

Highlights in Chemical Biology

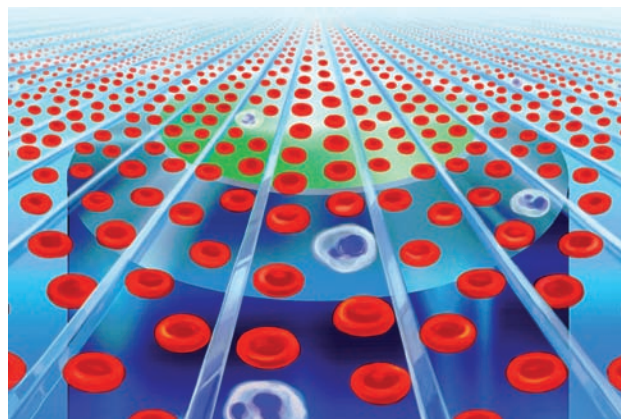
Analysing one million cells per second could improve disease diagnosis and treatment

Blood cell analysis on the highway

Scientists from the US have developed a miniature flow cytometer that can analyse up to one million blood cells per second.

Flow cytometry is a standard technique that can analyse several thousand blood cells every second. But, traditional flow cytometers require large bench-top equipment and are not easy to use at the point of care. Now, Dino Di Carlo and colleagues at the University of California, Los Angeles, have created a microfluidic-based cytometer that uses only a single pump and one camera.

Unlike normal flow cytometers, which only have one channel, Di Carlo's microfluidic device has 256 channels through which cells can flow and be analysed in parallel. A fluid, known as sheath fluid, is normally used as the delivery medium in flow cytometers, however, the team's device allowed the cells' momentum to position the cells for analysis within the channels, eliminating the need for the extra



fluid. 'By having the sheath fluid it is very difficult to have parallel focusing of cells, this is a limitation of flow cytometers - they operate in a serial manner like a one lane road. Now that you can operate in parallel you can have a highway - you can do detection in parallel and increase your throughput,' says Di Carlo.

Removing the sheath fluid also reduces the cost of consumables

Parallel focusing of blood cells allows high throughput analysis

Reference
S C Hur, H T K Tse and D Di Carlo, *Lab Chip*, 2010, **10**, 274 (DOI: 10.1039/b919495a)

and allows the devices to be made more suitable for portable use and in resource limited settings.

Pushing flow cytometry to higher throughputs could also enable analysis of rare cells, such as circulating endothelial cells, progenitor cells and circulating tumour cells, explains Di Carlo. 'This could have a very important impact for diagnosis, understanding disease and follow up of patient treatment,' he adds.

Frances Ligler, an expert in microflow cytometry at the US Naval Research Laboratory, Washington DC, US, comments, 'I doubt that there is anyone who has designed or fabricated a flow cytometer that has not dreamed of a massively parallel version. This is a major breakthrough.'

Di Carlo's team now plan to combine their microflow cytometer with wide-field imaging techniques and electrical techniques to allow parallel cell detection.

Jennifer Newton

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The point of access to chemical biology news from across the chemical sciences

Research highlights

A fluorescent tag may offer a way to 'watch' drug delivery in the body in real time

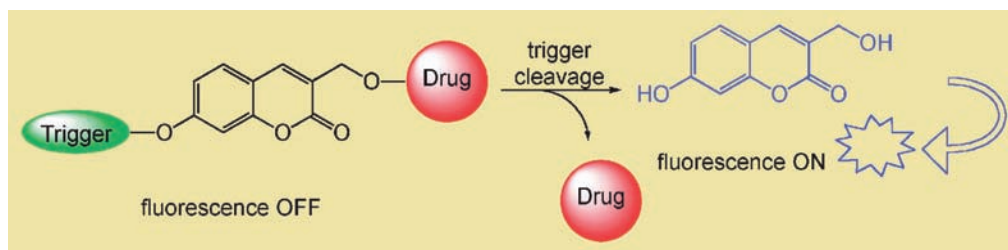
Monitoring drug release as it happens

A drug delivery system that could track the fate of drugs in the body has been developed by scientists in Israel.

Drug delivery systems transport medications to specific parts of the body and control the rates at which they are released. They overcome common problems associated with traditional drug treatments such as that of poor solubility or undesired side-effects.

Understanding just how the drug is released from the delivery vehicle is crucial for achieving good results. 'To date, this process could only be studied indirectly inside living organisms,' says Doron Shabat of Tel-Aviv University. 'Since the behaviour of drug delivery systems can vary extensively, depending on their surroundings, it is highly important to study them in their actual functional environment,' he adds.

Shabat and colleagues have designed a reporting drug delivery system that allows the direct, real-



Fluorescence is turned on as soon as the drug leaves the delivery vehicle

time visualisation of the drug release process in a non-invasive manner and have demonstrated its use *in vitro*. 'As a result, the process of drug release could be imaged for the first time, in real-time, inside living organisms,' says Shabat.

Shabat's system produces a fluorescent signal that depicts the status of the drug molecule. While the drug molecule is connected to the delivery vehicle, the fluorescent signal is off. On its release, the fluorescent signal is turned on and can be immediately detected and imaged.

Reference
R Weinstein *et al.*,
Chem. Commun., 2010, **46**,
553 (DOI: 10.1039/b919329d)

Rui Moreira, an expert in drug delivery systems (prodrugs) at the University of Lisbon, Portugal, welcomes the work. 'Real-time monitoring of prodrug activation allows a much closer insight to the kinetics in whole-cell systems. Gathering activity and activation data in a single set of experiments will speed up the design of more effective prodrugs,' he says.

Shabat says the next task will be using linkers that fluoresce at longer wavelengths to monitor drug release *in vivo*.
Sarah Corcoran

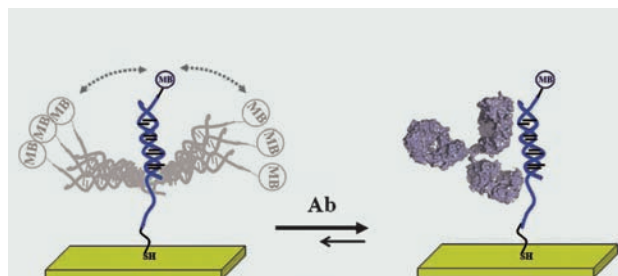
Bendy DNA probes allow fast detection of autoimmune disease biomarkers

Simple biosensors monitor immune disease

US and Italian researchers have developed a new sensor that tracks the progression of autoimmune diseases while dramatically reducing analysis time and requiring no extra reagents.

In autoimmune diseases like systematic lupus erythematosus – a disease that affects more than five million people worldwide – the body's immune system turns on itself and produces anti-DNA antibodies that attack various organs. While the quantification of antibodies in the bloodstream plays an important role in monitoring the severity of the illness, current detection methods such as enzyme-linked immunosorbent assay (ELISA) must be performed by skilled clinicians and require hours or even days to generate a result.

Francesco Ricci and colleagues at the University of Rome Tor Vergata have developed a biosensor electrode that can quickly detect anti-DNA



The flexibility of the DNA probes is altered by antibody binding, changing the sensor response

antibodies. The sensor uses a short sequence of single-stranded DNA which has been modified at one end with a redox-active tag. The other end of this DNA probe is modified with a thiol group that forms a strong bond to a gold electrode surface.

For efficient electron transfer to occur, the DNA must bend to allow the redox probe to touch the electrode surface. When anti-DNA antibodies in the sample bind to the DNA, the probe is much less flexible and reduces the efficiency with which the redox tag collides with the

Reference
F Ricci *et al.*, *Chem. Commun.*,
2010, DOI: 10.1039/b922595a

electrode. This interrupts electron exchange between the probe and the electrode, reducing the electrical current.

Arben Merkoçi, an expert at designing biosensors at the Catalan Institute of Nanotechnology in Spain, says 'this is a proof of concept of a very interesting alternative for the detection of antibodies against single and double-stranded DNA. It could open the way to develop novel assays for other analytes with interest for clinical applications.'

Ricci is keen to optimise the sensor design and hopes to commercialise the technology. 'The possibility of having miniaturised sensors, low cost and portable instrumentation, and of processing large numbers of samples in a time-effective way is a huge advantage of the electrochemical approach over other techniques which make it among the most suitable for point-of-care testing,' he states. *David Sharpe*

Removing residual cancer cells could prevent secondary cancer

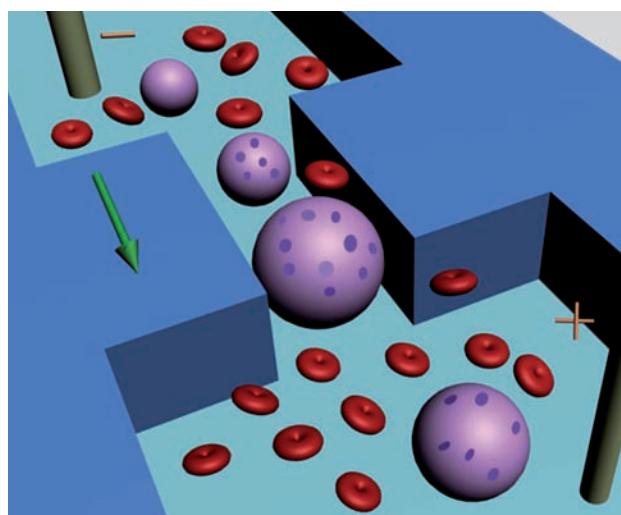
Tackling rogue tumour cells

Scientists in the US have developed a chip-based technique that could track down and destroy tumour cells in the blood of cancer patients.

Cells which detach from primary tumours can circulate in the bloodstream and finally settle in another area of the body. This spreads the disease causing metastatic cancer, which is a major cause of death among cancer patients who appear to have been successfully treated.

The detection and characterisation of circulating cells is well studied, but the possibility of removing them from the blood is less well known. Now Chang Lu from Purdue University, West Lafayette, and colleagues have used a technique called electroporation to selectively purge these circulating cells from the blood.

In electroporation, an external electric field is applied to a cell, creating numerous nanoscale holes in the cell membrane. These holes,



A flow-through electroporation technique studies different responses of blood cells and tumour cells to an electric field

or pores, allow foreign objects, such as drugs, to enter the cell and can eventually lead to cell death. Lu's team passed cells through a microfluidic channel and found that tumour cells were substantially

more susceptible to damage by electroporation than healthy cells.

Lu says that the simplicity and speed for treating cells makes it a very attractive method. 'We envision that our technique can be applied to destroy residual tumour cells in the blood after the removal of primary tumours,' he says.

Tilak Jain, an expert in electroporation at the Scripps Research Institute, La Jolla, US, finds the work innovative and exciting, saying 'combined with existing chemotherapeutics it could lead to a powerful dual attack force against circulating cells.'

Lu and colleagues are now turning their attention to proving the clinical value of their technique, in particular preserving the viability of white blood cells during the process. *Hilary Burch*

Reference

N Bao *et al*, *Integr. Biol.*, 2010, DOI:10.1039/b919820b

A microfluidic device makes it simple to observe the effects of ageing in worms

Worms living life on a chip

Have you ever wondered what happened to worms as they get old? Now it is possible to observe them over their entire life thanks to a microfluidic device developed by US scientists.

The device, made by George Whitesides and colleagues at Harvard University, Cambridge, houses individual worms (*Caenorhabditis elegans*) in an array of chambers and a network of microfluidic channels to deliver food and remove waste. Confinement in the chamber ensures that the worms do not move from the field of view without interrupting their normal swimming motions. Also the identities of the worms are kept, allowing repeated measurements of behavioural and physiological traits of each individual.

The properties of *C. elegans* make it useful for studying a wide variety of diseases and biological



Worms can be observed over their whole lifecycle

Reference

S E Hulme *et al*, *Lab Chip*, 2010, DOI: 10.1039/b919265d

processes, including Parkinson's disease, Alzheimer's disease and ageing. Although there are a number of microfluidic tools used to study worms, this is the first device that can be used to observe

individual worms over their entire life.

Whitesides demonstrated the new technology by tracking age-related changes in body size and swimming behaviour for individual worms over their entire adult life. 'Our device is designed to help worm biologists to carry out controlled experiments using statistically large numbers of worms,' says Whitesides. This will allow researchers to study the extent to which variation exists in populations of genetically identical worms, he adds.

Hang Lu, an expert in microfluidic technologies at Georgia Institute of Technology, Atlanta, US, remarks 'this is a simple and neat device to culture *C. elegans* for days and observe their locomotions, something that biologists that study ageing have long wanted.'

Keith Farrington

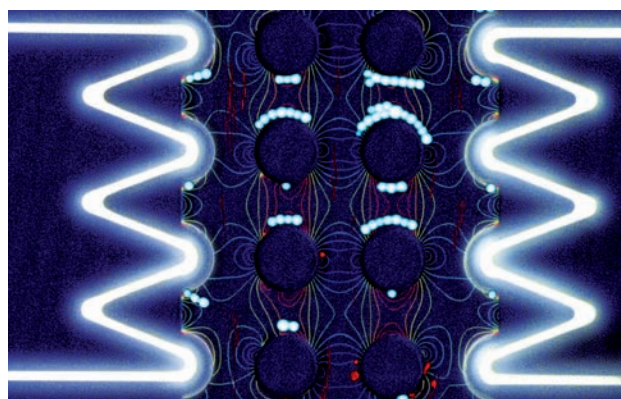
New technique isolates cells without sample contamination

Cancer detection by electrical signature

Separating live and dead leukaemia cells using an electrical technique could provide an automated system for early cancer detection, say American scientists.

Dielectrophoresis (DEP) uses an electrical field to separate particles according to their differing electrical properties. Dead cell membranes have higher conductivity than live ones as they are more permeable which allows ions to leak out, explains Rafael Davalos at Virginia Polytechnic Institute and State University (Virginia Tech), Blacksburg.

But conventional DEP requires direct contact between the electrodes and sample fluid, which lead to problems such as contamination and bubble formation. Davalos has developed a new approach to the technique where the electrodes are separated from the sample by a thin



barrier to avoid these problems. In contactless-DEP, the electrodes are inserted into two conductive microchambers, which are separated from the sample channel by thin insulating barriers.

Davalos says the ability to separate cells in this way is 'incredibly useful

Dead cells accumulate between the two electrodes

Reference

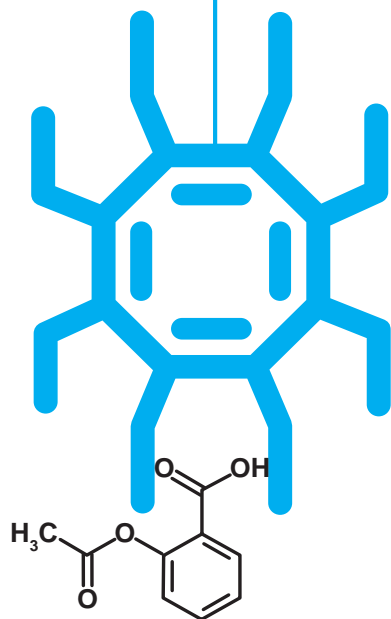
H Shafiee *et al*, *Lab Chip*, 2010, DOI:10.1039/b920590j

in research and medical settings where the investigation of a specific type of cell is hindered by the presence of many other cells.'

David Holmes, an expert in cell sorting and DEP at University College London, UK, says '[Davalos' method] avoids many of the problems associated with electrodes in contact with the fluid, and has promise in the area of cell separation.'

Although the prototype devices have achieved high efficiency, Davalos says he believes further improvement in the design is possible and the simple and inexpensive device fabrication could make it suitable for mass production. The team say that optimising the device could allow selective separation of cells from biological fluids for cancer diagnosis and differentiation of cells at different stages of the disease.

Erica Wise



New adventures on the web

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Interview

Finding answers in blood

Dana Spence on red blood cells, diseases and the importance of chemistry.
Interview by Jane Hordern



Dana Spence

Dana Spence is an associate professor at Michigan State University, East Lansing, US, specialising in quantitative biological chemistry. His current research looks into the role of red blood cells in diseases such as diabetes and multiple sclerosis.

What inspired you to become a scientist?

The real reason is because not many people do, and I like a challenge! I thought that if this university is taking in 10 000 new students this year and only 10 were going to do chemistry – I want to be one of those 10. I like being off the beaten track.

You are currently researching the role red blood cells play in different diseases. Which diseases are you looking at?

We are currently looking at diabetes, sickle cell disease, multiple sclerosis and cystic fibrosis. All these patient groups have red blood cells that do not function properly, so we are looking at them from the red blood cell side.

What benefits do you hope to provide for these diseases?

In some cases we hope to offer them some help. There is currently only one proven therapy for sickle cell disease (a drug called hydroxyurea). But the exact mechanism as to how it works is not known. We think that we may have possibly found out how this mechanism works, which could help design new improved drugs.

The work we have done with C-peptide and insulin could change the way in which insulin is administered to diabetics and may eliminate the complications that diabetes patients suffer. Also, now that cystic fibrosis sufferers live longer, many develop diabetes, which I believe is due to the red blood cells not disposing of the amount of glucose that they should. It is difficult to convince people of this, as most people don't believe red blood cells play a role in glucose levels in the blood stream. But we are going to keep at it – as I think it is really exciting.

What advice would you give to a young scientist about to pursue a career in chemistry?

There are many biological questions that have been out there for quite some time and progress is starting to be made, but in our group a lot of the questions we are beginning to answer are based on our chemical knowledge, which we learn through our general chemistry courses. When you have that root in the chemical sciences and you understand how things work at the molecular level, it helps explain things at many other different levels. We are getting a better understanding of pharmacological sciences and physiological sciences because of our background in chemistry. You can take that chemistry background and truly do a lot of neat things with it – it's all chemistry! Chemistry provides a great foundation for all the sciences.

Do you prefer to teach or do research?

I started out my career at Saint Louis University, US, which did not have a doctoral programme in the chemistry department so when I was there my teaching load was a lot heavier – sometimes doing two or three courses in a semester. But then I started working with a professor from the pharmacology and physiology department, Randy Spreg, on the work he was doing on red blood cells and then I started devoting a lot more time to research. But I still enjoy doing both and I especially like it when I learn something as well as the students!

Which scientist do you most admire and why?

Linus Pauling, who is considered one of the greatest chemist in the world and he did a lot of biological work too. I like people that have hypothesis that are so far of-the-wall that people think their ideas are impossible or crazy. Another is Otto Heinrich Warburg, who won a Nobel Prize, and towards the end of his career he tried to pitch to people that a lot of cancers were caused by dysfunctional mitochondria.

They thought he was crazy at the time, but in the last few years there has been work to show that he wasn't totally far of base. I like stories about people who proposed ideas 50 or 60 years ago and now it is being found that their ideas were right.

What eureka moment in science do you wish had been yours?

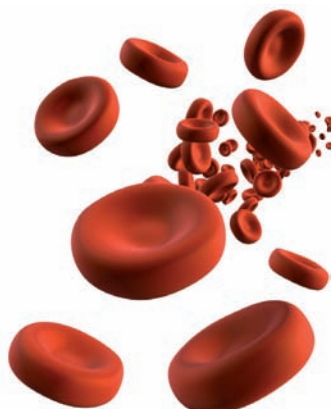
The story of Banting and Best when they administered the first insulin to children in Toronto in the 1920s. They had purified the insulin as they had the idea that insulin controlled blood sugar levels. They gave it to all these children in sugar comas in the hospital and by the time they got to the end of the ward, some had started to come out of their comas. It would have been utterly amazing to see it work right in front of you and know that you were right.

Can you tell us a little known fact about yourself?

I am a fairly open book, however, most people don't know that I met my wife on the playground at recess when I was nine years old (she was eight). Of course, we didn't marry until a few years later!

If you weren't a scientist what would you be?

I always wanted to be a medical physician so I could help people. But failing that I could also be a sports announcer.



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Speakers: Mike N R Ashfold, Mounqi G Bawendi, David C Clary, Jianguo G Hou, Tianquan Lian, Kopin Liu, Daniel M Neumark, Michel Orrit, Hongkun Park, Vahid Sandoghdar, Alec M Wodtke, Martin Wolf, Toshio Yanagida, Haw Yang, Xueming Yang.



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Join in – register today!

Understanding biological data

Ivano Bertini and Gabriele Cavallaro describe how bioinformatics is being used to make sense of the growing amounts of experimental data on the role of metals in biological systems

Bioinformatics is a central discipline in modern life sciences aimed at describing the complex properties of living organisms starting from large-scale data sets of cellular elements such as genes and proteins. For this wealth of information to provide useful biological knowledge, databases and software tools for data collection, analysis and interpretation are needed.

Recently there have been several advances in the design and implementation of bioinformatics resources devoted to the study of metals in biological systems, a research field traditionally at the heart of bioinorganic chemistry. Metal ions are essential constituents of living organisms. They play a role in fundamental processes from signalling and gene expression to catalysis. The function of many proteins depends critically on binding to specific metals, such as copper, iron, zinc or molybdenum. These proteins include metallothionein, crucial in maintaining the body's equilibrium and in detoxification processes, metallochaperones, which protect and direct metal ions through the cell, and extracellular proteins albumin and transferrin, essential for metal transport in human blood. Metal ions are also responsible for controlling the expression of these proteins in cells.

Bioinorganic chemistry plays a significant role in the challenge of studying whole living systems. This ambition has recently been boosted by the development of technologies such as genomics and proteomics producing virtually complete lists of key cellular components. But in order for bioinorganic chemistry to effectively contribute to modern biology, it must focus on determining the total

Reference

I Bertini and G Cavallaro
Metallomics, 2010, **2**, 39 (DOI:
 10.1039/b912156k)

metal content of living organisms, from the measurement of metal concentrations to the identification of all the individual metal species. This evolution into an information-rich discipline creates a strong, constructive link with bioinformatics, which is fundamental to manage and make sense of the huge amount of biological data continuously produced in biological research.

Bioinformatics is a relatively mature field, but its overlap with bioinorganic chemistry has been scarce, possibly due to difficulty in encoding the peculiar properties of metal species in a form suitable for computer analysis. Today, the growing awareness of the role of metals in cell physiology and disease are stimulating the creation of bioinformatics tools and resources centred on metals and metalloproteins.

Using bioinformatics, a protein's amino acid sequence can be used to predict whether it binds to a metal, and also which metal. These methods are based on the recognition of two different signatures diagnostic for metal binding, known as domains and structures, and are most accurate when the two signatures are used in combination. Currently this technique is limited to detecting proteins bearing a sequence similar to already known metalloproteins but alternative approaches based on neural networks capable of overcoming such limitations are fast becoming available. Applying these methods to all the proteins encoded in the genome of an organism, it is possible to predict all the metalloproteins of that organism (its metalloproteome) in a metal-specific manner. Such predictions are quite valuable as experimental techniques for metalloproteomics are not

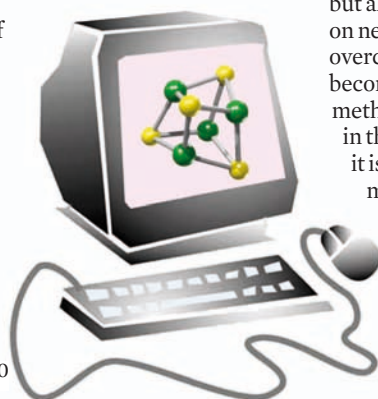
yet routinely available.

Functional information for metalloproteins of known structure can also be deduced using bioinformatics. Identifying structural similarity with known metal-binding sites can then provide key hints about protein function, and the structural and chemical parameters used to make up the 'fingerprint' of the site can be varied. In some methods this description includes not only the protein residues that coordinate the metal, but also those in the immediate surroundings, which are important in modulating metal function.

Bioinformatics is crucial in the support of bioinorganic chemistry databases, which lie at the heart of modern biology, forming the infrastructure for the collection, maintenance and provision of biological information. A classification of all known metal-binding sites based on these structural fingerprints could provide the framework for a comprehensive database on metalloproteins.

Finally, bioinformatics is central to the construction of descriptive and predictive models for cellular processes using interaction network diagrams as a platform. The development of methods and tools to integrate the information regarding metals and metalloproteins into such models in the most useful and efficient way is another foreseen benefit of the marriage between bioinformatics and bioinorganic chemistry, which will provide a major help to describe how inorganic elements are framed within living cells and achieve a deeper understanding of living systems.

Read more in the review 'Bioinformatics in bioinorganic chemistry' in *Metallomics*.



Essential elements

Launch of new beta platform



In early February, RSC Publishing will launch a new integrated content delivery platform allowing over 500 000 journal articles, book chapters and database records to be searched through one simple interface. The new platform will deliver faster browsing, intelligent searching and more intuitive navigation. It will be launched as a public beta.

A key benefit of releasing the platform as a beta is that early and frequent software releases help create a tight feedback loop between the platform development and our users, enabling us to listen and respond to user requirements. The 'release early, release often' philosophy empowers the user to help define what the platform will become.

Graham McCann, publisher at RSC Publishing is spearheading the project. His enthusiasm for the platform makes it clear

something exciting is happening: 'user testing and feedback has been integral to the development process, aiding our design and helping us to produce something that offers a superior online experience.'

RSC Publishing^{beta} is powered by Mark Logic Server, the industry's leading XML content server, which enables dynamic use of content in innovative new ways. State of the art navigational tools such as faceted browsing and topic clouds help users to find the content they are looking for quickly and discover related content simultaneously.

Here is a sample of some of the features on offer:

- Single search interface for journal, book and database content
- Faceted browsing – a technique that allows rapid filtering of search results

- Integrated tools for bookmarking, saving and sharing information
- Topic clouds to highlight latest research
- Saved searches and alerts
- Librarian login area and branding
- Latest news dynamically fed from blogs

Innovation has been at the forefront of the new platform. Expert software engineers worked closely with the RSC to architect, design, develop and integrate the new content delivery platform into RSC's existing technology infrastructure. 'RSC Publishing^{beta} is one of the most interesting and innovative sites we have developed. It has raised the bar as to how chemistry content can be engagingly presented' commented Melvyn Burgoyne, managing director at Rave Technologies, UK. RSC Publishing^{beta} will run alongside the existing RSC Publishing website for the first phase of beta testing. Links encouraging users to try the new beta site are available across the existing publications website.

We would love to hear your feedback about the new site. For example, tell us about:

- Functionality: what features do you like, what features are missing?
- Usability: what do you think about the user interface, could it be clearer, more intuitive?

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