Organic & Biomolecular Chemistry

An international journal of synthetic, physical and biomolecular organic chemistry

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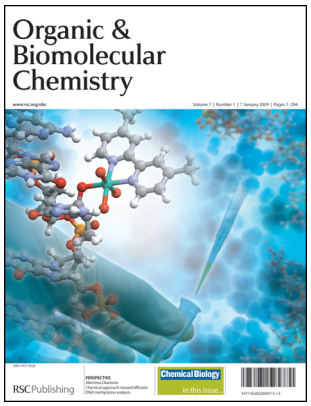
IN THIS ISSUE

ISSN 1477-0520 CODEN OBCRAK 7(1) 1–204 (2009)



Cover

See Akimitsu Okamoto, pp. 21–26. Chemical reactions at methylated cytosines can be a key technique for efficient epigenotyping analysis of DNA in cells.

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Inside cover

See Beate Koksch *et al.*, pp. 46–51. Organization of gold nanoparticles can be achieved by electrostatic interactions with a coiled coil peptide and can be switched on and off by pH in a repeatable manner.

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CHEMICAL BIOLOGY

Chemical Biology

January 2009/Volume 4/Issue 1

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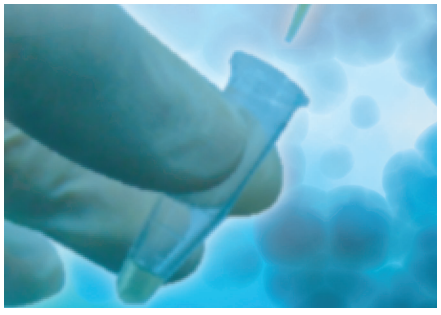
EDITORIAL



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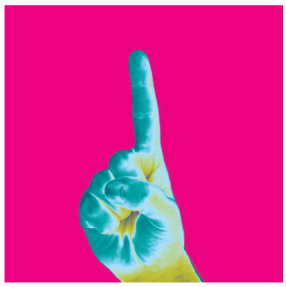

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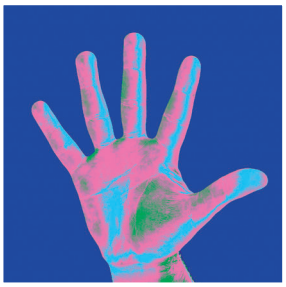

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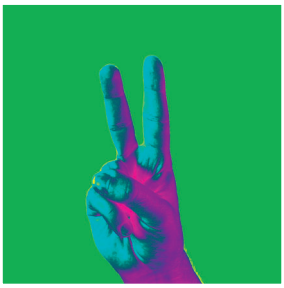

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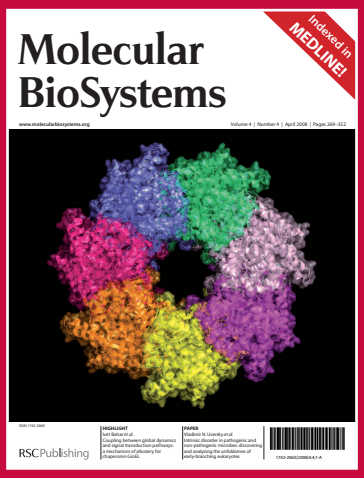
5 years of publishing

Molecular BioSystems...



Celebrating 5 years of publishing, *Molecular BioSystems* publishes cutting-edge research at the interface between chemistry, the –omic sciences and systems biology. *Molecular BioSystems* latest impact factor is 4.12 (2007 Thomson (ISI) Journal Citation Reports) - a sure indication of the significance of the work published in this exciting interdisciplinary journal.

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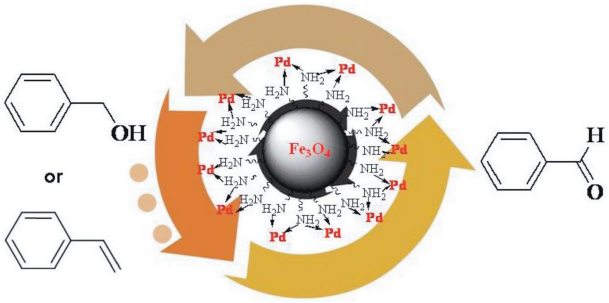

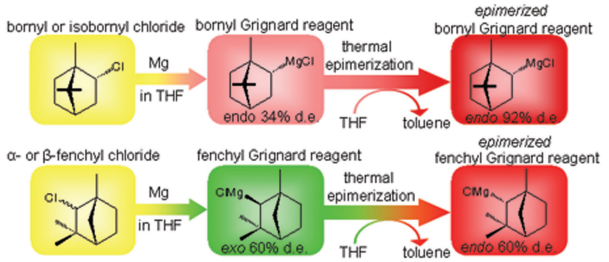

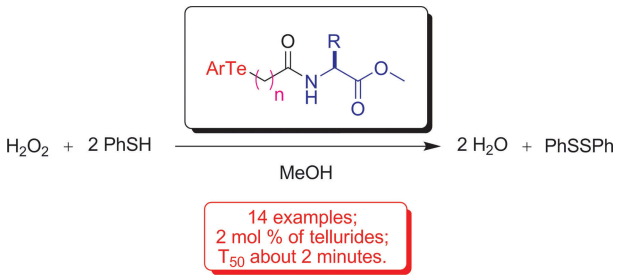

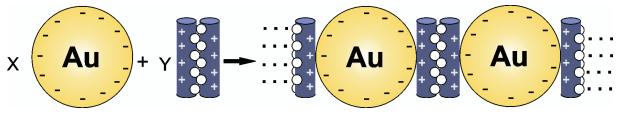

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20-22 January, Palm Springs, CA, USA
StemCellCongress.com

CO-LOCATED EVENTS

Screening Europe
23-25 February, Berlin, Germany
ScreeningEurope.com

MedChem Europe
23-25 February, Berlin, Germany
MedChemEurope.com

ADMET Europe
23-25 February, Berlin, Germany
ADMETEurope.com

Drug Discovery Latin America
26-27 February, Rio de Janeiro, Brazil
DrugDiscLA.com

Advances in Synthetic Biology
30-31 March, London, England
SyntheticBiologyAdvances.com

Advances in Synthetic Chemistry
16-17 April, Edinburgh, Scotland
AdvSynChem.com

DxRx Summit
Nucleic Acid Diagnostics & Therapeutics
12-13 May, Boston, MA, USA
DxRxSummit.com

RNAi World Congress
14-15 May, Boston, MA, USA
RNAiCongress.com

CO-LOCATED EVENTS

Lab-on-a-Chip European Congress
19-20 May, Stockholm, Sweden
LOAConference.com

Advances in Microarray Technology
19-20 May, Stockholm, Sweden
MicroarrayTechnology.biz

Molecular Diagnostics Europe
19-20 May, Stockholm, Sweden
MolecularDiagnosticsEurope.com

Cancer Proteomics
8-11 June, Dublin, Ireland
CancerProteomics.net

AgriGenomics World Congress
2-3 July, London, England
AgriGenomics.eu

SelectBiosciences.com

Target Discovery World Congress
4-5 August, South San Francisco, CA, USA
TargetDiscoveryCongress.com

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6-7 August, South San Francisco, CA, USA
Lab-on-a-Chip.net

Microarray World Congress
6-7 August, South San Francisco, CA, USA
MicroarrayWorldCongress.com

Molecular Diagnostics World Congress
6-7 August, South San Francisco, CA, USA
MolecularDiagnosticsCongress.com

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17-18 September, Berlin, Germany
RNAiEurope.com

Advances in qPCR
17-18 September, Berlin, Germany
qPCRadvances.com

Epigenetics World Congress
17-18 September, Berlin, Germany
EpigeneticsCongress.com

Peptides Europe
17-18 September, Berlin, Germany
PeptidesEurope.com

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Stem Cells Europe
23-25 September, Edinburgh, Scotland
StemCellsEurope.org

World Biobanking Summit
24-25 September, Edinburgh, Scotland
www.BiobankingSummit.com

CO-LOCATED EVENTS

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5-6 November, Barcelona, Spain
MetabolicProfiling.com

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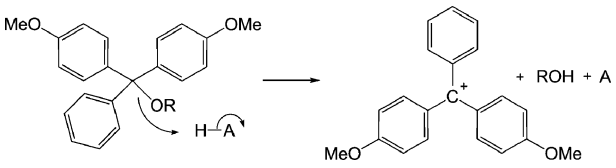
52

The kinetics and mechanism of the acid-catalysed detritylation of nucleotides in non-aqueous solution

Mark A. Russell, Andrew P. Laws, John H. Atherton and Michael I. Page*

Detritylation of protected nucleotides in non-aqueous solvents occurs by a concerted general acid-catalysed mechanism rather than a stepwise A1 process.

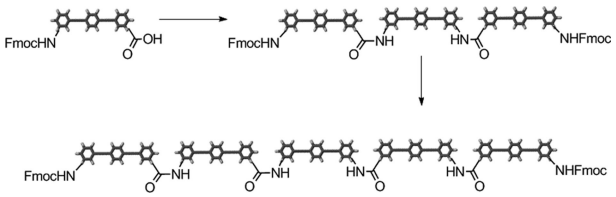


58

Synthesis of functional molecular rod oligomers

Casper S. Andersen and Kurt V. Gothelf*

We are presenting the synthesis of a phenylene ethynylene-based rod containing an Fmoc protected amino group and an activated acid which can be applied to peptide couplings. This linear amino acid analogue is applied to the synthesis of di-, tri- and pentamers.

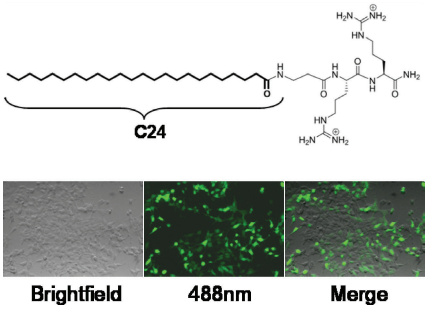


61

Very long-chain fatty tails for enhanced transfection

Aleksandra Liberska, Asier Unciti-Broceta and Mark Bradley*

The longer the better! In this manuscript we show how the use of fatty tails longer than usual (>C18) provides a means of increasing the transfection efficiency of arginine-based single-chained cationic lipids.

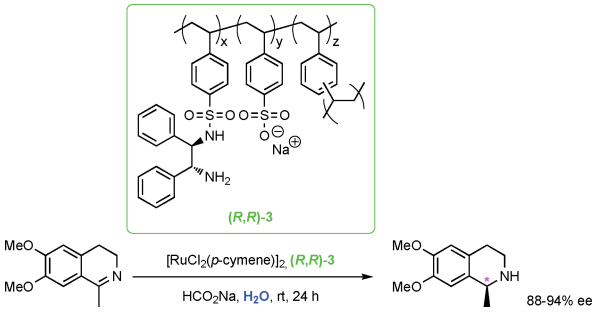


69

Asymmetric transfer hydrogenation of imines catalyzed by a polymer-immobilized chiral catalyst

Naoki Haraguchi,* Keiichi Tsuru, Yukihiro Arakawa and Shinichi Itsuno

The first asymmetric transfer hydrogenation of imines by utilizing a polymer-immobilized chiral catalyst was successfully performed both in organic solvent and in water to afford the corresponding enantioenriched amines.



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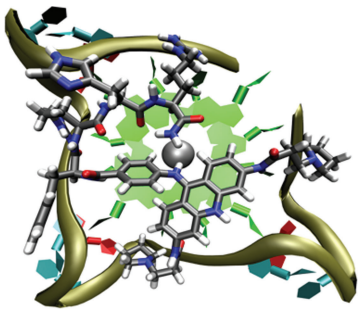
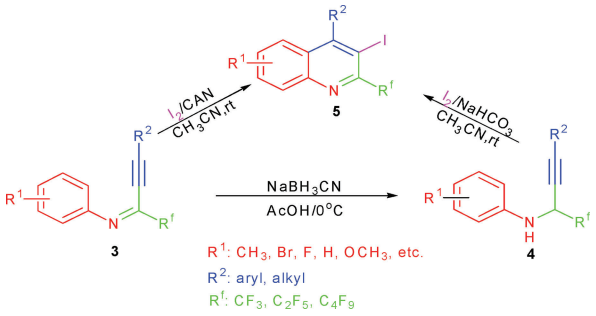
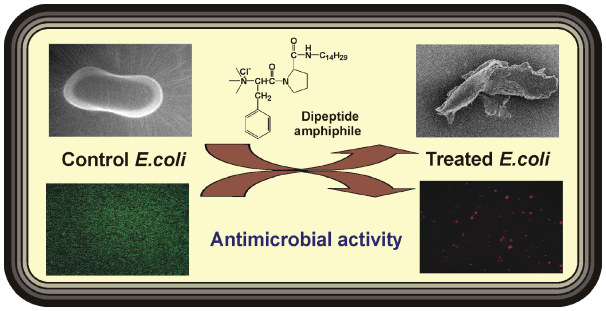
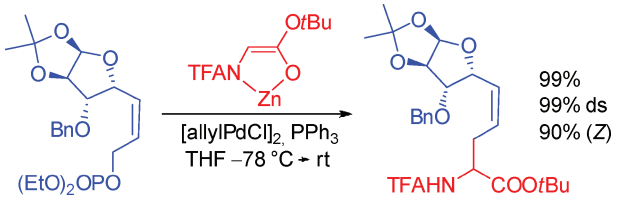
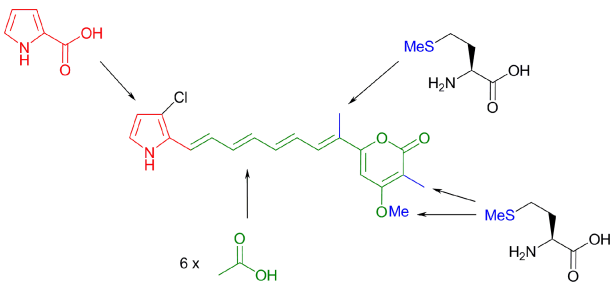








111

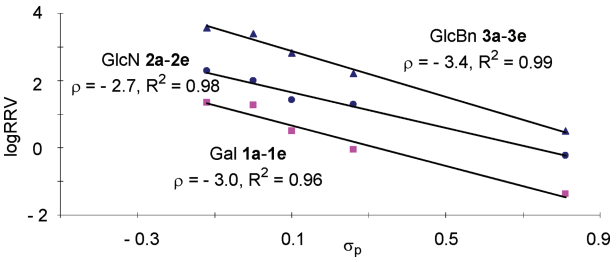


Biosynthesis of pyrrolylpolyenes in *Auxarthron umbrinum*

Benjamin R. Clark and Cormac D. Murphy*

The biosynthesis of the chlorinated pyrrolyl polyene rumbrin was investigated in *Auxarthron umbrinum*. Pyrrole-2-carboxylate, which originates from proline, was identified as a new starter unit in polyketide biosynthesis.

117

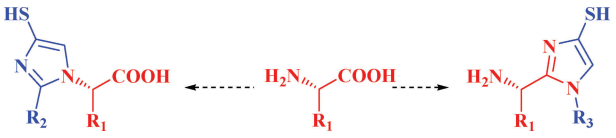


Thio-arylglycosides with various aglycon *para*-substituents: a probe for studying chemical glycosylation reactions

Xiaoning Li, Lijun Huang, Xiche Hu and Xuefei Huang*

Excellent linear Hammett correlations were obtained between relative reactivity values of three series of donors differing only in their aglycon substituents and σ_p values of the substituents.

128

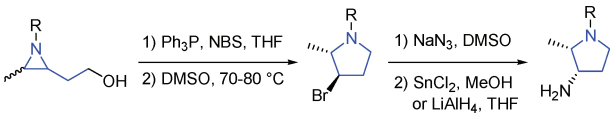


Aminoacid-derived mercaptoimidazoles

Alain Crépin, Nicolas Wattier, Sylvain Petit, Laurent Bischoff,* Corinne Fruit and Francis Marsais

Starting from suitably protected aminoacids, mercaptoimidazoles were synthesized either from the acid or including the amine nitrogen itself. Preliminary optimisation led to efficient conditions for generation of the imidazole ring, which were compatible with the presence of aminoacid or dipeptide scaffolds.

135



A new entry into *cis*-3-amino-2-methylpyrrolidines *via* ring expansion of 2-(2-hydroxyethyl)-3-methylaziridines

Matthias D'hooghe, Wim Aelterman and Norbert De Kimpe*

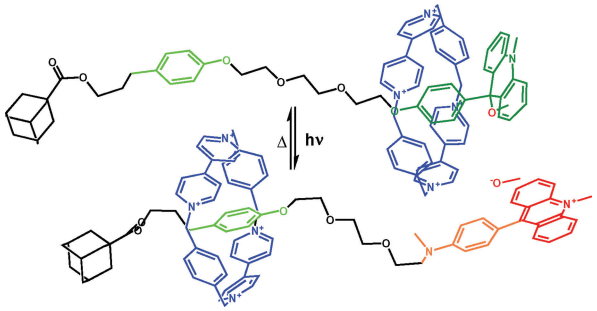
2-(2-Hydroxyethyl)-3-methylaziridines were transformed into 3-bromo-2-methylpyrrolidines *via* intermediate bicyclic aziridinium salts, followed by displacement of the bromo atom by azide and subsequent reduction towards biologically relevant *cis*-3-amino-2-methylpyrrolidines.

142

Photoswitchable rotaxanes using the photolysis of alkoxyacridanes

Werner Abraham,* Andre Wlosnewski, Karin Buck and Sabine Jacob

Photolysis of the acridane station generates a positive charge which, in the presence of an alternate station, repels the tetracationic cyclophane, moving it away from the acridinium stopper. The thermal back-reaction occurs on the time scale of minutes.

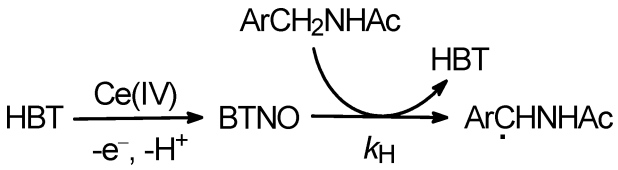


155

Hydrogen atom abstraction from C–H bonds of benzylamides by the aminoxyl radical BTNO: A kinetic study

Alessandra Coniglio, Carlo Galli,* Patrizia Gentili* and Raffaella Vadalà

Rate constants of H-abstraction from the benzylic CH_2-group α to nitrogen in X-$C_6H_4CH_2NHCOCH_3$ by the aminoxyl radical BTNO were determined in MeCN at 25 °C. The relevance of stereoelectronic effects is documented.

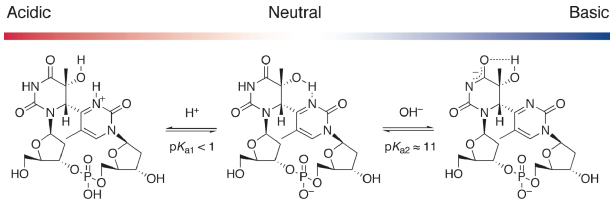


161

Spectroscopic analysis of the pyrimidine(6–4)pyrimidone photoproduct: insights into the (6–4) photolyase reaction

Junpei Yamamoto, Yoshiyuki Tanaka and Shigenori Iwai*

The protonation state of the pyrimidone N3 in the (6–4) photoproduct, which is one of the major UV-induced lesions in DNA, has been analyzed by spectroscopic methods, and the results suggested intramolecular hydrogen-bond formation.

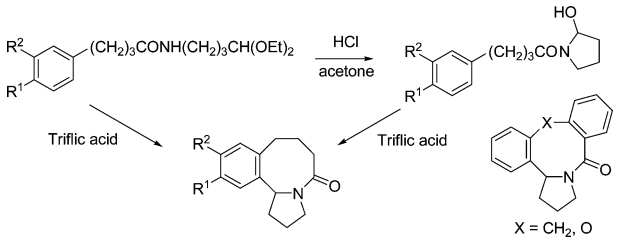


167

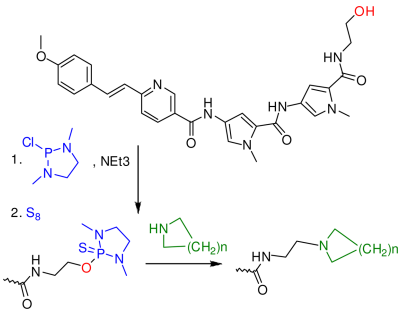
A facile synthesis of pyrrolo-(di)-benzazocinones *via* an intramolecular *N*-acyliminium ion cyclisation

Frank D. King,* Abil E. Aliev, Stephen Caddick, Derek A. Tocher and Denis Courtier-Murias

Triflic acid-mediated cyclisation of *N*-(4,4-diethoxybutyl)-4-aryl-butyramides or 1-(2-hydroxypyrrolidinyl)-4-aryl-butan-1-ones gave hexahydro-pyrrolo-benzazocin-3-ones. Similarly, pyrrolo-dibenzazocines were also prepared.



178

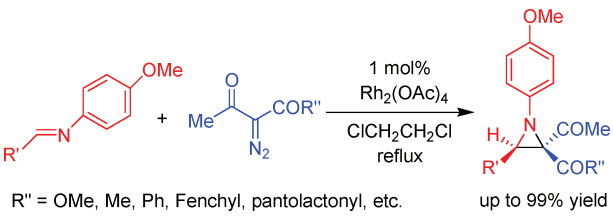


A divergent synthesis of minor groove binders with tail group variation

David Breen, Alan R. Kennedy and Colin J. Suckling*

2-Chloro-1,3-dimethyl-1,3,2-diazaphospholidine is used for the synthesis of antibacterial minor groove minders with *t*-amino tail groups.

187

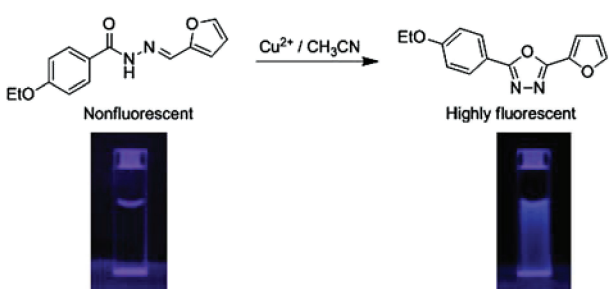


Catalyzed addition of diazoacetoacetates to imines: synthesis of highly functionalized aziridines

Xue-jing Zhang, Ming Yan* and Dan Huang*

Highly functionalized aziridines were prepared in good yields and with excellent *cis* selectivity by catalyzed addition of diazoacetoacetates to aromatic imines derived from *p*-methoxyaniline.

193



Oxidative cyclization of *N*-acylhydrazones. Development of highly selective turn-on fluorescent chemodosimeters for Cu^{2+}

Ai-Fang Li, Hui He, Yi-Bin Ruan, Zhen-Chang Wen, Jin-Song Zhao, Qiu-Ju Jiang and Yun-Bao Jiang*

Redox-based Cu^{2+}-chemodosimeters were developed following oxidative cyclization by Cu^{2+} of nonfluorescent *N*-acylhydrazones into highly fluorescent rigid 1,3,4-oxadiazoles, leading to enhanced fluorescence output despite the quenching character of Cu^{2+}.

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Chemical Biology

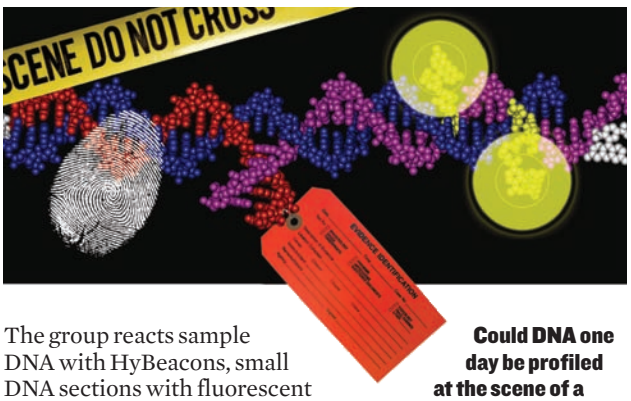
DNA fingerprints revealed by fluorescent probes

Forensic science hots up

Characters in television crime programmes will often get DNA profiling data back in the time it takes for you to boil a kettle, but in reality the process is much slower. Now, UK scientists at the University of Southampton and the Laboratory of the Government Chemist, Teddington, are working on a technique that could allow DNA evidence to be profiled at the scene of a crime.

DNA profiling doesn't sequence an entire genetic code – the Human Genome Project that finally did this took 13 years. Instead, the process searches for segments of DNA called short tandem repeats, or STRs, repeats of 2–6 DNA base pairs which appear throughout our genetic code. The number of times that each STR repeats varies from person to person, and so, by measuring the length of different STRs, you can identify an individual.

The approach taken by Tom Brown and colleagues exploits the fact that DNA of different lengths unwinds at different temperatures.



Could DNA one day be profiled at the scene of a crime?

The group reacts sample DNA with HyBeacons, small DNA sections with fluorescent probes attached. The HyBeacons bind to STR DNA and fluoresce as the probes are no longer free to interact with each other and quench fluorescence. When the sample is then heated, the STR sections of DNA unwind, the HyBeacons and STR-containing DNA separate and the fluorescence stops; the temperature at which this happens indicates the number of STR repeats.

Until now, STR lengths were measured by seeing how far they passed through a gel: the longer the strand the slower it moves and the shorter distance it travels. However, to have enough DNA for analysis, the STRs have to be copied many times and so the entire profiling process takes about a day in a laboratory. Using HyBeacons requires much less DNA and so eliminates the need for this time-consuming copying process.

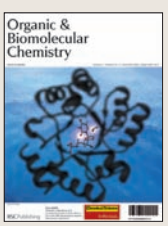
'This is an elegant approach,' says Duncan Graham, of the University of Strathclyde, Glasgow, UK, who works with chemically modified DNA. 'It offers significant advantages for forensic applications such as DNA fingerprinting.'

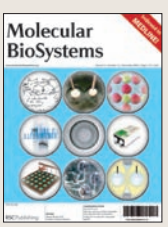
Indeed, the next goal for the team is developing the equipment to optimise the DNA analysis. 'DNA profiling has transformed forensic investigations over the past twenty years,' explains Brown. 'But,' he adds 'a holy grail is for the technology to become so rapid and portable that it can be applied at the point of crime, or suspect arrest.'

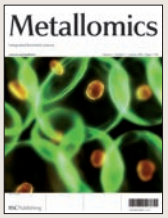
Laura Howes

Reference
N Gale *et al*, *Org. Biomol. Chem.*, 2008, **6**, 4553 (DOI: 10.1039/b813431f)

In this issue







Research highlights

Combining cell isolation and migration testing to monitor immune cell status

Immune function on a chip

A chip to test white blood cell response quickly from just a drop of blood has been developed by scientists in the US.

Neutrophils are the most common white blood cells in the body. They play a key role in immune function, being drawn to a site of infection or injury by a chemical concentration gradient, effectively a trail of attracting molecules released by the distressed cells. The new chip, developed by Daniel Irimia and a team at the Massachusetts General Hospital in Boston, can both isolate neutrophils from blood and monitor how they migrate in one rapid step.

Current migration-measuring techniques usually require a separate step to isolate neutrophils, involving large sample volumes and lengthy procedures not suited to miniaturisation. Irimia's method needs smaller volumes and avoids the extra step by capturing the neutrophils in the chip, in a chamber coated with cell adhesion molecules.

A single drop of blood contains enough neutrophils to test the cells' migration abilities

Importantly, these binding interactions are weak. This means that the captured cells can move when a concentration gradient of a chemoattractant is applied on the chip. The cells' movement is then monitored by microscopy.

The chip could find use in routinely testing individuals' neutrophil migration ability, says Irimia. This would help identify and monitor those with altered neutrophil function, such as children with repeated infections perhaps, he explains. It could also help find the balance needed between keeping neutrophils' protective effects and depressing their function when developing certain drugs, he adds.

Francis Lin, who also develops microfluidic devices for cell migration research, at Stanford University, Palo Alto, US, finds the work impressive. 'It is remarkable that it requires only a small drop of blood from the finger for initial cell loading,' he says. 'It allows repeated blood drawing from the same donor for more consistent experimental results or close follow-up tests,' he adds. 'This means it may find potential applications in systems biology-based research and personalised medical diagnosis.'

Frances Galvin

Reference
N Agrawal, M Toner and D Irimia, *Lab Chip*, 2008, **8**, 2054 (DOI: 10.1039/b813588f)

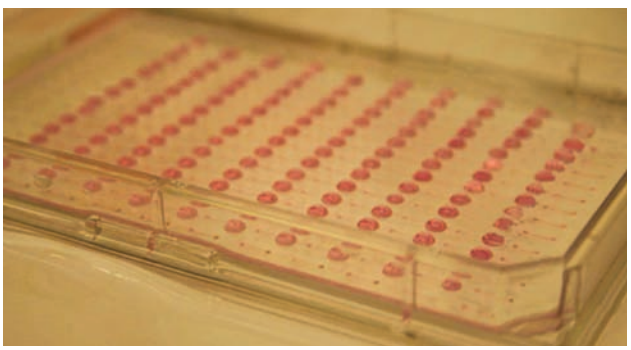
High-throughput screening for optimal protein expression conditions

Passive pumping promotes protein production

Laborious optimisation trials could be a thing of the past for scientists trying to create new proteins. A new time-saving device can rapidly screen numerous cell-free protein synthesis experiments and dramatically reduces the reagent quantities used.

Cell-free protein expression uses DNA templates to make proteins without using whole cells. But identifying the ideal conditions for the protein expression can be a time-consuming exercise. The optimum method can vary depending upon the protein, medium, and expression system used. With this in mind a US team led by Hugh Fan at the University of Florida in Gainesville and David Beebe from the University of Wisconsin-Madison, has created a lab-on-a-chip style device to rapidly screen experimental conditions.

The system is based on nutrient transfer between two droplets – one formed from a nutrient solution, the other, larger, droplet from a protein expression solution containing a DNA template. The transfer, or passive pumping, occurs because the two droplets are connected by a microchannel. 'As the droplets have different sizes they have different surface tensions,' explains Fan. 'Liquid flows between the droplets to balance the difference in the force.' The nutrients are then transported into the protein expression solution, allowing protein production.



Protein expression occurs at outlets in the microchannel device

The team demonstrated its system by optimising the production of a luciferase – an enzyme that catalyses a light-emitting process and so can be easily monitored. Varying the droplets allowed them to tune the expression conditions. They found that the device consumes up to 800 times less reagents than a commercial system and could run nearly 200 experiments in parallel. Also, the passive pumping approach increased the yield by almost five times compared to simply mixing the nutrient and expression solutions within a centrifuge tube.

Mengsu Yang, an expert in microfluidic technology from the City University of Hong Kong, says that 'the array technology combined with the passive pumping process provides an exciting new system for the high-throughput chemical or biochemical generation of diverse ranges of products. The technology could also be adopted for other applications such as drug screening and protein crystallisation.'

Russell Johnson

Reference
R Khnouf, D J Beebe and Z H Fan, *Lab Chip*, 2009, **9**, 56 (DOI: 10.1039/b808034h)

Red-shifted luciferase emits light with deeper tissue penetration

Light up your life processes

A modified enzyme could light the way to better imaging of brain tumours.

Ariane Söling from the Georg August University in Göttingen, Germany, and colleagues, in a collaboration with Bruce Branchini of Conneticut College, New London, US, have shown that light from Branchini's analogue of a firefly luciferase enzyme penetrates tissue more deeply than the unmodified version.

Luciferases catalyse a light-emitting reaction and the resulting bioluminescence can be used to monitor biological processes in vivo, such as tumour growth or metastasis. 'We are working on malignant brain tumours,' says Söling. 'In vivo studies are relatively difficult to conduct using bioluminescence imaging, as skull reduces the bioluminescent light signal emitted from the tumour 100-fold.' Branchini's enzyme produces light at a slightly longer wavelength than the unmodified luciferase, and she suggests that it is this red-shift that allows the light to penetrate tissue more deeply. 'Red light is known to be less absorbed by tissue,' she explains.

Fireflies use luciferase to create bioluminescence

'Red-shifted luciferase reporter proteins could greatly improve in vivo imaging in cancer research,' says Söling. 'New bioluminescent reporters will also allow simultaneous imaging of multiple molecular processes in vivo,' she adds, 'and may thus help to identify complex molecular interactions.'

Nikolai Rainov is a senior consultant neurosurgeon at the Augsburg Clinic, Germany, and carries out academic research in experimental neuro-oncology – the study of tumours of the nervous system. He says the most important finding of the work is that the light emission of the red-shifted analogue in living animals was up to 3.5 times more efficient than that of its unmodified counterpart, even though the in vitro activity was only a fraction of the activity of the unmodified luciferase.

He adds that 'one of the most interesting aspects of this luciferase is the profound change in the light emitting activity of the enzyme after substitution of a single nucleotide [in the DNA plasmid used to generate the luciferase]. This phenomenon is known with other proteins, but rarely demonstrated in such a highly visual way.'

Rachel Cooper

Reference

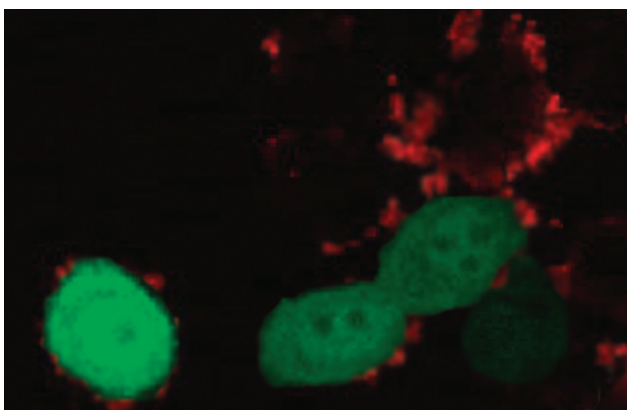
H Caysa *et al*, *Photochem. Photobiol. Sci.*, 2009, DOI: 10.1039/b814566k

Antibodies transported into infected cells to reduce viral production

Delivering the goods to tackle virus infection

A dendrimer that delivers antibodies into cells has potential for infectious disease treatment, say US scientists. Eva Harth, Peter Wright and colleagues, of Vanderbilt University, Nashville, developed the macromolecular antibody carriers to treat virus-infected cells.

In the body, antibodies identify foreign objects such as viruses so that they can be recognised by the immune system. Harth used an antibody specific for the respiratory syncytial virus (RSV), and attached it to a dendrimer by swapping it for a removable pyridinyldithio group. 'The preparation of the bioconjugates is very practical because of this exchange reaction and does not require additional reagents. It could be provided as a reaction kit, suitable to be used by any scientist,' says Harth. The disulfide bonds formed between the antibody and dendrimer are cleavable inside the cells and release the antibody in the biologically active state.



RSV infected cells display green fluorescence which weakens when the cells are treated with dendrimer–antibody conjugate

Reference

S Hamilton *et al*, *Mol. BioSyst.*, 2008, **4**, 1209 (DOI: 10.1039/b816645e)

The Nashville scientists tested their system on human epithelial cells infected with a genetically engineered version of RSV coupled to green fluorescent protein (GFP). GFP allowed the team to monitor the infected cells using imaging techniques such as confocal microscopy. The team noted that cells incubated with the dendrimer–antibody conjugate showed a reduction in viral production, with no evidence that the conjugate was toxic to the cells.

Craig Hawker, an expert on macromolecular assemblies and drug delivery, at the University of California, Santa Barbara, US, is enthusiastic about the research. 'This is extremely interesting and influential work,' he says. 'The reduction of 80–90 per cent in viral replication is a significant first step towards a new strategy for controlling disease,' adds Hawker. RSV remains the leading cause of bronchiolitis and pneumonia in infants and children. Although major advances have been made in bronchiolitis patient care, there is no effective treatment for the disease and the development of a safe and effective vaccine remains a major challenge.

Harth says that in the future, she hopes to extend the research to include not only other viruses such as HIV and rotoviruses, but also cancer and Huntingdon's disease.

Kathleen Too

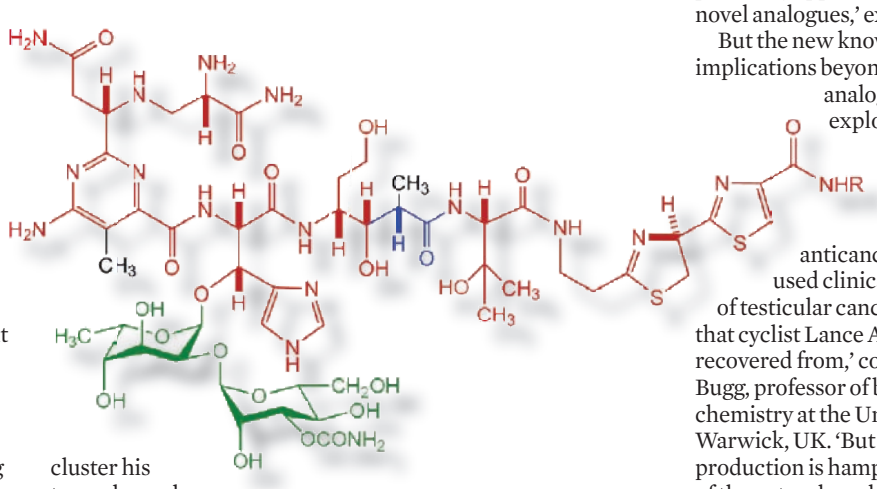
Programmable gene cluster could offer route to new anticancer drugs

Deciphering zorbamycin's genetic code

US scientists have revealed the genes that lead to an antitumor antibiotic. The team, led by Ben Shen at the University of Wisconsin-Madison, says the research could provide the tools to create new anticancer drugs.

'The idea is to use metabolic pathway engineering to make new analogues of zorbamycin, a member of the bleomycin family of antitumor antibiotics,' explains Shen. Modifying bleomycin's biosynthesis to create novel analogues has proved difficult as the organisms that produce it are not amenable to genetic manipulation. Now Shen and his team have identified the gene cluster responsible for synthesising zorbamycin – another glycopeptide antitumor antibiotic – in a different bacterium that is easier to manipulate.

Shen explains that knowledge of the zorbamycin gene cluster will 'allow us now to explore the potential of the zorbamycin scaffold.' The aim is to create new compounds by combinatorial biosynthesis methods. By analysing the antibiotic gene cluster his team showed that while the genetic code of the zorbamycin gene cluster contains 40 open reading frames – stretches of the genome that could encode a protein – only 22 of these were homologous to those found for bleomycin. 'Homologous parts of the biosynthetic machinery highlight their structural similarities, while the differences account for their structural variations, thereby providing opportunities to engineer novel analogues,' explains Shen.



Modifying the gene cluster responsible for zorbamycin could lead to bioactive analogues

But the new knowledge could have implications beyond new zorbamycin analogues – it could be exploited to prepare analogues on a larger scale. 'Bleomycin is an important anticancer agent that is used clinically for treatment of testicular cancer – the disease that cyclist Lance Armstrong recovered from,' comments Timothy Bugg, professor of biological chemistry at the University of Warwick, UK. 'But its large scale production is hampered by the yield of the natural product from the producing organism,' he explains. 'The isolation of further strains of *Streptomyces* able to produce compounds in this class offers the possibility of improving the yield of natural product by genetic manipulation, an application of biotechnology that could literally save lives in the clinic.'

Russell Johnson

Reference
U Galm *et al*, *Mol. BioSyst.*, 2009, DOI: 10.1039/b814075h

In the current issue of Research Articles...

Plant MTs—long neglected members of the metallothionein superfamily
Eva Freisinger, *Dalton Trans.*, 2008, 3782 (DOI: 10.1039/b809789e)

Towards quantitative predictions in cell biology using chemical properties of proteins
Michele Vendruscolo and Gian Gaetano Tartaglia, *Mol. BioSyst.*, 2008, **4**, 1170 (DOI: 10.1039/b805710a)

Novel strategies for the site-specific covalent labelling of nucleic acids
Samuel H Weisbrod and Andreas Marx, *Chem. Commun.*, 2008, 5675 (DOI: 10.1039/b809528k)

Chemical analogues relevant to molybdenum and tungsten enzyme reaction centres toward structural dynamics and reaction diversity
Hideki Sugimoto and Hiroshi Tsukube, *Chem. Soc. Rev.*, 2008, **37**, 2609 (DOI: 10.1039/b610235m)

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Thota Jyotsna *et al*, *Photochem. Photobiol. Sci.*, 2008, **7**, 1531 (DOI: 10.1039/b810422k)

Read more at www.rsc.org/chembiology

Interview

Integrative biology

Mina Bissell talks to Kathleen Too about the concept and future of integrative biology

Mina Bissell

Mina Bissell is Distinguished Scientist at the Lawrence Berkeley National Laboratory (LBNL). She is a world leader in cancer research and the recipient of numerous awards including the 2007 Pezcoller-AACR International Award in cancer research, the 2008 American Cancer Society's Medal of Honor and the Excellence in Science Award from the Federation of American Societies for Experimental Biology. Dr Bissell is chair of the editorial board of the RSCs new journal *Integrative Biology*.

How would you define integrative biology?
In order to better understand biology, where more and more complexity is unravelled, we need novel, intricate technologies. Usually, these technologies are developed by people who have not studied biological problems in depth. In turn, biologists are unfamiliar with what could actually be out there to help them answer the complex and exciting questions they are trying to solve. The time has come to bring technology to the service of biology. Integrative biology is that synergy of interdisciplinary skills to work towards solving a common biological problem. My hope is that there will be many integrative biology departments and institutes in the near future to encourage computational biologists, bioengineers, physicists, mathematicians, theoreticians and chemists to work together with cell-, molecular-, evolutionary- and cancer-biologists to answer emerging biological questions.

***Integrative Biology* is a new RSC journal to be launched in January 2009. Why is there a need for the journal?**
Integrative Biology will be a good forum to emphasize the synergy between biology and technology. The journal is going to be partial to papers that address an important biological problem using novel technologies; however, we do not want to be just a technology journal or a biology journal. We want to integrate these fields within each article.

A lot of journals write about different disciplines separately. Then there are the journals, like *Nature* and *Science,* that address all fields within their pages, but the articles themselves do not necessarily integrate these disciplines. I feel that there is now recognition that this kind of divide does not move biology forward. Biologists need to work with people from other disciplines to look at biological problems from a fresh perspective. This is why I believe that the field is ready for a journal like *Integrative Biology.*

How has your research led to the conclusion that technology needs to work hand in hand with biology?
Coming from a background of chemistry and bacterial genetics into research of higher organisms, I could see as early as the 1970s that to make real progress in biology, we would need to do more multidisciplinary research. We have looked into the concept of a relationship between tissue architecture and function by producing more and more high throughput work (what people refer to these days as 'systems biology') and have utilised novel technologies to answer some intriguing questions. One exciting and recent example of this kind of work from my laboratory will appear in the first issue of *Integrative Biology*.

Mark LaBarge, the first author of our paper, developed a combinatorial micropattern using special technology developed by Celeste Nelson to determine the conditions giving rise to specific daughter cells in 8000 cases at once. In the breast, there are two types of epithelial cells: luminal epithelial cells (the cells that produce milk and get cancer) and myoepithelial cells (those that control the movement of epithelial cells and surround the luminal epithelial cells). We found out the probability of cells becoming luminal or myoepithelial or remaining as precursor/stem cells. We used imaging and other technologies to determine which pathways and molecules were involved in determining whether a cell would be luminal, myoepithelial or precursor. These conclusions would not have been possible without the integration of these modern technologies and biology.

What does the future hold for integrative biology?
More departments and centres where people from different disciplines can work together will be established. Instead of having separate physiology, cell biology and molecular biology departments, for example, one would have a department of integrative biology. Granting agencies like the US National Institutes of Health are thinking of setting up interdisciplinary centres across the US to bring these fields together. The National Cancer Institute, for example, has issued a call for proposals to set up four to six interdisciplinary centres that would bring physicists, mathematicians, bioengineers and chemists together with cancer biologists to carry out cancer research. The time is ripe. Integrative biology is here to stay.

Interview

An analytical diagnosis

May Copsey talks to Maria Montes-Bayón about solving medical science problems and how analytical scientists must take the next big step

Maria Montes-Bayón

Maria Montes-Bayón is an associate professor at the University of Oviedo in Spain and a member of the *Metallomics* and *Journal of Analytical Atomic Spectrometry* advisory boards. Her research interests include elemental speciation studies of clinical biomarkers and metals in biological systems, using both atomic and molecular mass spectrometry.

What inspired you to become a chemist?

I was laughing about this the other day when someone asked me: 'Did you have a chemistry set when you were younger?' I really did have one! My father's company would give presents to the children every Christmas. One year we were too late to pick our presents and the only things left were chemistry sets, so I had one whether I wanted it not! But I was really amazed with it and it was my first step into chemistry. When I took chemistry in high school, I realised I was an experimentalist: I liked the creative side. I would never be a theoretician or a physical chemist.

What are the most exciting projects in your lab?

I'm really interested in clinical biomarkers at the moment and we plan to go further in that direction. Unfortunately, when you read the literature or study current methods for the measurement of clinical biomarkers, often they are not validated or even that rigorous. So I think that we can contribute a lot in this area. We are about to start a project to measure ferritin. Analysis of ferritin is a routine blood test measurement, which gives an idea of the iron deposits in an organism. Whilst not alone, it is one of the most frequently measured parameters. We are planning on developing a method that can allow us to detect ferritin at low levels and also to quantify it, which is another key issue. We can then compare our results with those provided by established methods. In fact, we are collaborating in the development of a certified reference material for ferritin. Clinicians recognise that they need this reference material for validating their methodologies, and so are asking us to do it by elemental mass spectrometry.

So is it a case of selling these analytical methods to medical science?

Exactly, not that I think they would use them on a regular basis; however, we can develop some methods that could be very useful to validate their clinical measurements. For example, recently we examined the validation of a method for measuring glycated haemoglobin. We are also working on cisplatin adducts with DNA, to see if we can predict if somebody will be resistant to an anticancer drug before they undergo trials. Medical scientists do not need to understand exactly what we do, but my goal is to help solve some problems for them.

Do you see the future of this area as a combination of molecular and atomic mass spectrometry?

It started off as a possibility and now I think that it is almost a must. Sometimes you cannot use both techniques. We have to keep in mind that the detection levels or the purity of the sample required are often completely different. For a long time we have been developing good speciation methods and I think it is time that we show that we can use them in real-life samples. This is the goal of analytical chemistry. Once these methods have been developed, we should use them and find a forum where they are needed and valued. Communication is the key. We need more cross-linking opportunities with other fields. This is why the conference in Japan (2007 International Symposium on Metallomics) and the next one in Cincinatti in 2009 are a great idea and will be a great forum to bring together people from different fields.

How do you come up with your ideas of research areas to study?

I read analytical journals, but I often need to check on clinical or biological chemistry. However, there is no specific journal that publishes clinical parameters of interest. I normally choose clinical parameters that I think we can study in a better or different way to complement the clinical science. Additionally, we collaborate with the University Hospital and with the Oncology Institute here in Oviedo and this gives you a closer idea of what doctors and clinical chemists are demanding from us. When you are from the analytical field, it's very difficult to persuade doctors that you can provide useful methods to help them to interpret their biological results, but little by little, we are convincing them. You always need this sort of connection.

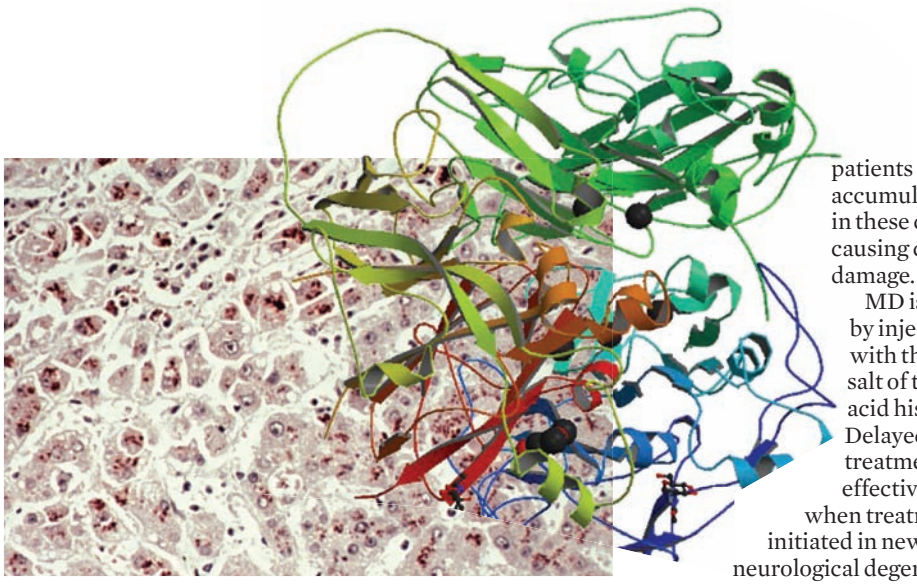
What do you like to do when you're not doing chemistry?

I'm a singer and I play the guitar a little, but just for friends. Sometimes I come home with my head full of concerns about experiments or teaching issues and then I take my guitar, close the door, and sing for half an hour. Then I'm ready to "rock and roll" again.

Instant insight

A delicate balance

Hiroko Kodama and Chie Fujisawa at the Teikyo University School of Medicine, Tokyo, Japan, weigh up why copper regulation is so crucial in the body



A mutation in gene *ATP7B* in Wilson's disease results in low levels of ceruloplasmin (right) and excess copper being deposited in the liver

All living organisms need copper. It is an integral component of many enzymes, from the respiratory enzyme cytochrome c oxidase to the copper-carrying ceruloplasmin, which plays an important role in iron metabolism. But, in excess, copper can result in the generation of reactive free radicals, leading to cellular damage. The body's tight regulation of copper levels – by adjusting its uptake, transport, storage and excretion – is therefore essential.

Disruption of this regulation is evident in three human genetic disorders: Menkes disease (MD), occipital horn syndrome (OHS) and Wilson's disease (WD). MD is a copper-deficiency disorder, which affects around 1 in every 140000 males. Typical features of the disease include neurological disturbances, connective tissue disorders, and hair abnormalities, and can be explained by the abnormally low activity of copper-dependent enzymes. The neurological disturbances, which become prominent from the age of 2, are severe and most patients die by the age of 3 years. The connective tissue disorders, including arterial abnormalities and osteoporosis, are also severe, and patients can suffer from internal bleeding and bone fractures. OHS is a rarer and milder form of MD characterised by connective tissue abnormalities.

WD affects around 1 in every 30000–35000 people. In contrast to MD and OHS, WD is characterised by a copper excess and symptoms are due to the toxic effects of chronic exposure to the metal. In typical cases, the liver and nervous systems are most severely affected. Symptoms include chronic or acute hepatitis, cirrhosis and liver failure; other symptoms, such as arthritis and anemia, can make an early diagnosis difficult.

All three diseases result from the absence or dysfunction of copper-transporting proteins due to genetic mutation. The gene mutated in MD and OHS is *ATP7A*, while *ATP7B* is mutated in WD. Both proteins encoded by these genes facilitate copper transport from the cell fluid to the Golgi apparatus, where the cell processes macromolecules such as proteins and lipids. In cells with compromised ATP7A/B protein function, copper remains in the cell fluid and cannot be excreted.

The difference in effect results from the specific cell types that make ATP7A or ATP7B proteins. ATP7A functions in almost all cells, so for patients with MD and OHS, when copper from the diet is absorbed by intestinal cells, it cannot be expelled and it accumulates, leading to a deficiency elsewhere in the body. ATP7B functions in hepatocytes – the cells that make up the majority of the liver – and in WD patients copper accumulates in these cells causing cell damage.

MD is treated by injection with the copper salt of the amino acid histidine. Delayed treatment is less effective but when treatment is initiated in newborns, neurological degeneration can be prevented, meaning early screening is of great importance. Copper–histidine does not improve symptoms associated with the connective tissue disorders, however, and therapies directed towards these need to be developed simultaneously. OHS patients typically are treated in a similar manner to those with MD.

For WD, while chelating agents and zinc are effective treatments, they are ineffective in patients with liver failure, for whom a liver transplant is the most appropriate option. Some patients with neurological diseases can show poor response to chelating agents and zinc and others may show poor compliance with drug treatment. Moreover, WD patients may be at risk of liver cancer and a better understanding of the relationship between WD and cancer is an important problem that needs to be solved in the future.

Read more in Hiroko Kodama and Chie Fujisawa's critical review 'Copper metabolism and inherited copper transport disorders: molecular mechanisms, screening, and treatment' in Metallomics.

Reference
H Kodama and C Fujisawa, *Metallomics*, 2009, DOI: 10.1039/b816011m

Essential elements

Double debut

This month sees the debut of two highly interdisciplinary new journals from RSC Publishing: *Integrative Biology: Quantitative biosciences from nano to macro* and *Metallomics: Integrated biometal science*.

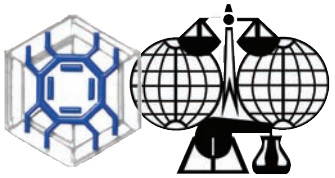
Integrative Biology is a unique journal focused on quantitative multiscale biology using enabling technologies and tools to exploit the convergence of biology with physics, chemistry, engineering, imaging and informatics. The first issue contains articles on human mammary progenitor cell fate decisions, the analysis of aptamer binding sequence–activity relationships using microarrays, and genome-wide transcriptome analysis of 150 cell samples and much more. Visit www.rsc.org/ibiology

Metallomics covers the research fields related to metals in biological, environmental and clinical systems and is expected to be the core publication for the emerging metallomics community. First issue articles include a look at the effect of vanadium(IV) in diabetic mice, cytotoxicity of chemical warfare degradation products, and identification and characterisation of metallodrug binding proteins. Visit www.rsc.org/metallomics

Authors from around the globe have submitted work of the highest quality, knowing that they can rely on RSC staff for overseeing a rigorous peer-review process, efficient manuscript handling and rapid publication.

The current issues of both new journals are freely available to all readers via the website. Free institutional online access to all 2009/2010 content will be available following a simple registration process.

InChI collaboration with ChemSpider



An InChI Resolver, a unique free service for scientists to share chemical structures and data, is to be developed via a collaboration between ChemZoo Inc., host of ChemSpider, and RSC Publishing.

Using the InChI – an IUPAC standard identifier for compounds – scientists can share, contribute and search molecular data from many web sources.

The InChI Resolver will give researchers the tools to create standard InChI data for their own compounds, create and use search engine-friendly InChIKeys to search for compounds, and deposit their data for others to use in the future.

'The wider adoption and unambiguous use of the InChI standard will be an important development for the future of chemistry publishing, and further development of the semantic web,' comments Robert Parker, managing director of RSC Publishing.

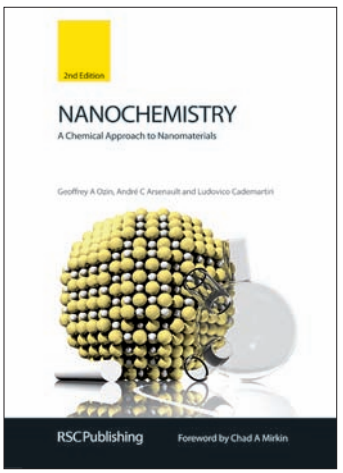
The InChI Resolver will be based on ChemSpider's existing database of over 21 million chemical compounds and will provide the first stable environment to promote the use and sharing of compound data. 'With the introduction of the InChI Resolver, we hope to expand the utility and value of both InChI and the ChemSpider service,' adds Antony Williams of Chemspider.

This collaboration sees RSC Publishing remain at the forefront of chemical information technology.

And finally...

Materials science researchers joined RSC Publishing last month at a celebration reception at the Fall MRS 2008 meeting. Authors and readers were thanked for their continued support, while RSC journal *Soft Matter* announced its increase in frequency for 2009 and five years of successful publication.

Delegates were invited to pre-order the latest edition of the bestselling textbook, *Nanochemistry* by Geoff Ozin, and take part in a prize draw to win a solar powered charger in celebration of the 2008 launch of *Energy & Environmental Science*.



Looking ahead, preparations are underway for the Third International *ChemComm* Symposium, which is to be held in China next month. The subject will be organic chemistry and keynote speakers include Professors Peter Kundig, Keiji Maruoka and Susan Gibson.

To find out more visit: www.rsc.org/chemcommsymposia

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