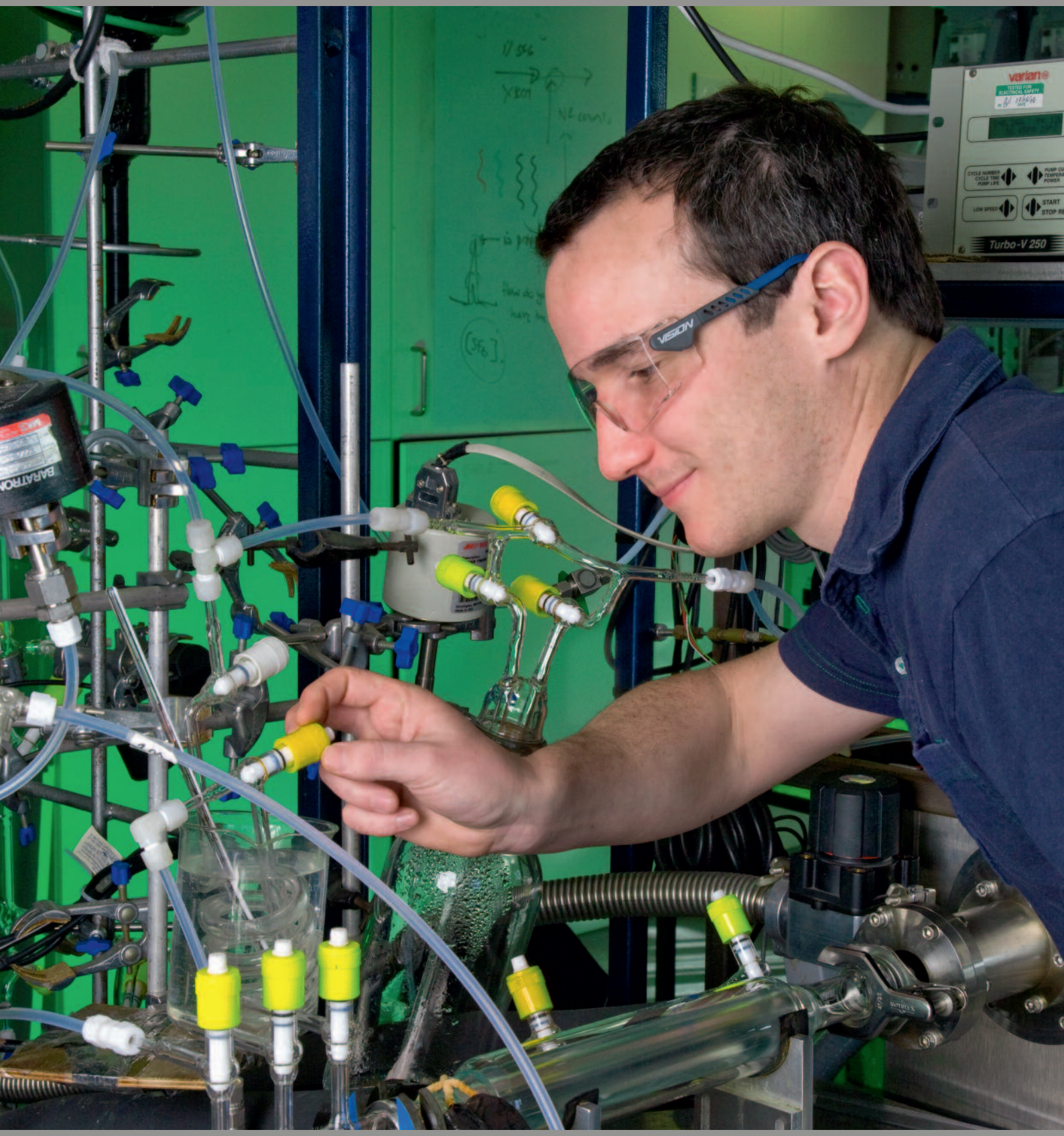
# chem cam

Chemistry at Cambridge Newsletter

Autumn 2008




**Mutant proteins** and cancer drugs

The possibilities of **metal structures**

Towards the **$1000 genome**

**What's next for** the CCDC?

## Colin Groom, the Cambridge Crystallographic Data Centre's new director, talks to Sarah Houlton about the centre and its future

### What's the CCDC all about?

It was set up in 1965 from the chemistry department, and became independent in 1989 as a not-for-profit company. This gives us a nice stable structure as a self-sustaining research institution, where we're not driven by maximising profit but by doing good science. Our activities fall into three strands, and the main one is the structural database, which now contains more than 450,000 small molecule crystal structures. It's used by well over a thousand institutions and companies around the world, including 100 or so commercial organizations. It's not just a repository – it also contains contextual data and software that helps scientists make proper use of the crystal structures.

The second strand is other software, developed primarily in the pharma area. The most well known is Gold, a ligand docking program. It is heavily used by industry, but also in academia, and we're continuing to develop it so that it allows much better virtual screening for active compounds. And the third strand is the research we do in the broad area of molecular interactions.

### Why is the database important?

I think it has become an essential tool for companies in developing new pharmaceuticals, reflected in the fact that all the major pharma companies use our database. It contains more information about molecular recognition than any other database, and the recognition that goes on between a small molecule and a crystal is very similar to that between a small molecule and a protein in the body. This allows us to derive computational descriptions of those interactions, which companies not only use to optimise the fit between the molecule and the protein, but also between a molecule and a lattice of other molecules in the materials science area.

In terms of molecular docking software, although some companies have gone down the route of screening millions of compounds against a target protein, this can only be done with compounds that already exist. With virtual screening, we can look at compounds that might exist but don't, opening up a whole new area of science.

It also reduces the need for physical testing – a company may have millions of compounds in their libraries but for a complex system they can only realistically test several thousand. We can direct them towards the most appropriate ones to test. There are two issues here – one is identifying whether a compound has the potential to bind to a protein, and the other defining the most probable binding mode. And these are really quite different problems, as in the latter you have to look very closely at the geometry of the ligand and the energetics of interaction between it and the protein. With virtual screening, we try to filter out those molecules that can't possibly bind and identify the ones that might.

### What uses does it have outside pharma?

While it is primarily used in pharma, it also has potential in crystalline materials. These are used in many applications and we would like to extend the database into this field. It's also being used by material scientists who are trying to understand crystal growth – this also has pharma applications where scientists are trying to find the best crystal form to use in a drug product. As well as organic molecules, the database contains metal organic compounds, for example, and these are of interest to material scientists in areas such as catalysis, gas storage and carbon capture. There's a huge range of possibilities for the database – and we're beginning to make people in those scientific communities aware of what the database can offer them. We don't yet know all its possible uses – we're hoping that people in other fields will be able to tell us as they know their science better than we possibly could.

### So what does the future hold for CCDC?

The primary thing, of course, is to ensure the database stays up-to-date, and available for scientists to use. And the secondary one, which is also essential, is to make sure it is used for the best scientific good. We do our own research with the database and collaborate with others, and we want to encourage users to get as much benefit as possible from the database. So we will continue to develop new tools to help scientists in their research, and the revenue we generate from providing the database allows us to develop these tools.

### Is the idea is that it will remain self-sustaining?

Absolutely. I think it is the most stable model for the centre, as we are not reliant on applying for grants every few years, which would leave the research community uncertain about the future of the database. Ultimately, someone has to pay, and I guess the taxpayer could pay for it through the research councils, but this way, with the funding coming from the current users, it is much more predictable.

### So you're looking forward to the future, then?

Absolutely. This is a fantastic place, and after 15 years in industry it's great to come somewhere that's a mixture of academia, biotech and industry, full of people who are really motivated by what they do. It's a great blend of academia with commercial reality. I also think the structure and ethos of the organisation encourages people to work with us – we're a charity and we exist to do great science. People like that and want to work with us. Industry doesn't just see us as a profit-driven software company – they see us as a research organisation with a great scientific pedigree which can help them with their own science. And that's really refreshing.

**Colin Groom**

**CV**

**Born:** Telford, Shropshire, when it was still a collection of little villages and before it became a New Town

**Status:** His wife, Kerrie, was a molecular biologist, and now works for various charities. They have two children – Thomas, who's 12, and 11-year-old Ellen.

**Education:** After the local comprehensive and sixth form college, he went to Leeds University to study biotechnology – one of the first universities to offer the subject as a degree course. He'd been sponsored by the RAF at school and for his degree, but realised that science was for him and he stayed on to do a PhD with Sandy Giddes. 'It was expensive as I had to pay the RAF back!' he says.

**Career:** After a postdoc in Leeds with Simon Philips, Tony North and John Findlay, he went to New Zealand for a second postdoc at Massey University – the outdoor lifestyle was a definite draw! Pfizer came calling in 1994 as they were setting up a protein crystallography group, so he returned to the UK and the company's Sandwich site, also spending a year helping set up a new research site in Cambridge, US. In 2002, he moved to Celltech to lead the computational group in Cambridge. He took up his new role at CCDC in October.

**Interests:** Much of his time is taken up with his family and other animals – his wife rescues sick creatures and there are chickens running round the garden. He's also a frustrated climber – Cambridge is far too flat for his liking, so he likes to travel to less flat places as often as possible.

**Did you know?** He's also a big footy fan – supporting both Telford United and Leeds United. And his choice of university was made on the strength of its proximity to Elland Road… 'I had a big club and a local club when I was a kid. The way things are going, Telford will soon be the big club!'

## Not just old girls!

Dear Editor
Your article 'The class of 1946 reminisces' prompted by Mary Ashworth's letter and photograph produced letters from four other 'old girl' students.

This letter is just to prove that at least one 'old boy' student still survives, thought Jennifer Turner's letter suggests that Peter Gray also survives.

I enjoy *Chem@Cam*, because it keeps me up-to-date on what the chemistry department is doing, but I do not pretend to understand the more advanced work – when we were students there were only 92 known elements. I particularly enjoy the Puzzle Corner, and was lucky enough to win a prize a couple of years ago. One of your puzzle setters, Keith Parsons, is a former colleague of mine at Bakelite.

After graduating, I decided to go into the chemical industry. The plastics industry was then fashionable, and Bakelite was in Birmingham, my home town. I had been away from home for seven years – four evacuated and three years at Cambridge. So I used my chemistry to develop new and, hopefully, improved thermosetting plastics, and was successful in so far as having half-a-dozen patents in my name. I stayed with Bakelite for 40 years!

It was an intellectually rewarding job in as much as we first did the laboratory work then, if we developed something promising, we did the pilot plant work. If it was still promising, we did the works trials, then the customer trials, then we had to make sure it was profitable.

We did all the entrepreneurial work, without the risk *and* without the rewards – apart from a reasonable salary and a good inflation-linked pension scheme, for which I am increasingly grateful!

**Yours sincerely**
**Reg Lewis**
**93 Buryfield Road, Solihull,**
**W Midlands B91 2DQ**

## Wonder and delight

Dear Editor
I was recently made aware of the article in the Autumn 2007 edition of *Chem@Cam* about pictures from the 1950s, which included a rather fine one of my father, Sandy Ashmore.

Ah, that picture of RGW Norrish. One of my friends at Emmanuel recounts still how he came across him in November 1968 (or so) flat on his back in the garden, saying to himself 'I've got a *@&*ing Nobel prize' in tones of wonder and delight! And I recall watching him at the Nobel prize ceremony with three Swedish student caps stacked on his head, in a decidedly jovial mood. A fierce man, but really kind underneath and with a great appetite for life.

**Yours sincerely**
**Fred Ashmore**
**fred@ashmores.me.uk**

## Class of 49, anyone?

Dear Editor
I was very interested to see the photograph of the Part II year of 1946. Can anyone provide a similar photograph of the 1948–49 year, of which I was a member?

It is noteworthy that the 1946 group contained nine girls and 21 men, whereas there was only one girl in my year of 50 students. She later became Mrs Ron Smith, and her husband was the head of the biochemistry department at the Rowett Research Institute near Aberdeen when I was working there.

Alan Sharpe, who appears in the 1946 group, was one of my demonstrators in 1949.

**Yours sincerely**
**Tony Care**
**Mill Farm, Manorowen, Fishguard**
**SA65 9PT**

chem@cam
Chemistry at Cambridge Newsletter

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**Cover**

This issue's cover star is Francis Pope, an atmospheric chemist in Tony Cox's group

**Photograph:**
John Holman and Nathan Pitt

This newsletter is published three times a year by the University of Cambridge Chemistry Department. Opinions are not necessarily those of the editor, the department, or the university.

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# Matt wins Novartis award

Matt Gaunt is one of this year's winners of the Novartis Early Career Awards in organic chemsitry. Two awards are made every year – one to a scientist working in Europe, and the other to one based in north America.

Recipients will have started their independent research careers within the previous 10 years, and work in the areas of organic or bioorganic chemistry in the broadest sense.

Matt was recognised for his significant contributions to palladium-catalysed C–H bond functionalisations and the development of new enantioselective organocatalytic reactions, including their use in the synthesis of architecturally complex molecules.

'It was an enormous surprise when I heard I'd won, but I was absolutely delighted!' Matt says. The award is a substantial unrestricted research grant, which will provide a fantastic contribution to support his chemistry efforts. 'The award is in dollars, and as sterling slides against the dollar, it is getting even more valuable!' he says.

Matt was rewarded for his C-H bond functionalisations and new chiral organocatalytic reactions

# A new computing regime

The department has a new computing and IT manager, Tim Dickens. He has a PhD in chemistry from the University of Kent, worked as a postdoc in the chemical crystallography department in Oxford, and then spent 24 at Glaxo (and its subsequent incarnations), first in computer graphics and then in IT infrastructure and service management. He started work here in Lensfield Road in September, and has already begun to implement a number of changes.

The first of these is a centralised 'trouble ticket' system to manage every request for IT help. 'We get about 300 requests for computer support a month,' he says. 'The new system is much more proactive, and makes sure nothing gets lost – we're now tracking everything.'

A virtual private network, or VPN, is currently being piloted. When connected to the VPN, it means that a computer will behave as if it were physically in the department. 'People will be able to access their data as if they were in the lab,' he says. 'This has a number of benefits, such as being able to work at home behind a firewall, access journals, and get at data when away at a conference. It should also help remote collaboration.

Another project he's working on is the possibility of implementing an electronic lab notebook. 'This would give huge benefits. For example, spectra could be indexed with chemistry information for the first time. Today, they are filed on the computer with name and date, but no chemistry information. With an electronic lab notebook, they could be linked to reaction conditions and yield in a searchable way.' It would also be possible to integrate safety assessments properly, and offer opportunities to manage the location and ordering of chemicals within the department.

'I'm really enjoying it here – it's a great place to work and there are fantastic opportunities,' Tim says. 'And I'm amazed by the diversity of equipment – that's one of the biggest challenges. For example, when we were setting up the VPN, we had to make it work on three different versions of Windows, three versions of Linux and two Mac systems. Issues are still crawling out of the woodwork.'

There have been a number of changes to the academic staff recently. Markus Kalberer is the new lecturer in physical chemistry. He joins us from the Paul Scherrer Institute and ETH in Zürich. Also new to the staff is Justin Benesch, who has been working with Carol Robinson for a while and is now a Royal Society University Research Fellow.

Meanwhile, we are sad to see two leave us. Stuart Mackenzie has moved to a lectureship at Oxford, and Royal Society URF Martin Smith has also taken up a lecturing post at Oxford. We wish them both well for their future careers.

# Nobel chemistry

Roger Tsien: honoured for his work on green fluorescent protein

One of the winners of this year's chemistry Nobel prize, Roger Tsien, has links to the department. The University of California San Diego scientist has a Cambridge PhD in physiology, but spent much of his time working here in chemistry, supervised by Jeremy Sanders. He was back in Cambridge in 2003 as our Todd Professor.

'Roger decided it was important to know the concentration of calcium in cells, and he had an entirely novel idea about how to measure it,' Jeremy says. 'His idea was to design a molecule that could get into cells and change its fluorescence when it bound to calcium ions. It was a brilliant conception, combining chemistry and biology.'

He spent his time in chemistry making the compound, and then returned to physiology to prove that the idea actually worked. 'His original compound and its descendants have transformed our understanding of how ion concentrations control cell biology. He has continued to work in this area, and is an inspiration to everyone who reads his work or hears him speak,' says Jeremy.

# Gone, but not forgotten!

Photo: Nathan Pitt

He may have returned to his native Australia a few years ago, but Andrew Holmes is far from forgotten here in Cambridge. Andy turned 65 recently, and numerous of his former students and collaborators gave talks on subjects ranging from natural product synthesis to materials chemistry to a packed audience one Friday in September. And the day concluded in suitable style with a dinner at Clare College.

Andy (in the centre with the purple tie) with a few familiar faces back for the day

Photo: Nathan Pitt

The latest addition to the department's collection of NMR spectrometers is an Avance III from Bruker. The 400MHz has a QNP cryoprobe which will give better sensitivity for $^{31}P$ and $^{19}F$ than our existing machines, as well as for conventional $^{1}H$ and $^{13}C$ spectra. And, according to Brian Crysell, it's also our first ultrashield plus magnet where the 5 gauss line (the 'safe' level) is within the footprint of the magnet itself, rather than outside it

# Plans well under way for the Chemistry Olympiad

Plans are well under way for next summer's Chemistry Olympiad, which is being held in the UK for the first time – here in Cambridge to coincide with the 800th anniversary of the university.

'The Olympiad is a really big deal internationally,' says teaching fellow Pete Wothers, who is chairman of the event – and who took part in the event himself back when he was at school. 'In some countries, students who do well get scholarships to go to university, and even excused from military service. Those who take part are the star chemists of the future.'

Being held between 18 and 27 July, students from 70 countries all over the world will take part. Each country can send up to four students and two mentors, and the competition itself consists of a five-hour written exam, and a five-hour practical test. They will be staying at Trinity, St John's and St Catharine's colleges.

The best students will be presented with medals at a ceremony in the chapel at Kings, followed by a dinner in a marquee on the backs at Kings. Social events will include the chance to sight-see in London followed dinner at the Natural History Museum while they're waiting for the results. Current students from the department will also be involved in helping the visitors.

The Olympiad's Cambridge coordinator, Emma Powney, is currently focusing on raising sponsorship for the event. Sponsors already include the Goldsmiths Company, the Salters Institute and the Royal Society of Chemistry, plus the Oxford and Cambridge University Presses, Cambridge Assessment and the Department of Innovation, Universities and Skills. Any further offers of sponsorship would be gratefully received; Emma can be contacted at elp23@cam.ac.uk

Pete accepts the official Olympiad Flag at the 2008 event in Budapest


# It's 50 years in Lensfield Road

Amazingly, it's now half a century since the chemistry department moved out of Pembroke Street and onto its current site here in Lensfield Road.

To coincide with the 50th anniversary of the official opening by Princess Margaret in November, a small exhibition of departmental memorabilia was held in the Todd-Hamied room. This included the silver salver presented by the building's architects on the occasion of the opening, and a signed photograph of Princess Margaret, which used to take pride of place on the walls of the old library.

The exhibition also featured some of the memorabilia electrician Roger Ward has 'rescued' over the years from various skips. These gave a fascinating insight into lab equipment of the past for those too young to remember the days before everything was electronic and computers were taken for granted.

Among Roger's 'haul' were various balances, hotplates, a machine for determining melting points, a timer, and even a centrifuge.

They may seem hugely out-of-date now, but in reality some are only 20 or 30 years old. It will be interesting to see what future generations of chemists make of the current state-of-the-art equipment we use today when they are rescued from skips!

Roger shows off his impressive collection of lab memorabilia

# More awards for Steve

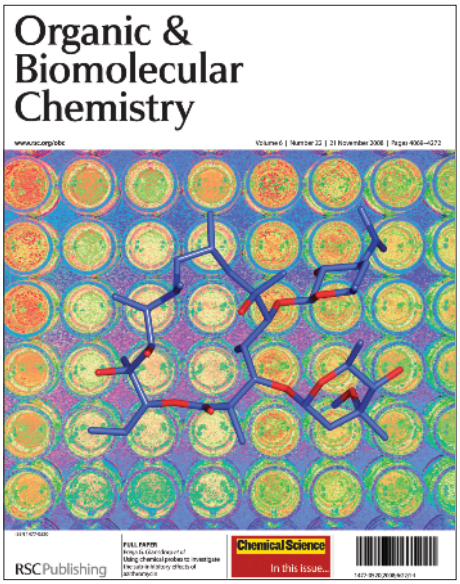
Steve Ley's international medal collection continues to grow. In 2008, he was awarded four more, including one from India, for different aspects of his science.

The Hans Herlo/Inhoffen Medal from the Helmholtz Zentrum für Infectionsforschung in Germany was made for his contribution to natural products chemistry, while he was given the Prous Institute/Overton and Meyer Award for new technologies in drug discovery by the European Federation of Medicinal Chemistry.

He also received the Royal Society of Chemistry's High Throughput Drug Discovery Methodologies award. And the Indian prize is the U.R. Ghatak Endowment Lecture and Gold Medal from the Indian Association for the Cultivation of Science. He's off to Kolkata in January to give the lecture.

To find out more about the exciting research that's going on in Steve's group, go to leygroup.ch.cam.ac.uk and leyitc.ch.cam.ac.uk






Several Cambridge chemistry groups have had their science highlighted on journal covers recently. First off is a joint effort from Steve Jenkins and postdoc Oliver Inderwaldi on *Chem Soc Rev*. The special issue in honour of Nobel prize winner Gerhard Ertl was an invited review of theoretical work on the synthesis and combustion of small alkanes.

The image features a hypothetical carbon cycle in which putrefaction of biomass creates methane, which is then converted to liquid fuel via partial alkane combustion and subsequent alkane synthesis; combustion of the liquid fuel emits $CO_2$ and water into the atmosphere, ready for photosynthesis to start the cycle again. Unlike present biofuels, the whole plant would be used, not just the part susceptible to fermentation. The image also includes schemes of some key reaction steps described in the review.

The *Angewandte* cover originates from Jonathan Nitschke's group. A pair of commercially available diamine and formyl–pyridine subcomponents were observed to come together with iron(II) ions in water to form a hollow tetrahedral cage moleule. Its crystal structure revealed the presence of an internal cavity 140Å$^3$ in volume, allowing the cage to serve as an excellent host for a small lipophilic guest molecule such as cyclohexane. Guest molecules could be liberated through the addition of a chemical signal – a triamine – which destroyed the cage, or the cage could be 'unlocked' in reversible fashion by lowering the pH.

And Dave Spring's work featured on the cover of *Org. & Biomol. Chem*. The molecule is azithromycin, which has clinically beneficial effects at sub-inhibitory concentrations against *Pseudomonas aeruginosa* infections. These effects are, in part, the result of inhibition of bacterial biofilm formation. The 96-well plate at the back is a biofilm assay showing that the molecule inhibits biofilm formation in *P. aeruginosa*.

## Daan's grant success

Head of theoretical Daan Frenkel has been awarded an Advanced Grant by the European Research Council. These are large personal grants for senior researchers, and Daan has been given 1.8m over five years.

'My proposal focused on the development of numerical tools to predict good strategies for inducing the spontaneous assembly of complex structures with nano- or micro-scale building blocks,' Daan says. 'The grants are highly desirable, and there was stiff competition – the success rate in my field was just 4%.'

## Gifted & Talented kids come to Cambridge

The chemistry department is pioneering a scheme whereby high-achieving sixth formers can take part in master classes. About a hundred 16 and 17 year old Year 12 students who are considering studying chemistry at university are spending four-and-a-half hours of their Saturday afternoons for 10 weeks here in Lensfield Road – four before Christmas, and six after it.

The idea is to introduce them to aspects of chemistry that are beyond what they will experience at school, and help them to understand what they are already learning. Topics that will be covered over the 10 weeks include the synthesis of medicines, analytical chemistry and green chemistry.

'It's going well,' says teaching fellow Pete Wothers. 'So far, we've had sessions on NMR, a talk on X-ray crystallography from John Davies, and they've been working on problems with a group of 10 student demonstrators.' He hopes they'll go back to their schools fired up to take part in the Chemistry Olympiad selection process.

The master classes are organised by Excellence East, the regional hub that links the Eastern Region Gifted and Talented Partnership with local schools and colleges. It's being coordinated by Joanna Taylor in the university admissions office, who believes it's a fantastic chance for sixth-formers to step outside the curriculum.

'The classes offer a unique opportunity to develop and deepen knowledge and understanding of this area of science in a university environment,' she says. 'But the classes aren't designed simply as revision-type sessions based on the A-level chemistry syllabus with the aim of improving A-level grades. The subject matter in some cases goes beyond the syllabus.'

One of the tasks they've already been set involves drawing the structures of isomers of organic molecules. 'I set them a challenge to come up with as many isomers for $C_5H_8O$ as they could, with a prize for the one who found the most,' Pete says.

'I rather recklessly added that if they could beat me, I'd give them £20. I've managed to draw more than 300, including enantiomers and exotic things like chiral allenes, so I'll be pretty impressed if any of them do manage to beat my tally!'

# Towards the $1000 genome

**A chat over a pint in the Panton Arms led to a faster, cheaper way of sequencing DNA for Shankar Balasubramanian and Dave Klenerman**


Photo: Nathan Pitt

Shankar and Dave back in the Panton Arms, where the story began

Filling a whole issue of *Nature* is a long way from a few doodlings on the back of a beermat. But that's exactly what's happened for Shankar Balasubramanian and Dave Klenerman – their idea of a way to sequence genomes quickly and cheaply has now been used to sequence the first Asian and African human genomes, as reported in three articles in the 6 November issue of the journal.

One summer afternoon back in 1997, Shankar, Dave and postdocs Colin Barnes and Mark Osbourne were bouncing ideas around over a pint or three in the Panton Arms. Back then, DNA was sequenced by separating it on a gel or by capillary electrophoresis, but it is synthesised attached to a solid support. What if a piece of DNA could be pinned to a surface and the natural monomers that DNA polymerases use could be engineered so they were colour-coded for the different bases? It might be possible to read off the colours to determine the sequence.

A little post-pub cogitation later, they realised they might be on to something. Inspired by the DNA microarrays that were becoming popular for genetic analysis, there was a realisation that if lots of DNA samples could be pinned onto the same surface, many sequences could be read in parallel, dramatically speeding up the process. A few preliminary calculations later – they'd moved on to the back of an envelope by now – and they figured that it might be possible to sequence a billion bases on a 1cm$^2$ chip.

They decided that the only way this was ever going to become a reality would be to spin out a company to do it. 'You can only go so far with a single postdoc!' Shankar says. 'The Wellcome Trust were interested, but we realised that one postdoc for three years wouldn't be enough. So we approached venture capital company Abingworth in November 1997. Our ideas were very ambitious – if not a little unrealistic – but they were very interested in having a 10,000-fold improvement in speed, capacity and cost.'

The due diligence process threw up some further challenges they'd not thought of, such as how to prepare the samples. 'You can't go spotting a million different samples on the surface – you'd have to prepare each one separately!' he says. 'Provoked by a due diligence challenge, I recall a "lightbulb" moment one Sunday afternoon – if you fragmented the DNA from a genome and could somehow immobilise the fragments randomly on a surface in a way that they remained in separate spots and didn't cluster together, then when you imaged the surface you would see each one as a single molecule. That way you could create maybe 10 million different samples that can be sequenced separately on one surface in a single step.'

In retrospect, he says, that probably seems obvious. But at the time, it was this realisation that allowed them to move forward and develop a massively parallel automated high-throughput system. They filed a foundation patent, and the company was born in June 1998 under the name Solexa. Initially, it sponsored a couple of postdocs in the university to prove the concept before the formal spin-out company was established in Chesterford Research Park in 2001. 'We raised money, and it grew and grew,' Shankar says.

## CHEMICAL CHALLENGES

While they faced many engineering challenges, Shankar believes the chemistry was pivotal. 'We had to engineer polymerase enzymes that would tolerate the structural changes to the DNA monomers that contained the colour markers,' he says. 'But another important development that affected the cost and usability of the instrument was finding a technology to amplify the fragments – reproducing each one to give several hundred copies to strengthen the fluorescent colour signal and making it easier to image.

'And, of course, it generates a lot of sequence data which need to be processed and then put back together to give the longer strands of DNA in the genome. So it started with chemistry, but it needed biochemists, geneticists, bioinformaticians, hardware and software engineers, and even fluidics experts to deliver a system that works.'

Their original aim was to deliver a system that could sequence a genome for $1000 in a day. They're not quite there yet – but Shankar believes it's now only a couple of years away. There are several competing systems, but he thinks that the focus on chemistry has provided an important edge. 'Beautiful systems and elegant hardware are all very well, but without chemistry it can't work. We invested a lot of effort in developing the chemistry we needed from scratch, which turned out to be essential in terms of competitive advantage,' he says.

The Genome Analyser was only launched in January 2007, and within a couple of months papers were appearing in journals using the technology. Several hundred machines are now in use. And it's now not only being used for genome sequencing – users are finding a variety of other applications such as RNA sequencing and mapping transcription factors onto their binding sites within the genome. 'These are all things we'd never thought of!' he says. 'If you put a new tool into the hands of scientists, they'll do creative, and often crazy things with it.'

Solexa itself was acquired by US company Illumina in Jan 2007, and Illumina UK (formerly Solexa UK) now employs 140 people and is moving into a new building near Cambridge in 2009. Both Dave and Shankar are delighted with its success. 'It wouldn't have been possible without the huge number of talented people within the company,' Dave says. 'There are 100 authors on our Nature paper, and the input of all of them was essential, from the science itself to developing the robust machine that is now being used in labs around the world.'

'It's been an amazing journey,' Shankar concludes. 'I've learnt many things from the process, and perhaps the most important is to be ambitious. Anything is possible, as long as you have the right team of people behind it.'

# Reactivating protein mutants


Photo: Nathan Pitt

**Alan Fersht has spent his career working with proteins, trying to understand how they fold, what makes them stable, and how they interact with molecules. Recently, he's been looking at a protein which can cause cancer when it goes wrong**

Alan with his recently awarded Royal Society Royal Medal and the GN Lewis Medal from Berkeley

The main focus of Alan Fersht's chemistry is protein engineering – understanding protein stability, how proteins fold and how enzyme catalysis works.

'It takes an enormous amount of effort just trying to understand the interactions within proteins, and with the molecules they interact with,' he says. 'Over the years, we have learnt a lot about proteins by putting mutations into them, and now know a lot about the strengths of the interactions and what contributes to protein stability. And for the past 15 years or so, we've been looking at mutations that cause disease.'

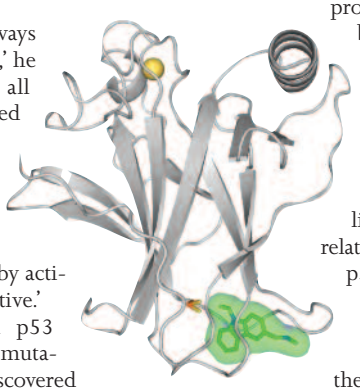
Perhaps the most important of these diseases is cancer, where the cell lifecycle becomes uncontrolled. 'Two types of proteins are involved – oncogenes which start the cell proliferation process, and at the other end there are tumour suppressors which stop the cell from proliferating. Mutations must happen in both of these types to cause cancer,' Alan explains.

'The protein suppressor p53 is one of the most important proteins in the cell, being implicated in processes from fertility to ageing. It is present in low levels in cells, and if there are any stresses in the cell that could lead to cancer, it becomes activated.'

If the cell's DNA has become damaged, it activates the genes controlling pathways that repair the damage. If it can't repair the damage, it activates genes that stop the cell cycle. But that's not enough – it has to go one stage further and kill the cancer, so it activates genes that are involved in programmed cell death, or apoptosis – the body's way of killing cells that are past their useful life.

'When p53 and all its pathways are active, cancer cells are killed,' he says. 'But in about half of all human cancers, p53 is inactivated by mutation. That's bad news – not only does it mean that the cancerous cells can proliferate, but in addition treatments such as radiotherapy and old-fashioned chemotherapy that work by activating p53 are rendered ineffective.'

Alan became interested in p53 because it was inactivated by mutation, and about 12 years ago discovered that about a third of the mutations that inactivate p53 do so simply by destabilising the protein structure. 'We discovered that normal p53 in a cell melts at 44°C, only just above body temperature. It then starts denaturing very rapidly. Many of the mutations that make p53 inactive simply make it less stable, and start melting at body temperature or below.'



The core domain of a mutant of p53, with the molecule they designed filling a cavity induced by the mutation

Since then, the group has been developing strategies to reactivate p53 mutants. The first tack was to design peptide molecules that could bind to p53 and stabilise it. 'We showed these peptides would stabilise p53 in a test tube, and in collaboration with Swedish colleagues that they could reactivate the p53 mutants that had become destabilised in cancer cells,' he says. 'One of our major goals now is to make small molecules that could become therapeutics by reactivating p53. Ideally, one would like to get molecules that would activate all mutants of p53, but it's not an easy target.'

They have now found that one mutant has a mutation at the 'wrong' end of the protein molecule, far away from its active end, which causes a deep cleft to form at the bottom of the protein structure, and it should be easier to find drug molecules that fit into it.

'We solved the structure of this mutant just over a year ago, and we are now looking for small molecules that bind in this cleft,' he says. 'We have identified a class of molecules that will bind there, and which stabilise the p53 protein – and we have preliminary biological data in cancer cells that show it does work.'

Alan is convinced that they will find a drug that works by binding to this cleft. 'Although this mutant probably occurs in only 1% of cancers, this still represents something like 70,000 new cases a year. And it's relatively easy and cheap to sequence p53, so this could be done routinely in cancer patients to see if a drug that acts there is likely to work.'

They have already discovered their first lead compounds, but these do not yet bind tightly enough to p53 to make a successful drug. 'It's pretty clear from our structural work where we need to build onto the molecule to make it bind to the protein more effectively,' he says. 'I'm sure we're going to get down from micromolar binding to

# – a new way to cure cancer?

Photo: Caroline Hancox

A team effort: Alan surrounded by his talented group of scientists

nanomolar or even picomolar very quickly. We've set up a reasonably high-throughput drug screening operation in our labs, and I'm very optimistic that it's going to work.'

Alan's group is also working on the structural determination of biological macromolecules. 'It's now 50 years since the first protein structure was solved, but we're used to proteins being beautifully folded molecules, with alpha helices, beta sheets and having a regular structure,' he says. 'But in recent years, it has been discovered that many important proteins have disordered regions in them. People had ignored these in the past, thinking perhaps that something had gone wrong with the protein, but we've now realised that maybe 40% of structures in the human proteome are disordered, like the denatured states of proteins. And tumour suppressor p53 is typical of this – it is a complex protein with some domains that are beautifully folded, and others which are disordered.'

Solving the structures of these intrinsically disordered regions remains something of a challenge. 'You can't crystallise them and find the structure by X-ray crystallography, because the disorder prevents them from crystallising,' he explains. 'So the only way to do it is to carry out experiments in solution, combining high field NMR to look at the folded regions and find domain–domain interactions, and other techniques such as small angle X-ray scattering. This method languished for a very long time, but with modern software you can carry out scattering experiments in a synchrotron and start reconstructing the molecules.'

Last year, they succeeded in solving the structure of the full length of p53 in solution using a combination of these methods. 'This is probably the first of these types of structures to be solved like this – I'm very pleased and it has opened up a whole new area of research,' Alan says. 'We're now trying to build up the structures of various other structures of complex proteins in solution using these techniques.

'These proteins tend to be involved in controlling the cell cycle and cell signalling, some of which work in conjunction with p53. It's now routine to determine the structures of protein crystals, and the challenge now is to look at those which you can't crystallise – it's not simple and makes for fascinating academic research.'

He is delighted that his group remains at the forefront of protein structure determination. 'We're moving forward very quickly – we had to as we needed the structures to solve the other problems we were looking at, such as p53,' he says. 'We are now looking at the complexes between p53 and various other proteins which interact with it – there are some very interesting questions about how it works that we are hoping to answer.'

## CV Alan Fersht

**Born:** London

**Status:** Married to Marilyn, a history graduate who's now retired, but does a huge amount of charity work and is chairman of a local fine arts society. Daughter Naomi is a consultant oncologist and radiotherapist and is married to a surgeon – they have two children (Joe 6 and Ruby 4). Son Phil lives in Boston in the US, and is an expert in outsourcing.

**Education:** He went to the local grammar school in Walthamstow. 'No-one ever got an exhibition or scholarship to Oxbridge from there, but in those days there were state scholarships. I managed to get one of these and Caius offered me a place to study natural sciences. He stayed on for a PhD with Tony Kirby.

**Career:** In 1968, he spent a postdoc year with physical organic chemist Bill Jenks at Brandeis University in the US. He returned to the Laboratory of Molecular Biology in Cambridge in 1969 to work on the mechanisms of protein activity. 'Those were heady days – you'd see Francis Crick in the canteen at lunchtime, Sydney Brenner put his head around the door, and Max Perutz and Aaron Klug were both around too,' he says. He moved to Imperial College in 1979 to hold the Royal Society Wolfson chair formerly held by Dorothy Hodgkin, and in 1988 moved back to Cambridge as Herchel Smith Professor of Organic Chemistry.

**Interests:** A former junior chess champion and president of the Cambridge university chess club, he's recently rekindled his interest in chess and has started collecting chess sets in between the large amount of travelling he does for work. His grandchildren also take up a lot of his time.

**Did you know?** Last year, Alan spent a month of evenings writing a small book on chess sets as an exercise in desk-top publishing. He found an academic publisher in Dorset, uploaded a 100Mb file to their website, and they printed it out on high-quality art paper. He's already sold enough copies of the book to cover his costs. 'I wrote one less review that year – and a book on chess pieces instead!'

# Metals and molecules

**Simon Humphrey's work on metals may lead to new ways of storing and separating gases, and novel metal catalysts**

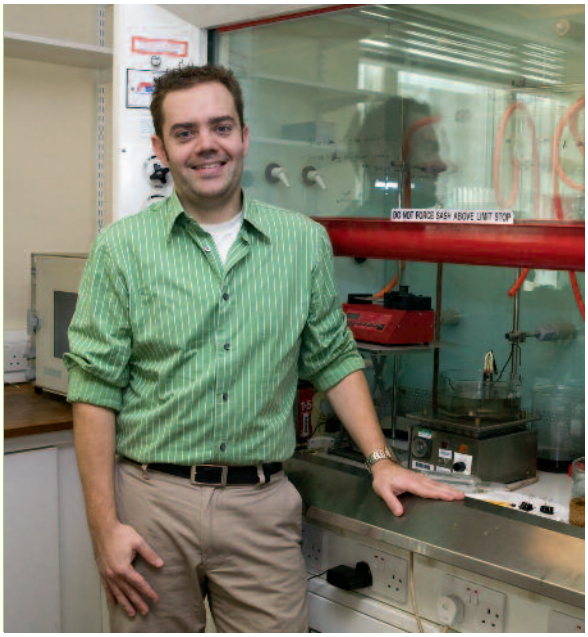


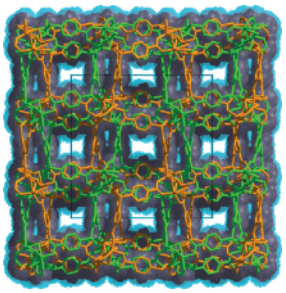
Photo: Caroline Hancox

Simon Humphrey's work is focused on two rather different aspects of inorganic chemistry – porous coordination polymers and metal nanoparticles. PCPs consist of metal ions linked together into lattices by organic molecules, with each metal bonded to a fixed number of ligand molecules. For example, an octahedral metal which likes to join to six ligands would give a box girder-type lattice structure.

'Early examples were targeted at applications such as hydrogen gas storage, but I'm interested in more niche markets as I'm not sure that the extremely stringent requirements for their applications in hydrogen storage that are being laid down by the US department of energy will ever be reached,' Simon says. 'However, they are also very good at separating different types of molecules. We've made a material that can separate nitrogen and oxygen – even though the molecules are about the same size; it also completely separates mixtures of nitrogen, oxygen, carbon dioxide and hydrogen in a single pass through the material, or carbon dioxide from methane at room temperature. We think the electronics at the pore mouth have an effect, and it may be that some molecules bind more strongly than others.'

The next step is to use more exotic organic molecules as the linkers, with extra functionality built in to allow the frameworks to induce 'smart' guest-responsive behaviour. 'I'm looking at phosphine ligands, where polar groups on the phosphines can lead to the formation of two separate but interlinked frames which are trapped together but still able to move,' he says.

'Effectively, this induces a "breathing" mode where the frameworks are weakly held close together to open the pores, and spontaneously spring apart to close them. As a result, argon gas may be absorbed at one temperature, for example, and the frameworks move apart to trap the argon inside; you can even apply a vacuum and the argon won't come out until the temperature is raised. This makes it possible to store a gas like argon that doesn't strongly adsorb to surfaces as it relies on a physical trapping effect.'



Right: Structure of a porous coordination material based on triphenylphosphine oxide and zinc hydroxide networks. The two interpenetrated networks are shown in green and orange

He's also looking at attaching catalytic metals to the phosphines. 'You could imagine taking a well known catalyst like Wilkinson's catalyst and turning it into a completely heterogeneous array. Even though it is a solid catalyst, it still has single active sites, just like in the homogenous catalyst. You can also change the shape of the pore mouth, which allows you to change the site selectivity of the catalyst – you can't do this in solution,' he says. 'By making the phosphine ligands bigger, you can tune the size of the channel opening. You could then take a mixture of, say, alkenes, and only those that can fit inside the pores will react. This raises the potential of applications in simultaneous separation and catalysis.'

Another idea is to make biologically inspired versions of the same materials, for example by using dipeptides as the ligands. 'Because they are naturally chiral, it might mean the frameworks could be used to carry out chiral separations,' he says. 'They are harder to put together because the peptides are "floppy", but work elsewhere shows that although the separation isn't great yet, if you can tailor the channel correctly you can get some selective absorption in the channel that could allow the separation of completely racemic mixtures.

'Our idea is to use easy-to-make dipeptides and tripeptides to give us more complex systems. It's too difficult to make chiral phosphine ligands that would coordinate into the framework, so we are focusing on biological molecules that will bond quite strongly to a metal through carboxylate groups. But they are still a challenge to make.'

His second focus is on metal nanoparticles. In collaboration with Richard Lambert here in Cambridge and Don Tilley in Berkeley, he is making rhodium, palladium, platinum and gold nanoparticles using a synthetic method that allows control over the kinetics of nanoparticle nucleation and growth. The precursor is added using a pump, and by controlling the rate of addition, they can control the shape and size of the nanoparticles.

'We can make core shell nanoparticles, where one metal sits inside another,' he says. 'They can be put onto inert supports like silica and used for solution or gas phase catalysis, and we're also looking at different metals in epoxidation reactions. They can also be heated up so the metals mix, giving bimetallic nanoparticles, or even inverted so the outside layer moves to the centre.'

## CV Simon Humphrey

**Born:** Wisbech, where his father has a farm and he spent most of his summers growing up driving tractors.

**Status:** His girlfriend is a biophysicist. 'I always said you should never date someone from your own subject,' he says. 'I failed!'

**Education:** He went to the local school his parents and grandparents had attended, in a small village, Gorefield, in north Cambridgeshire. He studied chemistry at UEA, spending time studying in Santa Barbara. He came to Cambridge in 2002 for a PhD with Paul Wood.

**Career:** Simon moved back to the Californian sunshine for a postdoc with Profs. T Don Tilley and Gabor A. Somorjai at Berkeley, before returning here in 2006 where he's now a Research Fellow at St John's College.

**Interests:** He spends his summers playing cricket, and squash and football in the winter, but claims he's only really any good at cricket. Playing for the chemistry department this summer he managed to take 4 for 5 off five overs, and three of the runs were wides! He's also a Peterborough United fan.

**Did you know?** Simon likes to go to Las Vegas a couple of times a year to play poker, and claims a successful trip is one where he wins enough to pay for his flight and hotel, and maybe make a small profit. 'I have a habit of playing very well against the tourists who are only there to lose money, and then getting too cocky when playing against the one guy who is sitting behind a mound of chips. Playing two kings when he has two aces is a good way to lose your money all at once!'

# And finally… we got the lot!

## It's taken a while, but it now looks like we've identified all of the faces in Mary Ashworth's 1946 photo

**At last – we have a full set of names. Unless you can identify any errors?!**
**Back row:** Olga Rutherford, E.C. Webb, J. Sawyer, V.M. Clark, Heather Platt, W. Rosenfelder, Helen Frenkel, W. Burne, Mary Ashworth; **Middle row:** Akbar Imam, Costi Edeleanu, Alec Sutton, A.J. Poynton, Reg Lewis, J. Cave-Brown-Cave, H.M. Kimberley, Fred Webber, Alan Sharpe, Peter Gray, A. Wild, D. Goodison; **Front row:** Susan Neuberger, Joan Banus, B. Whittaker, Leslie Hunt, A. Hutchinson, Ernie Elborn, Audrey Free, Jennifer Turner, Shirley Wickham-Jones.

### A plea from the editor...

In the process of the hard disk failure that caused so many problems with the last issue, all the submissions we'd been sent for the alumni page also went AWOL. So if you've sent in something to the magazine and it's not been used, it means it's vanished in a puff of expired silicon, and it would be fantastic if you could send it to us again. And, of course, any other contributions are extremely welcome!

Dear Editor
On the middle row, eighth from the left, is Fred Webber, a senior lab assistant working in the top floor lab of the physical chemistry department in Free School Lane when I was there in 1952 as a senior research student supervised by Professor Norrish.

Fred was a clever and very knowledgeable chap who had great skills as a glassblower, self-taught. He had great patience with the type of student who spends forever elaborating his apparatus and consequently fails to use it to get results of any value. Some of the structures were a sight to behold.

I found your reminiscences very evocative of the inhabitants of the lab in my time. We all used to meet for tea in the Perse Room – George Porter, Maurice Sugden, the Prof and so on.

**Your sincerely**
**Geoff Drinkwater**
**harolddrinkwater@btinternet.com**

Dear Editor
The few 1946 blanks can be filled in as follows: Back row second from left is physical chemistry technician E.C. Webb.

Fourth left on the middle row is A.J. Poynton, and eighth left is glassblower and physical chemistry technician Fred Webber.

**Yours sincerely**
**Peter Gray**
**2 Fendon Close, Cambridge**
**CB1 7RU**

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Thanks to the generosity of the department's Corporate Associates, we have been able to benefit the education and environment for students and staff. For example, the Associates pay for university-wide access to SciFinder Scholar and ChemOffice. They also make significant contributions to the library for journal subscriptions. Moreover, they provide exam prizes, faculty teaching awards and summer studentships, and have recently funded the refurbishment of a state-of-the-art meeting room with teleconferencing and display facilities.

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# A happy day in Dublin

Chem@Cam reckons no issue is complete without a good wedding. This time, it features two Cambridge chemists – Alan Sandercock, who did his PhD with Dudley Williams and is now a postdoc with Carol Robinson, and Susan Fowler, a former PhD student with Jane Clarke, who was also a postdoc with Chris Dobson, and now works for MedImmune on Granta Park in Cambridge.

The romance started seven years ago when they were both doing their PhDs. They bumped into each other at a mutual friend's birthday party Sam Barton – another Cambridge chemist, who was in Joe Spencer's group.

The happy couple tied the knot in Susan's home town of Dublin, with plenty of current and former Cambridge chemists in attendance. They then escaped to Italy for a romantic honeymoon in Venice and Florence, with short stopovers in Bologna and Pisa.

'The day flew past so quickly it's all a bit of a blur!' Alan claims. 'We were very lucky as the weather was absolutely glorious – bright sunshine and clear blue skies – which is really surprising for Dublin, especially this summer!'

# Four-wheel drive!

When Nick Handy retired a couple of years ago, he and his wife Carol left Cambridge and moved up to the Lake District. Their new abode is a farm that has been in Carol's family for some time, in the beautiful countryside near Bassenthwaite Lake. In the summer. John Pyle popped in to visit, and reports that they are loving the country lifestyle. And Nick has gone one better than the normal Cambridge bike – scooting around on the bright red four-wheel drive vehicle pictured above!

# Farewell to three

Three members of the assistant staff have moved on: physical sector secretary Anita Hudson (left), cleaner Barbara Partridge (above), and Katie Dryden-Holt, who worked for Steve Ley. We wish all three of them good luck for the future!

## Comings & goings

**New Staff**
Anita Klosowska
Rachael Jefferies
Robert Baron
Daniel Fisher
Glen MacElroy
Andrew Milner
Peter Hartley
Noah Maheya

**Leaving**
Henneli Greyling
Gabriela Ridlova
Rolandas Kvarinskas
Katie Dryden-Holt

**Retired**
Barbara Partridge
John Flanagan

# A sad goodbye to Gladys and Roy

Sad news reaches us of the death of two long-serving former members of the assistant staff. Gladys Fenning (left) started in 1962 as a cleaner in the department of physical chemistry, and stayed for around 20 years before moving to the Assistants Sports & Social Club. She retired in 1999 at the grand old age of 87. She was widowed in 1958, and later married Jack Fenning, one time chief storekeeper in chemistry.

Roy Denston (right) came to the lab in 1967 as an electrician in the maintenance department and stayed until he retired in 1993.

# What, no Sports Day rain?

**What better to do on a lovely sunny day (well, a non-rainy one, anyway!) than escape from the lab for a spot of cricket, football, croquet and even boules? Caroline Hancox's exercise was limited to her shutter finger to take these photos of Sports Day action!**

# The hills are alive…

**The annual organic sector postgrad symposium and welcome party in October was once again sponsored by Pfizer. This year's theme for the party was 'musicals', which gave plenty of opportunity for some rather imaginative costumes!**

Above right: Cats Sam Cheung and Patricia Garcia Dominguez; right and below: nun Shankar Balasubramanian, and Alessandra Polaro and Sebastian Muller from the Sound of Music

Above: Stars of the Wizard of Oz, Mike Cooke, Ben Haffmayer, Falco Magnus-Meyer and Jochen Brandt; left: Four members of the Gaunt group forgot their costumes; below: Georg Blaser, Fredrik Andersson, Leegyan Kwa, Zoë Waller in Chicago style, Kid from Fame Beth Ashbridge, and Keith McLuckie as a random soldier

Danny Allman failed to dress up, but instead he pinched James Shearman's hat; apparently he's the star of An Officer and a Gentleman, The Musical. No, neither have we…

# The return of ChemDoku!

And now… back by popular demand… it's ChemDoku!

And this time, the credit crunch has got us thinking where might be a safer place to invest our hard-earned loose change than the bank.

Under the bed is probably not the worst idea right now, but we went looking at precious metals instead. And if the current spot rates are to be believed, the most expensive option would appear to be rhodium.

All you have to do is to arrange the chemical symbols of the nine different precious metals in the grid so that each appears once – and once only – in each horizontal row, vertical column and 3x3 square. Easy!

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Ir | | | | Ru | | | | Pd |
| | Pd | | | | | | Au | |
| | | | Ag | | Ir | | | |
| | | Pd | Os | | Ru | Ag | | |
| Ag | | | | | | | | Pt |
| | | Ru | Pt | | Re | Os | | |
| | | | Rh | | Au | | | |
| | Re | | | | | | Os | |
| Rh | | | | Pt | | | | Ru |

£20 prizes are on offer for both puzzles. Send entries by email to jsh49@cam.ac.uk or by snail mail to Chem@Cam, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW

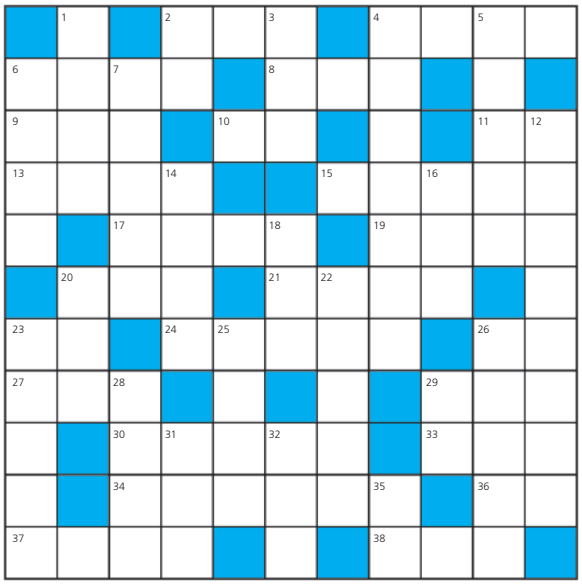
# Chemical crossword

We thought it was about time for another crossword, and as if by magic, Graham Quartly has sent us one.

As ever, each square has to be filled with the symbol for a chemical element in such a way that the resulting words fit the clues. For example, 'European language' requiring six elements couldn't be SPaNiSH as it's only five elements, but could be SPaNISH as that's six.

Graham reports that his team of crack crossword testers failed to get two of the answers – both of the number 6s – but he claims one is in the dictionary and the other is a common Spanish word.

As ever, a £20 prize will go to the first correct solution randomly picked out of whichever receptacle comes to hand.



**Across**

2. Cake or stone?
4. Relaxed, informal?
6. Swaying of water
8. Spanish town in Africa
9. Physical unit
10. Annoy
11. Central
13. Girl's name
15. Island tree
17. Celestial bodies
19. Blanket
20. Small bird
21. Sheepish
23. Equal
24. Element
26. Domestic animal
27. Ancient tribe
28. Spy fatale
30. Get better
33. Restriction to movement
34. Timepieces
36. Not out!
37. Future past
38. Single

**Down**

1. With more knowledge
2. Pronoun
3. Part of body
4. Earth shattering
5. Rough
6. Salsa move from the 70s
7. Sword
12. Misgiving
14. Acoustic tracker
16. Face down
18. Offspring
20. Caution
22. Instinctive and bloody
23. Lose resolution
25. Support
26. Gun
28. Stroke
29. Possesses
31. Stes up or triggers
32. Firm hold on sin
35. Girl's name

# Last issue's winners

## Molecular weights

Ah, the joy of open-ended questions... This one got a few brain cells working overtime! The highest allowable (assuming my sums and checking are correct – apologies if my caffeine-addled brain has failed in this task) answer sent in was 149, which could be achieved with three different molecules. Richard Brown suggested $CH_3BrClF$, Ian Potts $BrClFSiCH_3$ (which he admits is possible neither particularly common nor stable), and $CHClBrCO_2H$ from Roger Duffett (who also suggested a rather unlikely helium clathrate with inexplicable atoms of helium, beryllium, oxygen, aluminium, bromine and americium which has – or so he claims! – been discovered on Mars…). The prize goes to Richard Brown.

And a special mention to Annette Quartly who managed to get 530 (from $CH_2F.GeClAt_2$, which she claims is easily constructable with ball-and-stick models!), and 418 for the substituted ethane $C_2HAtBrClFI$ (which is only dubiously stable because of the short half-life of astatine). Her highest allowable total was 142 for chloromethylphosphonic acid which, apparently, costs £2/g (or did in her geriatric Sigma catalogue, anyway).

## Compound elements

The next four numbers are 50, 54, 83 and 85 – being the atomic numbers of elements that can be written out in elemental symbols, for example BiSmUTh.

This one had most readers stumped! And the prize goes to Andy Lynch (with help from Rose Lynch who's really the Cambridge chemist), whose brain was clearly exercised to the limits by it. Well done for getting there in the end!.

The setter's husband also got the answer – and says he was very frustrated it took him so long to work it out as he'd already made lists of elements that can be spelt like this for crossword-creating purposes!

We also had an imaginative but wrong answer from Richard Brown (who found place names loosely close to the atomic numbers in the question, and added the US towns of Silver, Tin City, Gold and Lead as the extra elements), and a marvellously surreal one involving the 12 Days of Christmas from Roger Duffett.

Do you think we'll find inspiration down the pub?

UNIVERSITY OF CAMBRIDGE

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