

# Chemical Biology

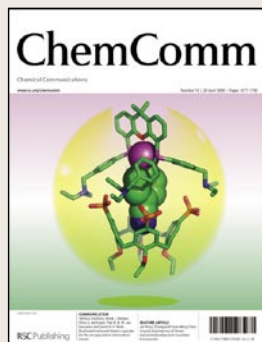
## How proteins fold proteins



Scientists in the UK have explained how bacterial proteins act as 'molecular chaperones' and assist other proteins to fold.

H Jones *et al*  
*Org. Biomol. Chem.*, 2006, **4**, 1223

## Mini buckets detect CJD



A diagnostic test to detect the pathogenic prion proteins responsible for BSE and Creutzfeldt-Jakob disease is being developed in France.

F Perret *et al*  
*Chem. Commun.*, 2006 (DOI: 10.1039/b600720c)

## Modelling attraction



Scientists in Israel have used computer simulations to understand how protons transfer across the surfaces of proteins.


M Gutman *et al*  
*Photochem. Photobiol. Sci.*, 2006 (DOI: 10.1039/b515887g)

## Chip to mimic cell junctions



A device for investigating cell signalling has been invented by researchers in the US, allowing controlled delivery of stimuli to individual cells.

T F Kosar *et al*  
*Lab Chip*, 2006 (DOI: 10.1039/b517475a)

 See [www.rsc.org/chembiology/](http://www.rsc.org/chembiology/) for full versions of these articles

# Research highlights

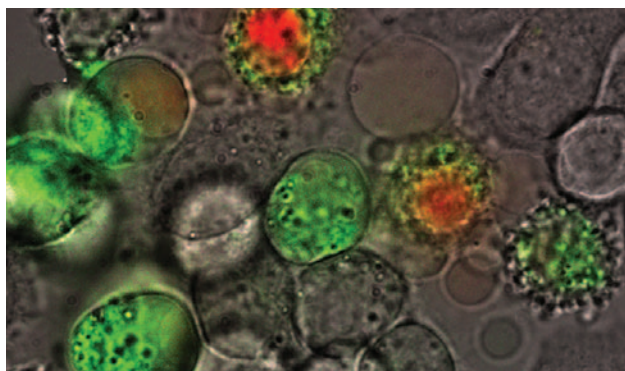
Peptide probe to monitor drug progress in cancer therapy

## Fluorescent sensor detects dying cells

A series of molecular probes that could allow doctors to tailor treatments to individual cancer patients has been developed by chemists in the US and Australia. A team led by Bradley Smith at the University of Notre Dame and Katrina Jolliffe at the University of Sydney, prepared a series of fluorescent peptides that bind selectively to dying cells.

Many cancer medicines kill tumour cells by triggering them to shut down in a programmed way, a process known as apoptosis. Smith and Jolliffe's peptide probes recognise apoptotic cells, and so can show whether a drug is acting effectively.

The probe works by detecting phosphatidylserine (PS), which appears on the cell surface during the early stages of apoptosis.



Because the probe operates instantaneously and can be monitored by fluorescence microscopy, Smith suggests it will make an ideal marker in high throughput cancer drug discovery. The probes could be developed into imaging agents to detect

**Probe highlights cancer cells targeted by drugs**

### Reference

K M DiVittorio *et al.*, *Org. Biomol. Chem.*, 2006 (DOI: 10.1039/b514748d)

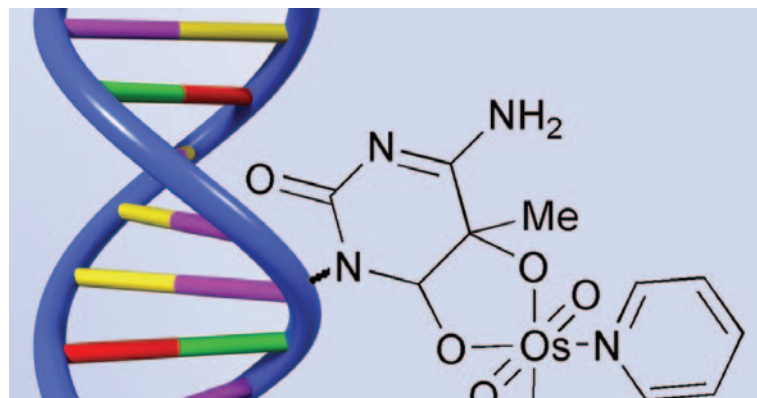
apoptosis in the body during cancer treatment, said Smith. Tom Fyles, an expert in cell membrane sensors at the University of Victoria in Canada, agrees. 'This is a great example of how synthetic molecular recognition elements can rapidly grow into truly practical imaging tools,' he said.

Imaging will enable doctors to test each patient's response to a cancer drug and adjust their treatment accordingly, said Smith, but the probe's future applications could extend further than cancer treatment. 'Apoptosis is also a key process in the cardiovascular system. Another long-term aim of this work is to develop minimally invasive, PS-selective agents that can detect cardiovascular disease in patients,' he said.

*James Mitchell Crow*

Position of methyl groups along DNA backbone could explain gene expression

## Pinpointing sites of altered DNA



Researchers could be closer to understanding how embryos develop and how normal cells turn into cancer cells, thanks to a discovery by Japanese scientists.

Akimitsu Okamoto and colleagues from Kyoto University have found a way to distinguish between the normal DNA base cytosine and its methylated counterpart 5-methylcytosine. The modified cytosine is often found in genomic DNA where it

regulates gene expression and cell differentiation, though how this works is largely unknown.

The researchers discovered that an osmium complex oxidises 5-methylcytosine, but leaves regular cytosine alone. A DNA strand pre-treated with the complex can be split specifically at the oxidised sites. If analysis shows that the DNA has split, this means it contained methylated cytosines.

The group were able to use their

**Osmium complex oxidises selected DNA bases**

### Reference

A Okamoto *et al.*, *Org. Biomol. Chem.*, 2006, 4, 1638

approach to determine whether a specific site in a DNA sequence was methylated. Pinpointing exactly which cytosines are methylated in a gene could help in understanding how methylation controls cell differentiation, answering such questions as why a healthy cell turns cancerous, said Okamoto.

The technique is more efficient than current methods, which are hampered by complicated procedures and long reaction times, said Okamoto. He now aims to develop a method to determine how many cytosines in a DNA sequence are methylated and which of these sites are important, for example in gene expression.

Guoping Fan, an expert in the field from the University of California, Los Angeles, US, is interested in Okamoto's discovery. 'The challenge in DNA methylation is to develop methods that are both high-throughput and quantitative,' he said, 'this method has good potential.'

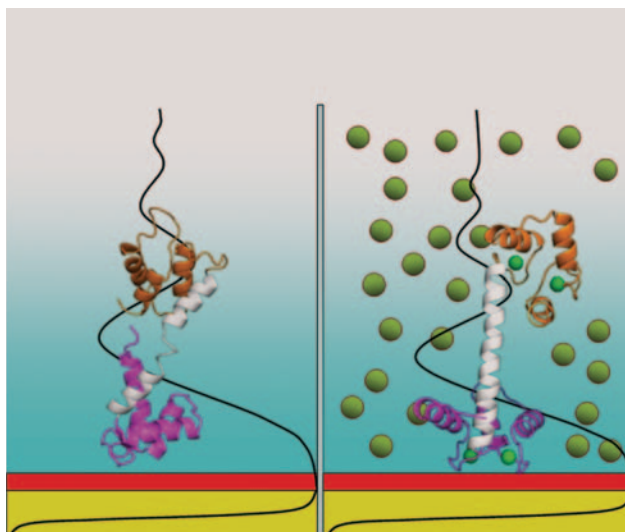
*Danièle Gibney*

## Waves propagate protein investigation

Chemists in Canada have demonstrated the potential of acoustic waves in the study of protein activity. Michael Thompson and colleagues at the University of Toronto used a technique called acoustic shear wave propagation to detect conformational changes in proteins attached to surfaces.

Thompson's group concentrated on the small protein calmodulin – which has a well-characterised role in calcium-mediated cell signalling. The group anchored the protein onto the surface of a sensor chip and bombarded the chip with high-frequency acoustic waves. Biochemical events on the chip surface caused changes in wave properties that were monitored with time.

The activity of calmodulin depends on its binding with calcium ( $\text{Ca}^{2+}$ ) ions. A reversible interaction with  $\text{Ca}^{2+}$  ions makes the protein change from a closed, unbound state to an open, calcium-bound state. For the chip-bound protein this causes the chip to thicken and decreases the resonant frequency of the acoustic device. By measuring the resonant frequency the extent of calcium binding can be monitored.



**Chip detects change in protein shape**

**Reference**  
X Wang *et al*, *Mol. BioSyst.*, 2006, **2**, 184

This is 'the first semi-quantitative detection of a protein conformational shift using an acoustic wave device,' said Thompson. This label-free biosensor methodology can be used to follow protein behaviour in simulated natural environments and has potential for miniaturisation and lab on a chip applications, he said.  
*Michael Spencelayh*

## Sugars are the weakest links in DNA chain

Disintegrating sugars are bringing researchers a step closer to understanding how tumours are destroyed by radiation therapy.

Irradiation with fast protons or heavy ions is a common treatment for malignant tumours. The treatment damages DNA in cancerous cells, but the mechanism is largely unexplored at the biological level. Thomas Schlathöler and colleagues at the University of Groningen, the Netherlands, have found that DNA damage is dominated by the disintegration of deoxyribose, a sugar found in the backbone of the DNA double helix.

The group used an ion beam to bombard deoxyribose molecules with a stream of fast heavy ions and protons. The irradiation



**Reference**  
F Alvarado *et al*, *Phys. Chem. Chem. Phys.*, 2006, **8**, 1922

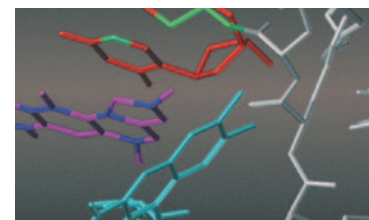
split the molecules into small fragments, which were detected by time-of-flight spectrometry. The fragmentation pattern followed a power law, meaning the fragmentation occurs in a statistical, and therefore predictable, manner. The researchers compared the deoxyribose fragmentation pattern with that of adenine, one of DNA's complementary bases, and found that adenine is significantly more stable than the sugar.

This research appreciably advances our understanding of how irradiation kills tumour cells, said group member Fresia Alvarado. Future investigations will look to correlate what happens in isolated molecules with more realistic and complex systems like cells and organisms, she said.  
*Nina Athey-Pollard*

## FAD stage down to the dUMPs

An unexpected discovery could lead to new antibiotics claim researchers in the US.

Amnon Kohen, at the University of Iowa, and colleagues were investigating the mechanism of the enzyme FDTS (flavin dependent thymidylate synthase). FDTS catalyses the conversion of dUMP, a derivative of the nucleoside uridine, to its thymidine analogue, dTMP, used in DNA formation. Kohen found that the substrate dUMP activates an initial stage in the enzyme's catalytic cycle: the reduction of the cofactor FAD (flavin adenine dinucleotide).



In the absence of dUMP, the FAD reduction step was delayed – a lag phase. Further experiments showed that dUMP concentration affected how long this lag phase lasted, implying that dUMP assists FAD reduction. Kohen suggests that to do this dUMP makes the enzyme change shape.

According to Ursula Liebl at the École Polytechnique in France, this 'represents the first thermodynamic evidence for earlier proposals that dUMP binding causes conformational changes in FDTS.'

Kohen suggests that the lag phase phenomenon could be a feature of other biological systems, hidden by the experimental conditions used.

Hannu Myllykallio of the Université Paris-Sud in France said that Kohen's research 'provides interesting hints towards the rational design of new antimicrobial compounds.' Kohen aims to extend the work to study FDTS from pathogenic bacteria.

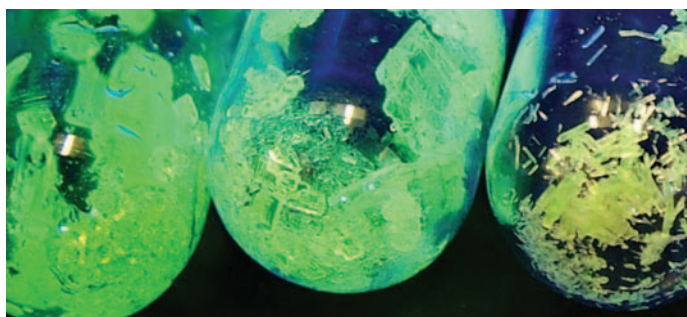
*Rachel Warfield*

**Reference**  
A Mason *et al*, *Chem. Commun.*, 2006, 1781

## Royal recognition for green technology

One of the Queen's Anniversary Prizes for Higher and Further Education was recently awarded to Queen's University Ionic Liquids Laboratories (QUILL), Belfast, UK for their groundbreaking work on the development of ionic liquids as alternatives to conventional solvents.

Professor Ken Seddon, Director of QUILL, is widely recognised as a pioneer in the field of ionic liquids. He has been associated with the RSC's *Green Chemistry* journal since it was first launched in 1998. Currently a member of the journal's International Advisory Board, he has published a number of very highly cited papers in this



exciting area of chemistry. His work has contributed to the establishment of QUILL as the world's leading centre in ionic liquids research.

'Ionic liquids act as solvents for a broad spectrum of chemical processes and can dissolve a

wide range of materials – even rocks, coal and almost anything organic, amazingly well,' explained Seddon. 'However, unlike conventional solvents, they do not emit vapours. Put quite simply, they have remarkable properties which

have tremendous applications in the development of clean technology for manufacturing processes. They are the basis of a whole new industrial technology.'

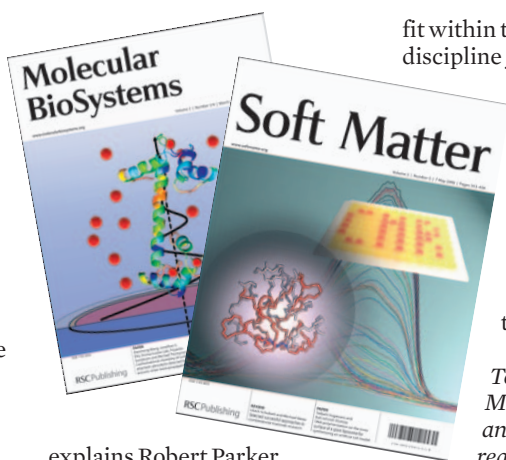
Ionic liquids are non-volatile organic salts with melting points often lower than room temperature. Used in place of more traditional organic solvents, they have the advantage of eliminating VOC (volatile organic compound) emissions and also improving yields.

To find out more about QUILL, visit: [quill.qub.ac.uk](http://quill.qub.ac.uk)  
To read the latest research on ionic liquids and related topics, visit: [www.rsc.org/greenchem](http://www.rsc.org/greenchem)

MARTIN EARLE, QUILL

## New journals free for all

Celebrating a successful first year of publication, RSC Publishing will provide free access to all readers of its two new interdisciplinary journals, *Soft Matter* and *Molecular BioSystems*. The offer will be available for three months and will allow readers to access all of the original research, high profile reviews, news articles and editorials that have propelled the journals to the forefront of their respective fields. 'The motivation to launch two interdisciplinary journals originated from a need identified from within the research communities'



explains Robert Parker, Editorial Director at the RSC. 'New research areas were developing but the work did not

fit within the scope of traditional discipline journals. Our two new journals have offered a unique and targeted forum for communication for these communities. We have been overwhelmed by the positive response they have received.'

To find out more about *Molecular BioSystems* and *Soft Matter*, and to read articles published so far, please visit:

[www.molecularbiosystems.org](http://www.molecularbiosystems.org) and [www.softmatter.org](http://www.softmatter.org)

## And finally....

Over 200 people gathered at the RSC reception in the Hilton Hotel, Atlanta on 26th March. Coinciding with the 231st ACS National Meeting, the reception provided the opportunity to meet with newly-appointed Chief Executive Richard Pike, and find out more about recent developments from the Royal Society of Chemistry. Highlights from RSC Publishing included news of the weekly journals, *PCCP* and *Dalton Transactions*; the success of new journals, *Soft Matter* and *Molecular BioSystems*; and the celebration of 21 years of publication for *JAAS (Journal of Analytical Atomic Spectrometry)*.

*Chemical Biology* (ISSN: 1747-1605) is published monthly by the Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge UK CB4 0WF. It is distributed free with *Organic & Biomolecular Chemistry*, *Molecular BioSystems*, *Natural Product Reports* and *Photochemical & Photobiological Sciences*. *Chemical Biology* can also be purchased separately. 2006 annual subscription rate: £199; US \$364.

All orders accompanied by payment should be sent to Sales and Customer Services, RSC (address above). Tel +44 (0) 1223 432360, Fax +44 (0) 1223 426017. Email: [sales@rsc.org](mailto:sales@rsc.org)

**Editor:** Celia Clarke

**Associate editors:** Neil Withers, Nicola Nugent

**Essential elements:** Melanie James, Valerie Simpson

**Publishing Assistant:** Kate Nussey

**Publisher:** Adrian Kybett

Apart from fair dealing for the purposes of research or private study for non-commercial purposes, or criticism or review, as permitted under the Copyright, Designs and Patents Act 1988 and the copyright and Related Rights Regulations 2003, this publication may only be reproduced, stored or transmitted, in any form or by any means, with the prior permission of the Publisher or in the case of reprographic reproduction in accordance with the terms of licences issued by the Copyright Licensing Agency in the UK. US copyright law is applicable to users in the USA.

The Royal Society of Chemistry takes reasonable care in the preparation of this publication but does not accept liability for the consequences of any errors or omissions.

Royal Society of Chemistry: Registered Charity No. 207890.

RSC Publishing