nobel Prize for his research on a wide range of organic compounds, died. ***Jacques Lucien Monod***, the French biochemist who, with Jacob, did much to elucidate how genes regulate cell metabolism, was born on February 9, 1910. ***Per Teodor Cleve***, the Swedish chemist and geologist who discovered the elements holmium and thulium, was born on February 10, 1840. The ***Van de Graaff*** patent for his Electrostatic Generator design was issued on February 12, 1935. ***Pierre-Louis Dulong***, the French chemist and physicist who helped formulate the Dulong-Petit law of specific heats, was born on February, 12, 1785. ***Robert John Kane***, the Irish chemist known for his 1845 book, *The Industrial Resources of Ireland*, died on February 16, 1890. ***Oswald Avery***, the Canadian-American biochemist and immunologist whose research on pneumococcus bacteria made him one of the founders of immunochemistry, died on February 20, 1955. ***Henrik Dam,*** the Danish biochemist who shared (with Doisy) the 1943 Nobel Prize in Physiology or Medicine for research into anti-haemorrhagic substances and the discovery of vitamin K, was born on February 21, 1895. ***Smithson Tennant***, the English chemist who discovered the elements iridium and osmium in the residues from platinum ores in 1803, died on February 22, 200 years ago. ***Henry Cavendish***, the English physicist and chemist who researched in his private laboratory and identified hydrogen as a separate gas, studied carbon dioxide, and determined their densities relative to atmospheric air, died on February 24, 1810. On February 27, 1900 German chemist ***Felix Hoffmann*** was issued a US patent for acetyl salicylic acid (aspirin) assigned to the Farben-Fabriken of Elberfeld Company, of New York. Hoffmann had discovered the chemical compound on 10 Aug 1897 while a researcher at the Bayer Company. Nylon was discovered by Dr. ***Wallace H. Carothers*** of DuPont on February 28, 1935.

Archer Martin, the British biochemist awarded (with Synge) the 1952 Nobel Prize for development of paper partition chromatography, was born on March 1, 1910. ***Michelangelo*** was born on March 6, 1475 while on this same date in 1665, 350 years ago, the first issue of the *Transactions of the Royal Society* appeared; it is oldest continuing periodical in the world. ***Stanley Lloyd Miller***, the American chemist who made a series of experiments to determine the possible origin of life from inorganic chemicals on the primeval, just-formed earth that began in 1953, was born on March 7, 1930. He passed electrical discharges through mixtures of the reducing gases

hydrogen, ammonia, methane and water, believed to have formed the earliest atmosphere. Analysis days later showed the resulting chemicals to include the simplest amino acids glycine and alanine. Also on this day in 1900 was born ***Fritz Wolfgang London,*** the German-American physicist who with Heitler, devised the first quantum mechanical treatment of the hydrogen molecule while working with Schrödinger. Sir ***Alexander Fleming***, the Scottish bacteriologist who discovered penicillin, died on March 11, 1955. On this day in 105 AD, ***Ts'ai Lun*** invented paper in China, making it from bamboo, mulberry, and other fibres, fish nets and rags. ***John Frederic Daniell***, born on March 12, 1790, was the British chemist and meteorologist who invented the Daniell cell, a major improvement on the voltaic cell used in the early days of battery development. He died on March 13, 1845. ***Arthur Rudolf Hantzsch***, the German who gained fame at the age of 25 for devising the synthesis of substituted pyridines then studied stereochemistry of such nitrogen compounds, died on March 14, 1935, 80 years ago. He synthesised pyridine (1882), cumaron (benzofuran, 1886) and thiazole (1889), and provided a nomenclature for heterocyclic compounds. This same day in 1960 saw the Grand Isle sulfur mine begin operation about 7 miles off the Louisiana coast. On March 17, 1950, 65 years ago, element 98 (californium) was announced by scientists at the University of California at Berkeley. ***Frédéric Joliot-Curie*** was born on March 19, 1900. He was the French physical chemist and husband of Irène, jointly awarded the 1935 Nobel Prize for Chemistry for their discovery of artificial radioactive isotopes of new elements. They were the son-in-law and daughter of Nobel Prize winners Pierre and Marie Curie. Sir ***Norman Haworth***, the British carbohydrate chemist, died on his 67th birthday, March 19, 1950. ***Torbern Olof Bergman***, the Swedish chemist who experimented with carbon dioxide named *aerial acid* by him, which Priestley called *fixed air*, was born on March 20, 1735, 280 years ago. On March 21, 1925, ***Wolfgang Pauli*** published his exclusion principle in *Zeitschrift für Physik*. On March 22, 1960, the *first laser* was patented by ***Arthur Schawlow*** and ***Charles Hard Townes*** under the title *Lasers and Laser Communications System* and one day later but in 1840, chemist ***John William Draper*** took the first successful photo of the Moon. ***Wilhelm Conrad Röntgen***, a recipient of the first Nobel Prize for Physics, in 1901 for his discovery of X-rays, was born on March 27, 1845. ***Wilhelm Körner***, the German organic chemist who showed how to determine the positions of the substituents on di- and tri-substituted isomers of the benzene ring in 1878 by counting product or source isomers, died on March 28, 1925. Sir ***Lawrence Bragg*** was born on March 31, 1890. ***Isidor Traube***, the German physical chemist who founded capillary chemistry and whose research on liquids advanced knowledge of critical temperature, osmosis, surface tension and colloids, was born the same day in 1860. ***Hans Fischer***, the German biochemist who was awarded the 1930 Nobel Prize for Chemistry for his research into the constitution of haemin and chlorophyll, and especially for his synthesis of haemin, the non-protein part of haemoglobin that gives blood its red colour, died on March 31, 1945.

Richard Zsigmondy, the Austro-German chemist who was awarded the 1925 Nobel Prize for Chemistry for his demonstration of the heterogeneous nature of colloid solutions and the methods which have since become fundamental in modern colloid chemistry, was born on April 1, 150 years ago. ***Marc Antoine Augustin Gaudin***, the French crystallographer and chemist who contributed to the early chemistry of photography, died on April 2, 1880. ***Richard Wilhelm Heinrich Abegg***, the German physical chemist who, with Boländer proposed a theory of valency to explain the capacity of an atom to combine with another atom in light of the [then (1899) newly discovered] presence of electrons within the atom, died on April 3, 1910. ***Edmond H. Fischer***, the American biochemist who shared (with Krebs) the 1992 Nobel Prize for Physiology or Medicine for the discovery of *reversible protein phosphorylation as a biological regulatory mechanism,* was born on April 6, 1920. On April 7, 1795, France adopted, by law, the metre as the unit of length and the base of the metric system. ***William Prout***, the English biochemist and physiologist who is noted for his discoveries concerning digestion, metabolic chemistry, and atomic weights, died on April 9, 1850. ***Julius Lothar Meyer***, the German chemist who discovered the Periodic Law at about the same time but independently of Dmitry Mendeleyev, died on April 11, 1895. ***William Cookworthy***, the English chemist who pioneered the manufacture of porcelain in Britain, was born on April 12, 1705. ***Charles Fredrick Cross***, the English chemist who, with Bevan and Beadle, discovered that cellulose could be produced (1891) by the dissolution of cellulose xanthate in dilute NaOH and in 1892 found that cellulose dissolved in CS_2 producing a solution he called *viscose* capable of extrusion into what became known as viscose, died on April 15, 1935. ***Albert Einstein*** died on April 18, 1955 as did ***Gerardus Johannes Mulder***, the Dutch chemist known for his analysis and naming the 'protein', 1800. ***Percy L. Julian***, the African-American chemist, whose 100 patents include the synthesis of cortisone, various hormones and other products from soybeans, died on April 19, 1975. ***Aleksandr Oparin***, the Russian biochemist noted for his studies on the origin of life from chemical matter, died on April 21, 1980.

Patent proze

Indian patent wars

Katherine Hebditch

Baldwins Intellectual Property, PO Box 5999, Wellesley St, Auckland
(email: *katherine.hebditch@baldwins.com*)

In the past couple of years there have been some interesting and at times very contentious decisions regarding patent practice in India. We have previously reported on a couple of court decisions[1, 2] and there are no signs of the battles abating.

Cipla asks Indian Government to revoke five Novartis patents

Generic drug maker Cipla has recently asked the Indian government's Department of Industry Policy and Promotion to consider revocation of five Novartis patents related to their product Onbrez. Onbrez has the active ingredient indacaterol and is used to treat chronic obstructive pulmonary disease. Cipla estimates more than 15 million Indians are affected by the disease, but believe only a fraction of this need is being met by the current imports of Onbrez.

Cipla is launching a generic product with the active indacaterol under the name Unibrez. Cipla has indicated Unibrez will be sold at about a fifth of the price of Onbrez. Once Unibrez is on the market, it seems very likely Novartis will take court action against Cipla for infringement of their patents. The request to have the Indian government revoke the patents is likely a pre-emptive strike against this.

There have been similar situations in the past in India, but this case is notable for a new tactic being employed by Cipla.

In previous cases patents have been revoked or refused because they have not met the requirements to be granted a patent.[1] While the requirements to be granted a patent can vary slightly between countries (which can cause tensions itself), this is the standard way of overturning a patent. An alternative tactic used in a case in India in 2012 was to use the "compulsory licence" provisions of the patent system. This was alarming to big pharma as it allowed the court to force Bayer Corporation to grant a licence to their patent so that a generic manufacturer could sell the patented product if they paid a relatively modest licence fee.[2]

In this latest case it seems likely these previous tactics will also be employed, but Cipla also goes one step further and has asked that the government revoke the patent on the ground it is *mischievous to the state or generally prejudicial to the public*.[3] This could be seen as cutting to the heart of the patent system. Are patents *mischievous to the state or generally prejudicial to the public*?

The basic intention of the patent system is to reward and encourage innovation. In return for developing a new product or process and publically releasing the details of how to perform the invention, a monopoly is granted for up to 20 years.[4] At the end of the term of the patent, anyone should be free to use what was described in the patent. However, in some cases where there are multiple patents around a product (an approach sometimes called *evergreening*), even when one patent expires it can still be difficult to put a generic product on the market.

Clearly there is a fine balance between granting a monopoly so that others cannot immediately copy a product that has taken years and great expense to develop, while still ensuring a product that is desired by the public is available on reasonable terms.

Innovator drug companies would likely argue without their research and development programs new drugs would not even exist, and without the patent system it would not be economically viable to carry out the level of research and development required for these new drugs. However, if a patent is granted does it give the owner the right to wholly dictate on what terms they will supply the product? Is this just a problem with the patent system or does regulatory and competition law have a part to play? Is there, perhaps, a difference between first, second and third world countries when considering these issues?

This is clearly a very difficult and complex problem. All eyes are presently on the Indian government to see how they will deal with this request and whether it will open another pathway for others to challenge Indian patents.

If you have any queries regarding intellectual property related matters (including patents, trademarks, copyright or licensing), please contact us.

References

1. Chemistry in New Zealand Volume 77, No. 3, July 2013, Patent Proze, "Indian patent decision highlights the bond between politics and patent law".
2. Chemistry in New Zealand Volume 77, No. 3, July 2012, Patent Proze, "First compulsory licence in India serves as a wakeup call to global pharmaceuticals firms".
3. Section 66 of Indian Patents Act 1970.
4. The standard term of a patent is 20 years but renewal fees must be paid to keep it in force. In addition in some specific circumstances the term can be extended in some countries.

Katherine Hebditch of Baldwins Intellectual Property in Auckland specialises in chemistry and biotechnology patents. Katherine obtained her PhD in organic chemistry from the University of Manchester in the UK in 2004. She is currently working towards registration as a patent attorney.