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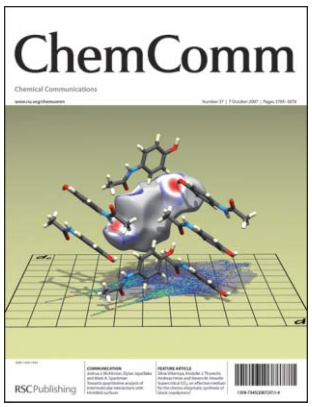

Cover
See Joshua J. McKinnon *et al.*, page 3814.
Hirshfeld surface tools highlighting O···H intermolecular contacts in form I paracetamol.
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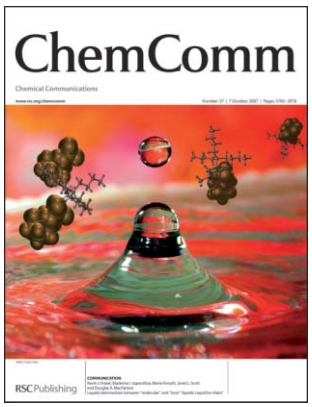

Inside cover
See Kevin J. Fraser *et al.*, page 3817.
Phosphonium-based ionic liquids in some cases exhibit properties that reflect strong ion association, including low viscosity and a degree of volatility.
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CHEMICAL BIOLOGY

B73

Drawing together research highlights and news from all RSC publications, *Chemical Biology* provides a 'snapshot' of the latest developments in chemical biology, showcasing newsworthy articles and significant scientific advances.

Chemical Biology
October 2007/Volume 2/Issue 10
www.rsc.org/chembiology

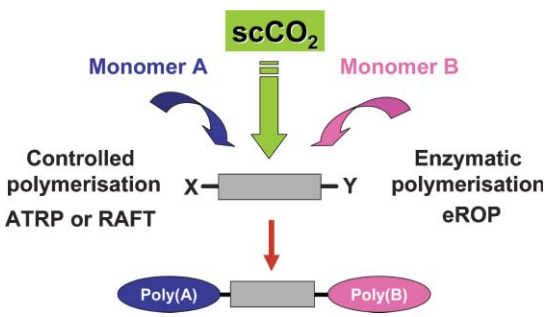
FEATURE ARTICLE

3805

Supercritical CO_2: an effective medium for the chemo-enzymatic synthesis of block copolymers?

Silvia Villarroya,* Kristofer J. Thurecht, Andreas Heise and Steven M. Howdle*

In this review, we describe the combination of enzymatic polymerisation and controlled free radical polymerisation in supercritical carbon dioxide for the preparation of a range of block and graft copolymers.



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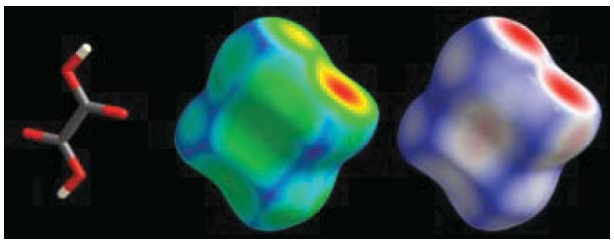
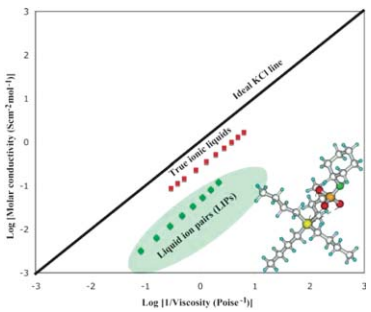
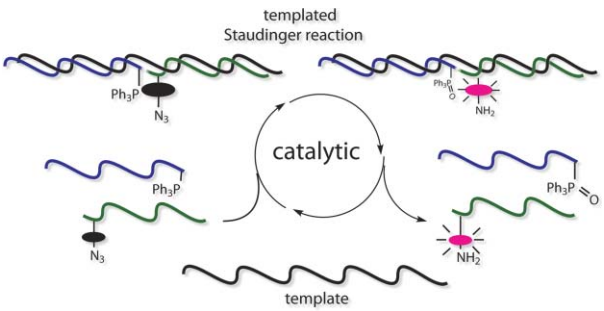
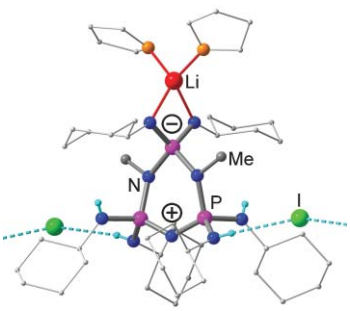








Tissue Engineering in Microsystems

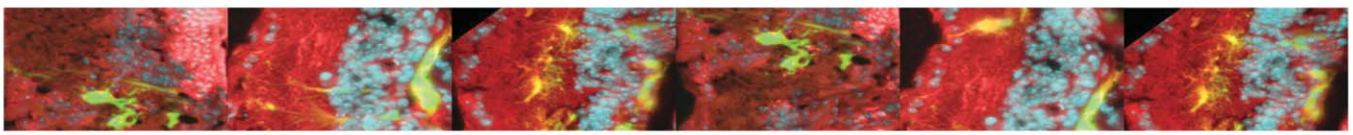
Lab on a Chip has gathered together a series of articles highlighting the very best research on cell and tissue engineering in microsystems.

Guest editors Sangeeta Bhatia (MIT) and Christopher Chen (University of Pennsylvania) have commissioned articles from leading researchers to contribute to this *Lab on a Chip* issue, dedicated to state-of-the-art research on tissue engineering in microsystems.

The issue includes a critical review of cell micropatterning techniques; a tutorial review of perfusion culture of mammalian cells; and several high quality full papers on topics covering cell culture, patterning of biomaterials, stem cell differentiation, biocompatible implants, 3D tissue culture, embryoid bodies, cell cytotoxicity analysis and cell-cell communication.

"Tissue engineering is probably the most promising area of biology and biotechnology, this is an excellent issue featuring the best authors at the leading-edge of on-chip tissue engineering, — congratulations to Chris and Sangeeta"

Andreas Manz, ISAS, Dortmund



PAPERS INCLUDE:

A chip-based platform for the *in vitro* generation of tissues in three-dimensional organization
Eric Gottwald, Stefan Giselbrecht, Caroline Augspurger, Brigitte Lahni, Nina Dambrowsky, Roman Truckenmüller, Volker Piotter, Thomas Gietzelt, Oliver Wendt, Wilhelm Pfleging, Alex Welle, Alexandra Rolletschek, Anna M. Wobus and Karl-Friedrich Weibezahn, *Lab Chip* 2007, **7** (6)

Understanding microchannel culture: parameters involved in soluble factor signaling
Hongmei Yu, Caroline M. Alexander and David J. Beebe, *Lab Chip* 2007, **7** (6)

Efficient formation of uniform-sized embryoid bodies using a compartmentalized microchannel device
Yu-suke Torisawa, Bor-han Chueh, Dongeun Huh, Poornapriya Ramamurthy, Therese M. Roth, Kate F. Barald and Shuichi Takayama, *Lab Chip* 2007, **7** (6)

Micro-bioreactor array for controllable differentiation of human embryonic stem cells
Elisa Figallo, Christopher Cannizzaro, Sharon Gerecht, Jason A. Burdick, Robert Langer, Nicola Elvassore and Gordana Vunjak-Novakovic, *Lab Chip* 2007, **7** (6)

Survival, migration and differentiation of retinal progenitor cells transplanted on micro-machined poly(methylmethacrylate) scaffolds to the subretinal space
Sarah Tao, Conan Young, Stephen Redenti, Yiqin Zhang, Henry Klassen, Tejal Desai, Michael J. Young, *Lab Chip* 2007, **7** (6)

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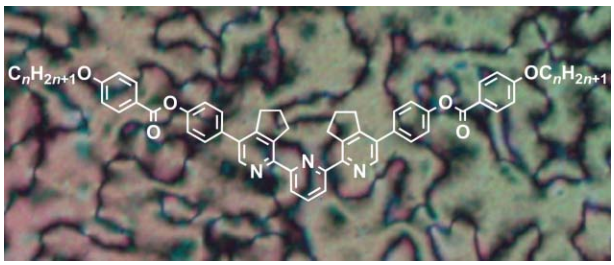

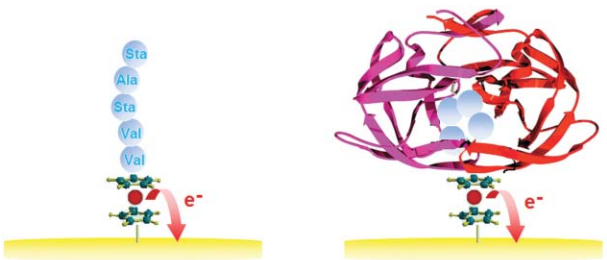

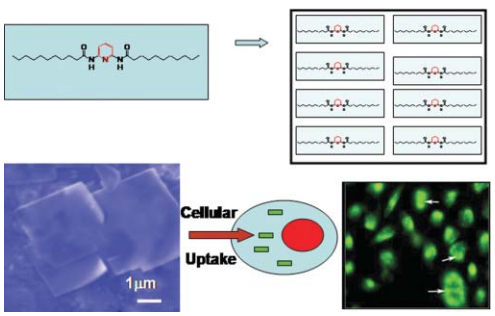

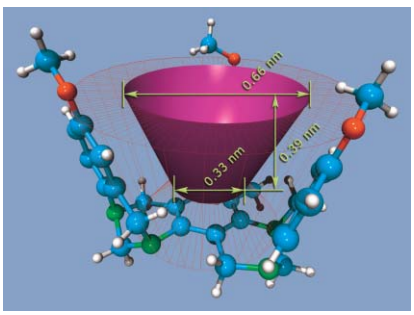

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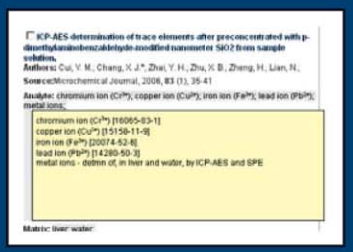

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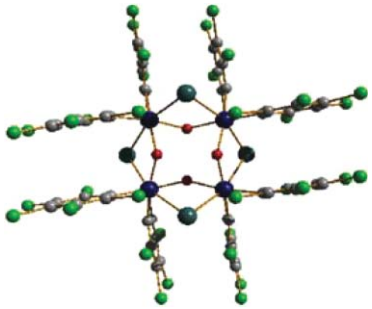
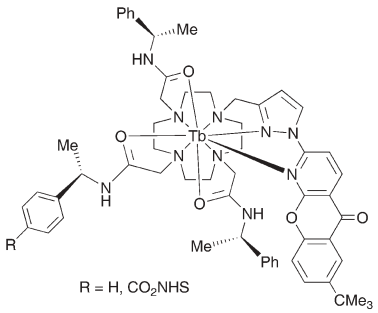
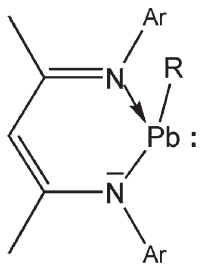
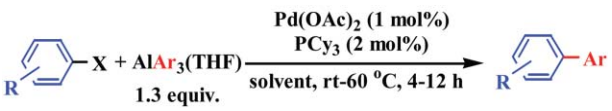


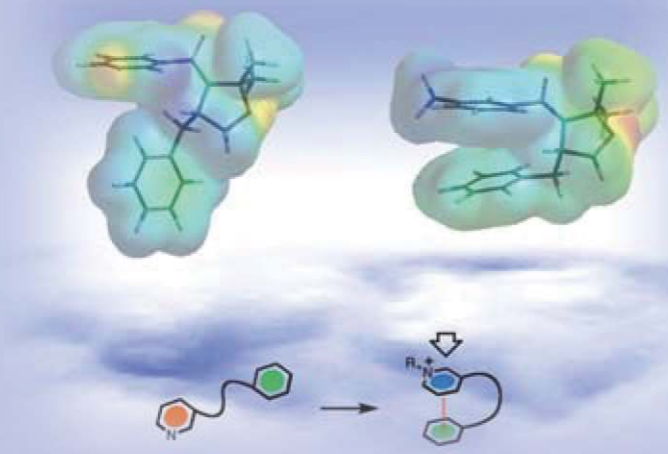




Ar = $C_6H_3Pr^i_2$-2,6

2a: R = phenolate
2b: R = $N(SiMe_3)_2$
2c: R = $P(SiMe_3)_2$
3: R = $P{=}Si(SiBu^t_3)Aryl$





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Forthcoming Articles

Perspective

Synthesis of azabicyclic systems using nitrogen-directed radical rearrangements
David M. Hodgson, UK

Emerging Area

Catalytic enantioselective stereoablative reactions: an unexploited approach to enantioselective catalysis
Brian Stoltz, US

Articles

Synthesis and biochemical evaluation of *O*-acetyl-ADP-ribose and *N*-acetyl analogs
John M. Denu, US

Preparation of 3-(4-chlorophenyl)-2-(2-aminothiazol-4-yl)-5-methoxybenzo[b]furan derivatives and their leukotriene B4 inhibitory activity
Yoshitaka Ohishi, Japan

Glutathione traps formaldehyde by formation of a bicyclo[4.4.1] undecane adduct
Kevan Shokat, US

Effects of caffeine on stereoselectivities of high cell density biotransformations of cyclic ß-keto esters with *Saccharomyces cerevisiae*
Martin Bertau, Germany

An efficient and mild bismuth triflate-catalysed three-component Mannich-type reaction
Thierry Ollevier, Canada

Evaluating β-amino acids as enantioselective organocatalysts of the Hajos-Parrish-Eder-Sauer-Wiechert Reaction
Stephen G. Davies, UK

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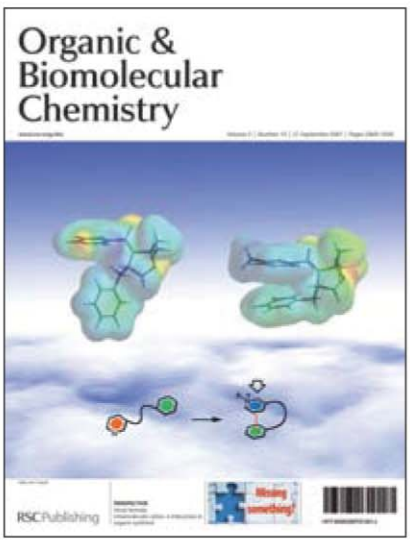

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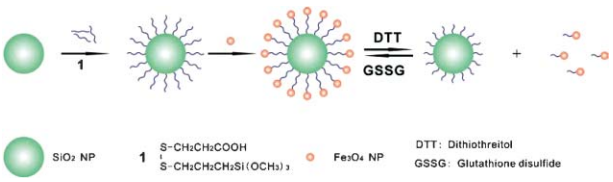
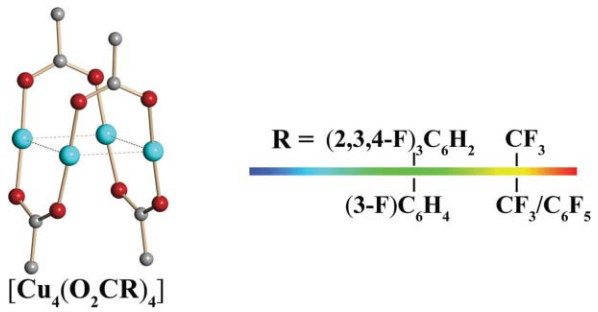
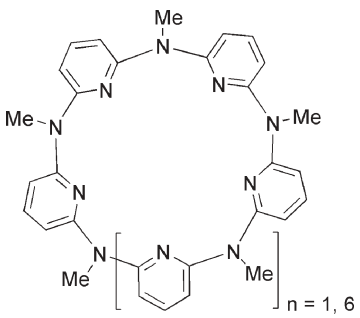
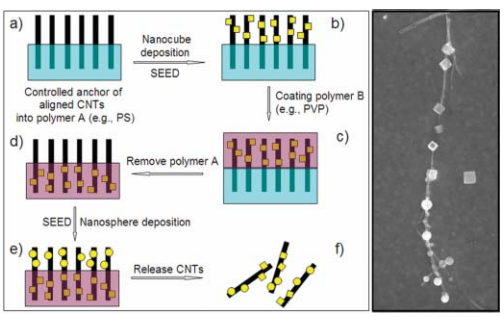
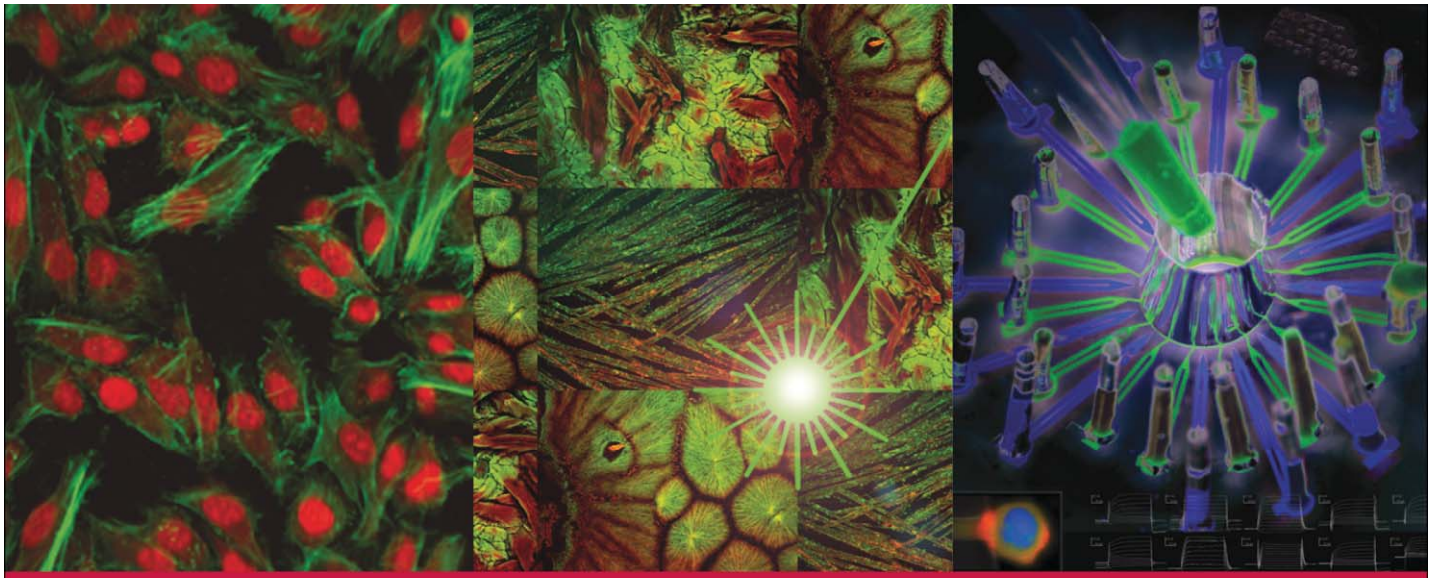


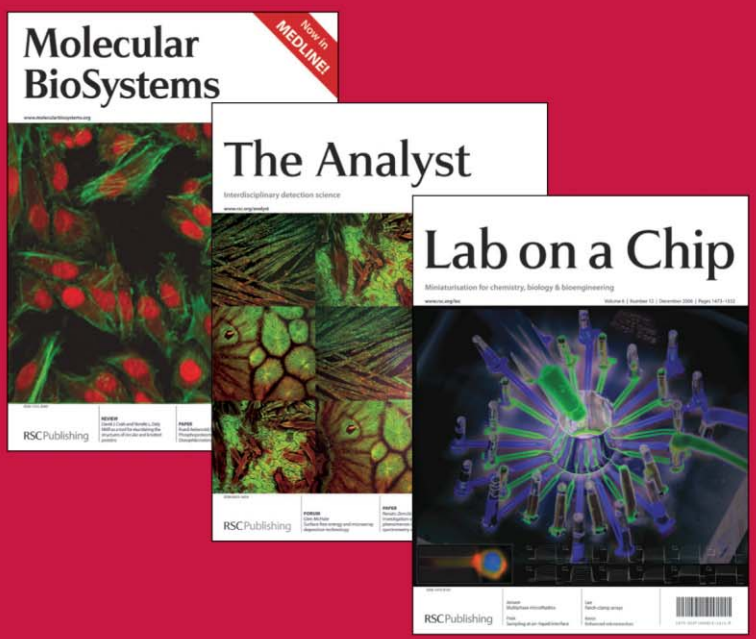








Biology in Focus



Biology in Focus highlights and draws together research in key areas at the chemistry/biology interface. Each quarterly instalment will showcase a different subject area, providing scientists with an opportunity to browse and view related science on specific themes. Research material is primarily drawn from three RSC journals: *Molecular BioSystems*, *Lab on a Chip* and *The Analyst*.

Theme 2: Microarrays

… deposition technology … in vitro neuronal networks … aquatic toxicology … novel amperometric sensor … pathogen immunoassay … and much more …

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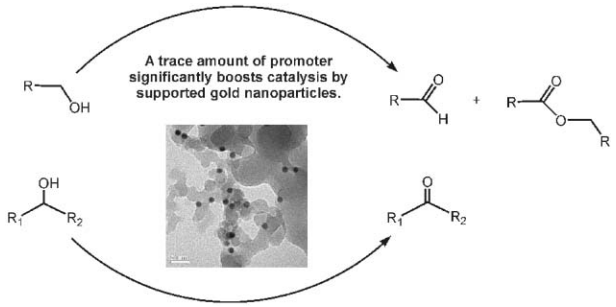

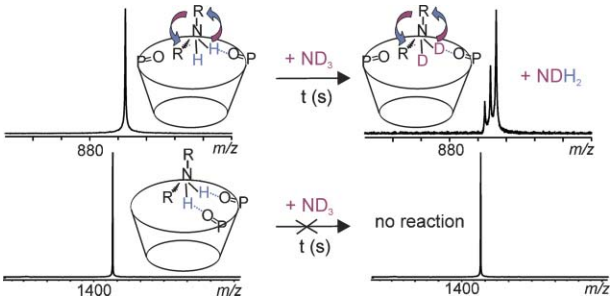

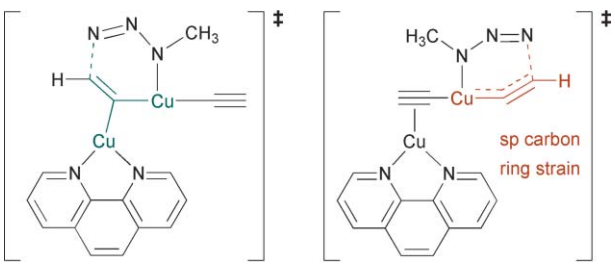

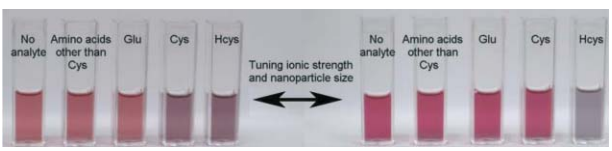

3874

A new type of heteroleptic complex of divalent lead and synthesis of the *P*-plumbyleniophosphasilene, $R_2Si{=}P{-}Pb(L)$: (L = β-diketiminate)

Shenglai Yao, Stefan Block, Markus Brym and Matthias Driess

3874

Self-assembly of β-D glucose-stabilized Pt nanocrystals into nanowire-like structures

Juncheng Liu, Poovathinthodiyil Raveendran, Gaowu Qin and Yutaka Ikushima

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October 2007 / Volume 2 / Issue 10 / ISSN 1747-1605 / CBHIBN / www.rsc.org/chembiology

Chemical Biology

Copper targets specific residues in Parkinson's-linked protein

Promise for Parkinson's

Research from Poland could lead to a better understanding of the causes of Parkinson's disease. Teresa Kowalik-Jankowska from the University of Wrocław and her colleagues have studied how copper-catalysed oxidation damages a protein linked to the condition.

Patients with Parkinson's disease have significantly increased copper levels in their cerebrospinal fluid, suggesting that the metal is somehow involved in promoting the condition, said Kowalik-Jankowska. The protein α-synuclein plays a central role in a number of neurodegenerative diseases and oxidation with copper(II) ions is known to cause it to aggregate *in vitro*. α-Synuclein aggregation *in vivo* is believed to trigger lesions called Lewy bodies to form, added Kowalik-Jankowska, and these abnormal protein deposits are found in the brains of patients with Parkinson's disease.

AP PHOTOS

Actor Michael J Fox is an advocate for Parkinson's research

To examine the precise role of copper in α-synuclein aggregation, the Polish team studied how copper(II) ions interact with fragments of a mutant form of α-synuclein that is particularly prone to aggregation. They found that the ions bind to the peptide fragments primarily through histidine, methionine and lysine residues. Copper binding makes these residues more susceptible to reaction under oxidising conditions, said Kowalik-Jankowska. 'We can say that copper(II) ions will react in a similar way with the whole protein.'

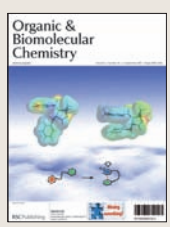
In future research, the group will take a closer look at the products formed by copper(II)-catalysed oxidation of fragments of non-mutant α-synuclein.

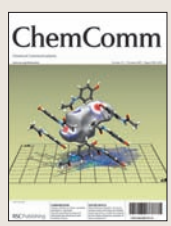
Danièle Gibney

Reference

T Kowalik-Jankowska *et al*, *Dalton Trans.*, 2007, 4197 (DOI: 10.1039/b709069b)

In this issue





The point of access to chemical biology news and research from across RSC Publishing

Research highlights

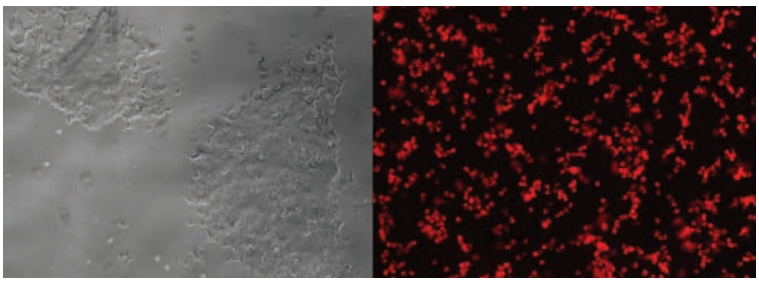
Turning into glass means reduced stress for cells

Cell preservation all wrapped up

Freezing cells inside glass cages could potentially improve human fertility treatments.

Utkan Demirci and Grace Montesano, at Harvard Medical School and the Massachusetts Institute of Technology in Cambridge, US, have developed the first high-throughput cell vitrification method for automated cell preservation. Demirci and Montesano's research involves cell encapsulation in droplets; 'the aim is to apply the technology to real problems in medicine,' said Demirci.

Demirci and Montesano's cell preservation method works by trapping single cells in droplets of a cryoprotectant – a liquid that prevents cell damage on freezing – and the droplets are then vitrified. Vitrification is a rapid freezing process in which a fluid turns into a glass-like solid without crystal formation. The new procedure can preserve cells at rates as high as thousands of cells per second while retaining cell viability. It also allows lower concentrations of toxic cryoprotectant such as 1,2-propanediol to be used, leading to significantly reduced osmotic stress on the cells. Furthermore, automation avoids human error and minimises mechanical stress to the cells due to manual handling.



Vitrified cells (left) can be thawed (right) and remain viable

Among the different cells preserved were liver cells and mouse embryonic stem cells and Demirci suggests that future work could provide controlled vitrification methods for reproductive (germ) cell preservation. 'This could have impact in extending human fertility, allowing higher yields and success,' said Demirci. 'One challenge in vitrifying germ cells is their larger size compared to other cell types. We will optimise our system to address challenges in this arena by changing the droplet sizes and concentrations.'

David Juncker, an expert in high-throughput cell analysis from McGill University, in Montreal, Canada, explained that 'cell preservation and manipulation is of great interest. The method seems versatile,' he added, 'I could imagine using it for rare stem cell collection and conservation.'

Kathleen Too

Reference
U Demirci and G Montesano, *Lab Chip*, 2007, DOI: 10.1039/b705809h

Gold device proves cheap for biomolecular study

Reflections on protein surfaces

Scientists now have a cheaper tool for probing biomolecules thanks to Japanese researchers. By measuring two different physical properties simultaneously, Yoshio Okahata and co-workers at the Tokyo Institute of Technology can study protein hydration and viscoelasticity.

The new approach uses a sensitive mass-measuring device – a piezoelectric quartz crystal microbalance (QCM) – to detect protein immobilisation on a surface. As a protein solution flows past the QCM, covalent coupling immobilises the protein onto an activated gold face of the QCM crystal, changing the crystal's resonance frequency. In liquids, however, this resonance frequency depends not only on the change in mass accompanying protein deposition, but on protein hydration and viscoelasticity, so protein quantification becomes difficult.

The change in blue light reflection indicates how much protein has bound to a gold surface

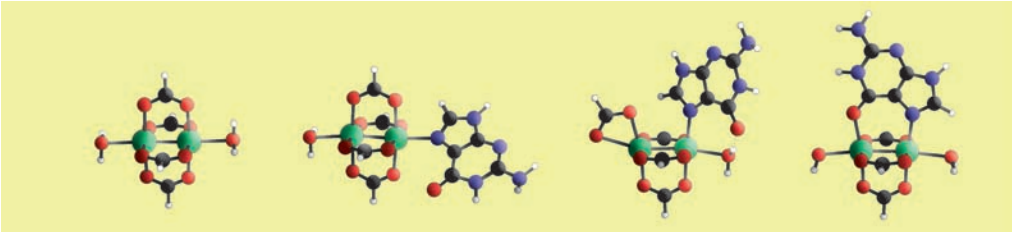
To overcome this hurdle, Okhata's team followed the protein immobilisation by measuring the change in reflection of blue light from the gold surface. While the QCM resonance frequency is affected by several factors, the change in reflection corresponds only to the thickness, and so the mass, of the immobilised protein layer. Combining these two measurements means that changes in the resonance frequency due to mass can be separated from changes associated with hydration and viscoelasticity, allowing scientists to assess the effect of hydration and viscoelasticity on biomolecular adsorption.

Previous methods to measure protein binding have involved combining the QCM with another surface measurement technique, surface plasmon resonance, which requires a complicated and expensive optical set-up. Okahata's set-up is simpler and cheaper. Looking to the future, Okahata said 'this system could be applied to other biomolecular interactions.'

Russell Johnson

Reference
Y Manaka *et al*, *Chem. Commun.*, 2007, 3574 (DOI: 10.1039/b708901e)

Complex DNA binding unravelled



The dirhodium complex (left) binds to guanine through a series of intermediates

Understanding how an anticancer complex binds DNA has brought metal–metal based antitumour drugs one step closer. Dirk Deubel at the Swiss Federal Institute of Technology Zurich (ETH Zurich), Switzerland, and Helen Chifotides at Texas A&M University, in College Station, US, have calculated the binding mechanism of complex dirhodium tetracarboxylate to the DNA base guanine.

Increasing attention is being paid to metal–metal based anticancer complexes as potential inhibitors of DNA replication. 'DNA–complex binding is believed to be the key reaction responsible for the anticancer activity of these compounds,' said Judit Šponer, a specialist in computational analysis of metallopharmaceuticals at the Academy of Sciences of the Czech Republic in Brno. Whilst the reactants and products in this step can be identified through conventional experiments, the mechanism is not always clear. Clarifying the mechanism is useful for redesigning ligands to improve the effectiveness of potential drugs.

Using a combination of computational approaches, Deubel and Chifotides managed to identify the possible intermediates in the DNA–complex binding reaction and the transition states between them. They then calculated the free energies of these states to discover the lowest energy pathway.

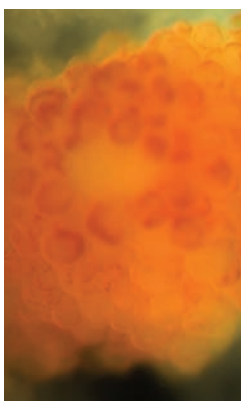
Looking to the future, Deubel said: 'Potentially, computational approaches could be used to screen ligands by predicting the energy of intermediates and transition states.' *Russell Johnson*

Reference
D V Deubel and H T Chifotides, *Chem. Commun.*, 2007, 3438 (DOI: 10.1039/b709209a)

Neuropeptides go with the flow

US scientists are following peptide trails to look at how neurons communicate. Jonathan Sweedler and colleagues at the University of Illinois at Urbana-Champaign have made microfluidic devices to monitor the peptides released by neurons. By interfacing the devices with a mass spectrometry (MS) imaging technique, the team can both identify the peptides and map their release from the cells.

The team's system includes a neuron reservoir to which reagents can be added. The team treated the cells with a solution of potassium chloride, stimulating the cells to release peptides. These peptides then flowed through microchannels attached to the reservoir where they were captured by an octadecyl-coated layer on the channel bed. The researchers were able to control solution flow through three different channels so that they gave separate results for before, during and after stimulation.



Neurons (above) release peptides to communicate

To analyse the captured peptides, the group separated the peptide layer from the device and examined it using matrix-assisted laser desorption/ionisation (MALDI) MS. This was combined with imaging software to show where the peptides were on the layer and their identities.

Robert Kennedy, an analytical chemist at the University of Michigan in Ann Arbor, US, welcomed the research. 'This adds substantially to the armamentarium of both microfluidics and single neuron studies as a simple approach to MALDI-MS imaging of chips,' he said. 'It should prove useful in answering long-standing questions about how neurons use peptides to communicate.' *Rachel Warfield*

Reference
K Jo *et al*, *Lab Chip*, 2007, DOI: 10.1039/b706940e

News in brief

Metals leave their mark on transgenic soya

A plant's metallic make-up could be used to identify it as genetically modified, say researchers in Brazil.

See **www.rsc.org/chembiology** *for a full version of this article.*

This month in *Chemical Science*

Robots with a heart

Robots small enough to roam the human body and powered by living heart muscle have been built by scientists in Korea.

Contaminants still present in breast milk

A US study has shown that levels of some flame retardants and organochlorine pesticides in breast milk are still high enough to warrant concern.

Glowing report for nerve agent detection

A chemiluminescent sensor could be used to detect sarin with a glow response, say US scientists.

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This month in *Chemical Technology*

Sizing up the danger of volcanic ash

Analysing the grain size of volcanic ash particles might provide a quick and easy way to calculate their potential threat to human health, according to a British scientist.

The phantom of the bone scanners

Research by Swiss scientists could open the way to better diagnosis and treatment for osteoporosis sufferers.

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Assay exploits phosphate charge to register protein kinase in action

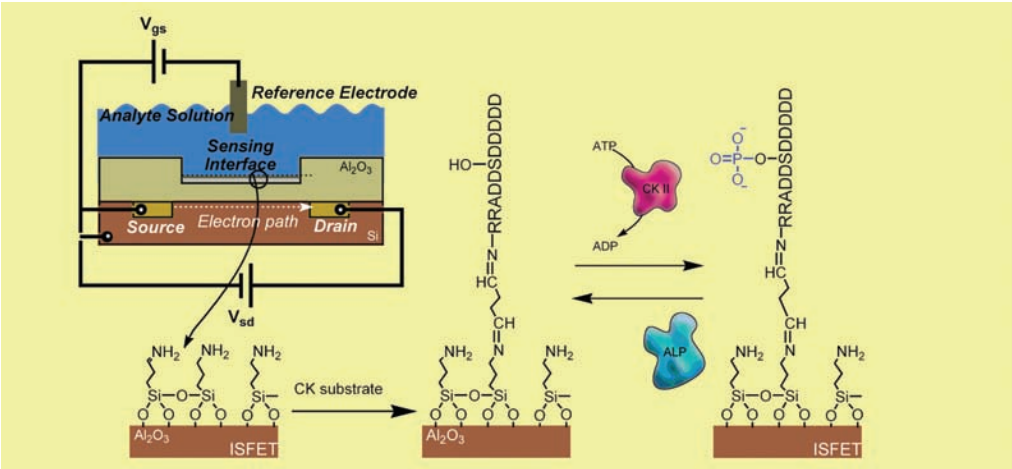
Activity of an aberrant enzyme

Israeli scientists have developed a simple activity assay for an enzyme linked to the HIV virus life cycle.

Protein kinase enzymes regulate many cellular pathways, including metabolism and cell movement. While the enzymes are essential for normal cellular function, abnormal protein kinase activity has been implicated in a number of diseases. So assays for protein kinase activity and kinase inhibitor screening have great potential use in medical science laboratories.

Now, Itamar Willner and co-workers from the Hebrew University of Jerusalem have developed an activity assay for the protein kinase casein kinase II (CK2), a target of some HIV-1 transcription inhibitors.

Since protein kinases work by attaching phosphate groups to proteins, the team took advantage of the charged nature of the phosphate products to use a field effect transistor (FET) in the assay. A FET registers a change in conductivity as charged species attach to a gate on its surface. In Willner's assay a peptide that is recognised by CK2 is attached to the gate and exposure of the FET to CK2 and adenosine 5′-triphosphate (ATP) results in phosphorylation of the peptide. This changes the charge at the gate, indicating CK2 activity.



A field effect transistor (top left) detects protein kinase (red) activity as a change in conductivity

Most protein kinase activity assays monitor either take-up of radiolabelled ATP or fluorescently labelled antibodies as they bind phosphorylated amino acid residues. These typically have poor specificity for the protein kinase of interest and limited sensitivity. In contrast, Willner's assay is specific for CK2 and is label-free, removing the potential hazard of any radioactive, toxic or carcinogenic markers and cutting sample-processing steps. Furthermore, said Willner, 'the sensor reveals good performance in terms of sensitivity, reusability, versatility and ease of operation.'

The Israeli team aims to extend its assay to analyse other kinases and to test potential kinase-targeting drug candidates. They anticipate that as more protein kinase-controlled bioprocesses are discovered, quantitative assays for these enzymes will be in demand. *Freya Mearns*

Reference

R Freeman, R Gill and I Willner, *Chem. Commun.*, 2007, 3450 (DOI: 10.1039/b707677k)

In the current issue of Research Articles...

A dual near-infrared pH fluorescent probe and its application in imaging of HepG2 cells
Bo Tang *et al*, *Chem. Commun.*, 2007, 3726 (DOI: 10.1039/b707173f)

Multifunctionalised cationic fullerene adducts for gene transfer: design, synthesis and DNA complexation
Cédric Klumpp *et al*, *Chem. Commun.*, 2007, 3762 (DOI: 10.1039/b708435h)

Bioreductive activation and drug chaperoning in cobalt pharmaceuticals
Matthew D Hall *et al*, *Dalton Trans.*, 2007, 3983 (DOI: 10.1039/b707121c)

β-Amino acid-containing hybrid peptides—new opportunities in peptidomimetics
Marie-Isabel Aguilar *et al*, *Org. Biomol. Chem.*, 2007, **5**, 2884 (DOI: 10.1039/b708507a)

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Nicole F Steinmetz and David J Evans, *Org. Biomol. Chem.*, 2007, **5**, 2891 (DOI: 10.1039/b708175h)

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Yurong Cai *et al*, *J. Mater. Chem.*, 2007, **17**, 3780 (DOI: 10.1039/b705129h)

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Lars Kunz *et al*, *Photochem. Photobiol. Sci.*, 2007, **6**, 940 (DOI: 10.1039/b708456k)

Ultrafast light harvesting dynamics in the cryptophyte phycocyanin 645
Tihana Mirkovic *et al*, *Photochem. Photobiol. Sci.*, 2007, **6**, 964 (DOI: 10.1039/b704962e)

Read more at www.rsc.org/chembiology

Interview

The art of chemistry

Richard Kelly talks to Stefan Matile about painting, fake tongues and flamenco

Stefan Matile

Stefan Matile is a professor of organic chemistry at the University of Geneva, Switzerland. His research is at the interface of organic, biological and supramolecular materials chemistry, allowing him to explore applications such as porous biosensors and artificial photosynthesis.

What inspired you to become a scientist?
Science was actually my second choice. After school and college, I wanted to become an artist so I went to art school. It was a disaster. I had no talent, but somehow I developed an interest in chemistry, particularly through the materials. I saw the pigments and etchings and wondered 'why is yellow yellow?' and 'why is blue blue?' Failing at art school was the start of my chemistry career.

Was it easy for you to change from art to chemistry?
I had very little scientific experience so at first it was very tough. However, I didn't really see this as a disadvantage. Of course I had to work, but I was at an age where I was much more able to learn new things. Later on, I felt I benefited from the underlying similarities. After all, making new discoveries requires the same skills whatever the subject. Artists are probably more knowledgeable about using their intuition than chemists.

What motivated you to study in your particular area?
At the heart of it is the creativity of the chemistry. I am very interested in the ability to make new architecture that can do something interesting. This drove me to organic chemistry, where the construction of molecules is a strong theme. I branched into biological chemistry because I wanted to work with very large molecules and very big questions, ending up with very useful functions.

What are you working on at the moment?
We are building large molecules that can do interesting operations. For example, we are developing an artificial tongue which we use as a multifunctional sensor device that can analyse a variety of substances. We hope to develop this commercially for use in diagnostics and drug discovery and simply to detect enzymes, as many enzymes are difficult to detect using existing techniques, or need radio labelling which is expensive and wasteful.

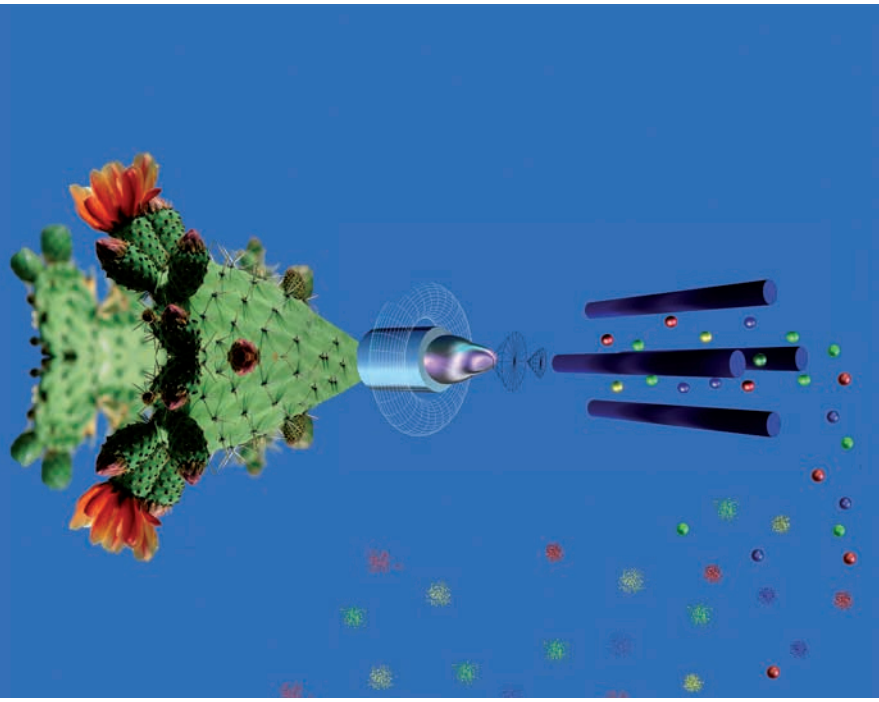
You are also interested in artificial photosynthesis. Can you give a brief overview of what this is?
The definition of photosynthesis is the conversion of photonic energy into chemical energy. The classical reaction is the splitting of water. However, there is also a parallel approach, which is not photosynthesis, but converts photonic energy into electrical current. From an energy point of view, it doesn't really matter which solution is found, but from the scientific point of view, it is probably easier to make a current.

You started your academic career in the US. Are there many cultural differences working in the US compared to Europe?
Yes, there are many differences. What I like most about the US is the passion and the optimistic attitude. In Europe, I find that people treat science more as a profession than a passion. However, I think that science is structured better here.

What can be done to encourage young people to study the chemical sciences?
This is a big problem and a very important point. The biggest problems that society faces, for example energy, will need to be solved by chemists, together with physicists and other scientists. We need to attract the most creative and talented young people to solve these problems. This needs to start with the teaching. Also, it is very important for scientists to be in the news, letting the general public know how important science is to today's problems. Unfortunately, many scientists do not enjoy being in the spotlight.

If there was one chemical problem that you could solve what would it be?
The energy problem. Of course, there are other important areas such as drug discovery. I can see enormous potential at the interface with immunology, for example. Analytical tools from genomics and proteomics can lead to targets being identified much more easily. However, if you look at the world as a whole, the energy problem is just so much more important. It is almost like a holy grail!

What do you do in your spare time?
Unfortunately, part of being a scientist is that you don't have much spare time! However, science does give me the opportunity to visit other countries and meet friends with the same passion, which is fantastic. I used to enjoy flamenco dancing. I was never good but I loved it. The rhythm is very difficult and the style is very powerful.



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Critical Review

Advanced nuclear analytical techniques for metalloproteomics
Yuxi Gao, Chunying Chen and Zhifang Chai, ***J. Anal. At. Spectrom.,*** 2007, **22**, 856
DOI: 10.1039/b703323k

Articles:

Investigation of the selenium species distribution in a human B-cell lymphoma line by HPLC- and GC-ICP-MS in combination with HPLC-ESIMS/MS and GC-TOFMS after incubation with methylseleninic acid
Heidi Goenaga Infante, Simon P. Joel, Emma Warburton, Christopher Hopley, Ruth Hearn and Simone Jüliger, ***J. Anal. At. Spectrom.,*** 2007, **22**, 888
DOI: 10.1039/b708620b

Laser ablation-ICP-MS assay development for detecting Cd- and Zn-binding proteins in Cd-exposed *Spinacia oleracea* L.
Aleksandra Polatajko, Marisa Azzolini, Ingo Feldmann, Thomas Stuezel and Norbert Jakubowski, ***J. Anal. At. Spectrom.,*** 2007, **22**, 878
DOI: 10.1039/b703245e

Analysis of phytochelatins in nopal *(Opuntia ficus)*: a metallomics approach in the soil–plant system
Julio Alberto Landero Figueroa, Scott Afton, Kazimierz Wrobel, Katarzyna Wrobel and Joseph A. Caruso, ***J. Anal. At. Spectrom.,*** 2007, **22**, 897
DOI: 10.1039/b703912c

Mass spectrometric analysis of ubiquitin–platinum interactions of leading anticancer drugs: MALDI *versus* ESI
Christian G. Hartinger, Wee Han Ang, Angela Casini, Luigi Messori, Bernhard K. Keppler and Paul J. Dyson, ***J. Anal. At. Spectrom.,*** 2007, **22**, 960
DOI: 10.1039/b703350h

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Instant insight

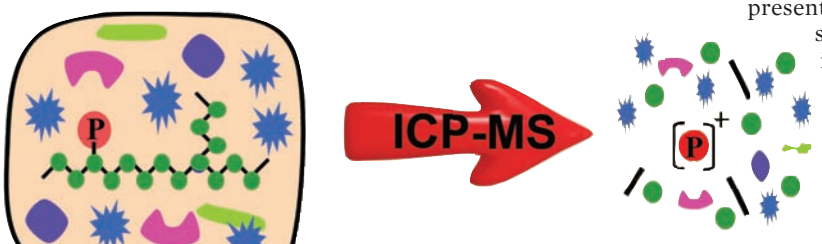
‘Absolute’ phosphorylation

Ana Pereira Navaza, Jorge Ruiz Encinar and Alfredo Sanz-Medel of the University of Oviedo in Spain explain why elemental mass spectrometry is a high flier in the world of quantitative phosphoproteomics

Proteins carry out most of the biological functions in a cell. So a thorough understanding of cell functions and biochemical mechanisms in cells requires information about the proteins present, how and why they interact, their functions and when exactly they carry them out. Also, dynamic control of a protein’s conformation, and hence its function, is achieved mostly through chemical changes after it has been translated from messenger RNA – so-called post-translational modifications. Of these, phosphorylation is implicated in regulating protein activity and signalling pathways in cells and has received enormous attention recently, due mainly to its connection with cancer.

However much phosphoprotein analysis is needed though, it is far from being straightforward. Firstly, phosphoproteins function at very low levels within cells. Secondly, a single protein can be phosphorylated and dephosphorylated by different kinases and phosphatases, respectively, on one or more different residues, and at different times. These variations may lead to very important biological effects, which should be detectable only if quantitative information (quantitative phosphoproteomics) is possible.

Classical approaches to analysing protein phosphorylation have consisted of labelling the proteins with radioactive ^{32}P or Western Blot analysis, which uses gel electrophoresis to separate proteins of different length or structure. However, only advanced molecular mass spectrometry (MS)-based methodologies developed during the past decade have really boosted quantitative phosphorylation analysis.



Phosphopeptides in complex samples (left) are destroyed and ionised during ICP-MS (right) and can be quantified using the ^{31}P signal obtained

Quantitative data in phosphoproteomics are often obtained as relative phosphoprotein levels between two cell states. Relative strategies are very useful to evaluate phosphorylation changes with experiment, but they fail to provide absolute phosphopeptide abundance levels. In fact, absolute quantification of phosphoproteins at given phosphorylation sites has barely been addressed using molecular MS. Moreover, the few methods reported for this purpose so far require the previous chemical synthesis of each individual phosphopeptide, preferably as an isotopically-labelled form. Therefore, application of these methods is restricted to proteins with well-known phosphorylation behaviour and is limited by the availability of the labelled phosphopeptides.

Absolute phosphoprotein concentration determination by molecular MS techniques is constrained by the fact that they provide matrix- and species-dependent signals. Conversely, elemental MS (for example inductively coupled plasma MS, ICP-MS) gives an analytical response that can be made directly proportional to the absolute amount of the element present (P in this case). The ^{31}P signal obtained will be independent of the amino acid sequence of the phosphopeptide and of the matrix in which it is analysed.

As a highly accurate and precise method, ICP-MS will allow very small changes in protein phosphorylation levels to be followed, aiding, for example, cell signalling studies. The exceptional features of the ICP-MS technique also open the door to species-independent calibration, providing a generic approach for absolute quantification of biomolecules containing ICP-MS heteroatoms (elements different from C, H, N and O). In heteroatom-tagged proteomics, absolute quantitative results can be traced directly to a simple certified P standard and so will allow sound data comparisons among different laboratories.

Yet plasma MS comes with a price: the loss of molecular information. Complex biological mixtures call for high resolution separation and molecular MS of the individual components is still mandatory to find the amino acid sequences of the phosphopeptides quantified by ICP-MS.

Complementary techniques, both molecular and elemental MS are required to translate an amount of phosphorus into an absolute amount of phosphopeptide and, of course, to determine the phosphorylation sites in the peptide – the first step to quantitative phosphoproteomics.

Read Navazza, Encinar and Sanz-Medel’s critical review ‘Quantitative protein phosphorylation analysis: the role of ICP-MS’ in issue 10 of Journal of Analytical Atomic Spectrometry.

Reference
A P Navaza, J R Encinar and A Sanz-Medel, *J. Anal. At. Spectrom.*, 2007, DOI: 10.1039/b703555a

Essential elements

And the winner is...

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Receiving the award at the ALPSP Annual Dinner in London on September 13th, project manager Richard Kidd declared: 'RSC Publishing is proud to win the 2007 award, which is great recognition for the work our publishing staff and academic partners have put into the development and evolution of *Project Prospect*.'

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