# **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(13) 2657-2820 (2009)



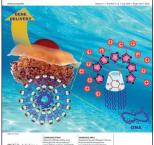


**Cover** See Ahmed M. Zaed *et al.*, pp. 2678–2680. Asymmetric synthesis of the tropane alkaloid (+)-physoperuvine from *Physalis peruviana* Linne (background) *via* 

a one-pot tandem rearrangement and ring closing metathesis reaction. Background photograph reproduced with permission from Christine Ashe.

Image reproduced by permission of Andrew Sutherland from *Organic & Biomolecular Chemistry*, 2009, **7**, 2678.





#### Inside cover

See Alejandro Méndez-Ardoy et al., pp. 2681–2684. Jellyfish-like polycationic amphiphilic cyclodextrins assembled by click chemistry efficiently compact plasmid DNA, forming nanometric complexes (CDplexes) with remarkable gene delivery capabilities.

Image reproduced by permission of José M. García Fernández from *Organic & Biomolecular Chemistry*, 2009, **7**, 2681.

#### CHEMICAL BIOLOGY

#### B49

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**

#### July 2009/Volume 4/Issue 7

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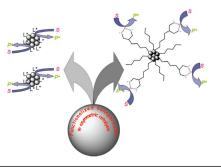
#### **EMERGING AREA**

#### 2669

### Functionalized nanoparticles as catalysts for enantioselective processes

Sarabindu Roy and Miquel A. Pericàs\*

Functionalized nanoparticles find increasing application as catalysts for enantioselective transformations. In this account the different strategies followed for the preparation of chirally modified nanoparticles and their application in asymmetric catalysis are reviewed.



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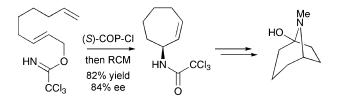
Royal Society of Chemistry: Registered Charity No. 207890

#### 2678

# A stereoselective synthesis of (+)-physoperuvine using a tandem aza-Claisen rearrangement and ring closing metathesis reaction

#### Ahmed M. Zaed, Michael D. Swift and Andrew Sutherland\*

A one-pot tandem process has been developed for the asymmetric synthesis of the tropane alkaloid, (+)-physoperuvine.



#### 2681

#### Preorganized macromolecular gene delivery systems: amphiphilic β-cyclodextrin "click clusters"

Alejandro Méndez-Ardoy, Marta Gómez-García, Carmen Ortiz Mellet,\* Natalia Sevillano, M. Dolores Girón, Rafael Salto,\* F. Santoyo-González and José M. García Fernández\*

Polycationic amphiphilic cyclodextrins featuring segregated amine and fatty ester domains, a new family of discrete and well-characterized macromolecular nucleic acid vehicles, have been built by Cu(I)-catalyzed azide-alkyne coupling (click chemistry).

#### 2685

#### Mechanistic insight into TEMPO-inhibited polymerisation: simultaneous determination of oxygen and inhibitor concentrations by EPR

Marco Conte, Yun Ma, Colin Loyns, Peter Price, David Rippon and Victor Chechik\*

Convolution-based fitting of EPR spectra makes it possible to simultaneously determine concentrations of TEMPO and oxygen in TEMPO-inhibited polymerisations and autoxidations; this method is useful for understanding the chemistry of inhibitor mixtures.

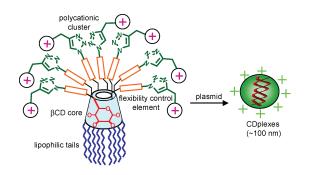
#### PAPERS

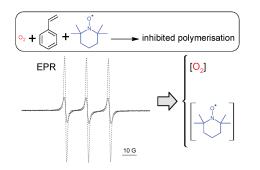
#### 2688

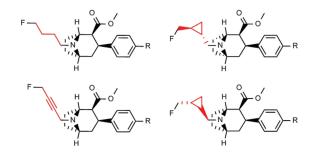
#### Synthesis and monoamine uptake inhibition of conformationally constrained 2β-carbomethoxy-3β-phenyl tropanes

Patrick Johannes Riss,\* René Hummerich and Patrick Schloss

A series of novel phenyl tropanes have been prepared from natural cocaine as potential selective DAT-ligands. These compounds were tested for monoamine uptake inhibition in HEK293 cell lines.









# Drug Delivery Summit

2 - 4 September 2009 London, England

The summit includes three one-day symposia on the following subjects:

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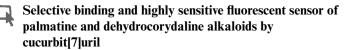
#### Agenda Topics:

- Image Guided Delivery Systems
- Delivery Systems for Nucleic Acid
- Delivery of Peptide and Protein Therapeutics

#### DRUGDELIVERYSUMMIT.COM



#### 2699



Chunju Li,\* Jian Li and Xueshun Jia\*

Palmatine (P) and dehydrocorydaline (DHC) alkaloids exhibit dramatic fluorescence enhancement upon complexation with cucurbit[7]uril (CB7), and the intensity of the emittance is strong enough to be readily distinguished by the naked eye.

#### 2704

#### Poly(1,1-bis(dialkylamino)propan-1,3-diyl)s; conformationally-controlled oligomers bearing electroactive groups

Roger W. Alder,\* Niall P. Hyland, John C. Jeffery, Thomas Riis-Johannessen and D. Jason Riley

The preparation, structure, and electrochemistry of oligomers (up to the hexamer) containing 1,8-bis(methylamino)naphthalenes is reported.

#### 2716

#### Quantum mechanics/molecular mechanics investigation of the mechanism of phosphate transfer in human uridine-cytidine kinase 2

Adam J. T. Smith, Ying Li and K. N. Houk\*

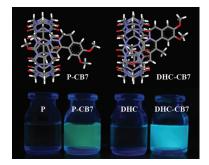
A concerted transition state for UCK2 phosphate transfer was obtained from QM/MM computations.

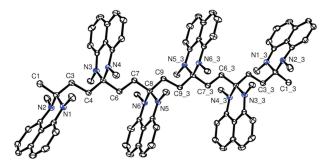
#### 2725

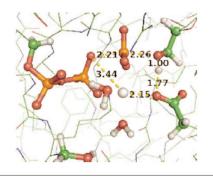
#### A fluorescent cyclotriveratrylene: synthesis, emission properties and acetylcholine recognition in water

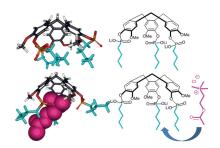
Marie-Laurence Dumartin, Cécile Givelet, Pierre Meyrand, Brigitte Bibal\* and Isabelle Gosse\*

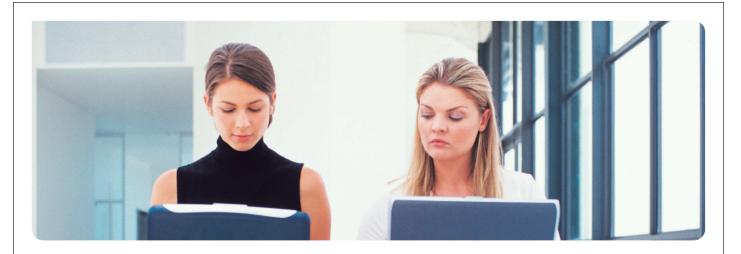
A fluorescent cyclotriveratrylene **1** was synthesized and characterized in water. Soluble in physiological media, compound **1** has binding properties towards acetylcholine. This detection is direct, contrary to most fluorescent systems.











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#### 2729

#### Design and synthesis of novel hybrid metal complex-DNA conjugates: key building blocks for multimetallic linear DNA nanoarrays

Sumana Ghosh, Isabelle Pignot-Paintrand, Pascal Dumy and Eric Defrancq\*

The synthesis of novel metal complex–ODN conjugates is described. Hybridization of two complementary bis-ODN tethered metal complexes at a 1 : 1 ratio gave rise to a self-assembled nanometric linear network, which was characterized by non-denaturing gel electrophoresis and TEM studies.

#### 2738

#### Glycosidase inhibition by ring-modified castanospermine analogues: tackling enzyme selectivity by inhibitor tailoring

Matilde Aguilar-Moncayo, Tracey M. Gloster, Johan P. Turkenburg, M. Isabel García-Moreno, Carmen Ortiz Mellet, Gideon J. Davies\* and José M. García Fernández\*

Synthesis of a panel of iso(thio)urea-type ring-modified castanospermine analogues bearing a freely mutarotating pseudoanomeric hydroxyl group results in tight-binding  $\beta$ -glucosidase inhibitors with unusual binding signatures.

#### 2748

#### 1,3,4,6,7,9-Hexamethylbenzo[1,2-*c*:3,4-*c*':5,6*c*'']trithiophene: a twisted heteroarene

Yao-Ting Wu,\* Chia-Cheng Tai, Wei-Chih Lin and Kim K. Baldridge\*

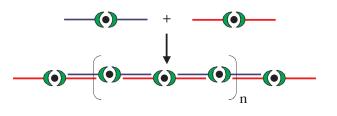
The twisted structure of 1,3,4,6,7,9-hexamethylbenzo-[1,2-c:3,4-c':5,6-c'']trithiophene is confirmed by X-ray crystal analysis. This compound has the [6]radialene character. The central "cyclohexane ring" lacks aromaticity and the conjugation between any adjacent thiophene rings is low.

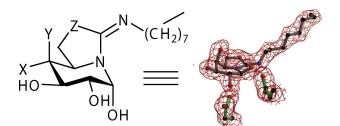
#### 2756

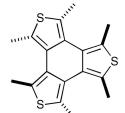
### Allosteric effects in a tetrapodal imidazolium-derived calix[4]arene anion receptor

Charlotte E. Willans, Kirsty M. Anderson, Lydia C. Potts and Jonathan W. Steed\*

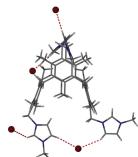
A novel 1,3-alternate calix[4]arene based imidazolium anion receptor exhibits multiple  $CH \cdots$  anion interactions accompanied by unusual allosteric behaviour in the binding of a second anion.



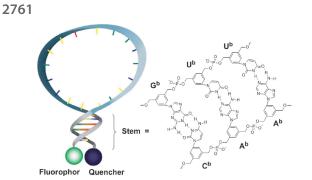


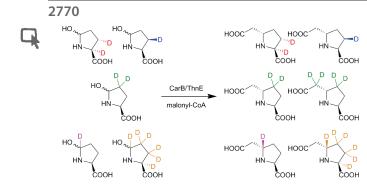






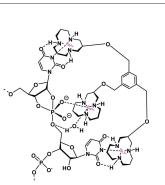




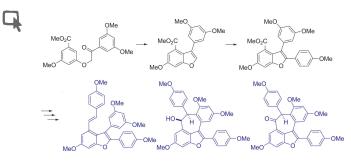


2780

Q



2788



#### Synthesis and properties of a novel molecular beacon containing a benzene-phosphate backbone at its stem moiety

Yoshihito Ueno,\* Akihiro Kawamura, Keiji Takasu, Shinji Komatsuzaki, Takumi Kato, Satoru Kuboe, Yoshiaki Kitamura and Yukio Kitade\*

Synthesis and properties of a novel molecular beacon containing a benzene-phosphate backbone at its stem moiety are described.

# Synthesis of regio- and stereoselectively deuterium-labelled derivatives of L-glutamate semialdehyde for studies on carbapenem biosynthesis

Christian Ducho, Refaat B. Hamed, Edward T. Batchelar, John L. Sorensen, Barbara Odell and Christopher J. Schofield\*

A set of selectively labelled derivatives of L-glutamate semialdehyde were synthesised and converted into labelled *trans*-carboxymethylprolines using the carboxymenthylproline synthases CarB and ThnE from carbapenem biosynthesis.

#### Base moiety selectivity in cleavage of short oligoribonucleotides by di- and tri-nuclear Zn(II) complexes of azacrown-derived ligands

Maarit Laine, Kaisa Ketomäki, Päivi Poijärvi-Virta\* and Harri Lönnberg

Di- and trinuclear  $Zn^{2+}$  complexes of 1,5,9-triazacyclododecane have been used to modulate RNA phosphodiester cleavage by simultaneous interaction with the base and phosphate moieties at oligonucleotide level, *i.e.* in the presence of a plethora of binding sites.

#### A versatile approach to oligostilbenoid natural products – synthesis of permethylated analogues of viniferifuran, malibatol A, and shoreaphenol

Ikyon Kim\* and Jihyun Choi

A versatile approach to oligostilbenoid natural products is described, to give permethylated analogues of viniferifuran, malibatol A, and shoreaphenol.

#### 2796

#### A new entry to phenanthridine ring systems *via* sequential application of Suzuki and the modified Pictet-Spengler reactions

Anil K. Mandadapu, Mohammad Saifuddin, Piyush K. Agarwal and Bijoy Kundu\*

A mild, efficient and versatile method has been developed for the two step synthesis of phenanthridine ring systems. It involves the synthesis of a substrate in which an aryl amine is tethered to an activated arene ring at the carbon ortho to the activated carbon nucleophile, facilitating the formation of a phenanthridine ring via  $\pi$ -cyclization.

#### 2804

#### Facile two-step synthesis of 3-substituted indazoles using diazo(trimethylsilyl)methylmagnesium bromide

Yoshiyuki Hari,\* Ryosuke Sone and Toyohiko Aoyama\*

Diazo(trimethylsilyl)methylmagnesium bromide readily reacted with various ketones and aldehydes to give the corresponding 2-diazo-(2-trimethylsilyl)ethanols. These were efficiently converted to indazoles bearing hydroxymethyl units at the 3-position by intermolecular [3 + 2] cycloaddition with benzynes.

#### 2809

#### A straightforward microwave method for rapid synthesis of N-1, C-6 functionalized 3,5-dichloro-2(1H)-pyrazinones

Johan Gising, Pernilla Örtqvist, Anja Sandström and Mats Larhed\*

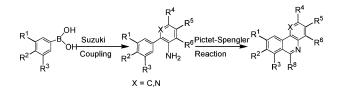
A fast microwave protocol for the preparation of N-1 and C-6 decorated 3,5-dichloro-2(1H)-pyrazinones was developed. The protocol was used to synthesize two novel 2(1H)-pyrazinone-containing Hepatitis C virus NS3 protease inhibitors.

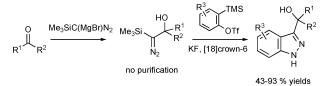
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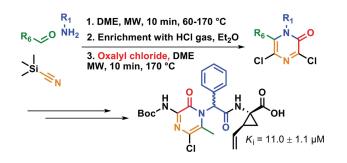
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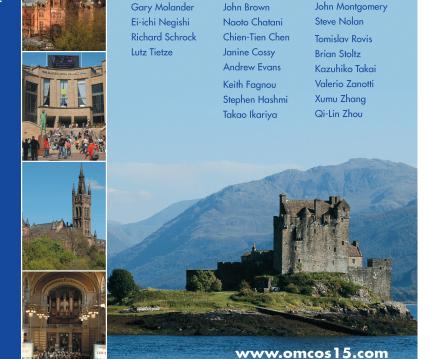
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David Milstein

#### I 5TH IUPAC INTERNATIONAL SYMPOSIUM ON ORGANOMETALLIC CHEMISTRY DIRECTED TOWARDS ORGANIC SYNTHESIS (OMCOS I 5)

26th - 30th July 2009, Glasgow



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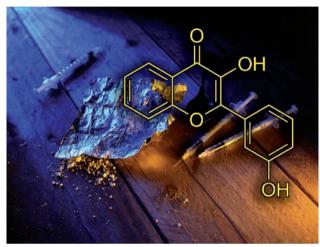
# **Chemical Biology**

# Inhibiting enzymes in the brain could provide treatment for drug addicts **Forget drugs, get inhibited!**

Promising compounds which may help patients overcome drug addictions have been identified by US and Korean scientists.

Drug abuse causes long-term chemical changes in the brain which remain many years after the abuse has stopped. These changes maintain a 'memory' of the addiction, leaving patients vulnerable to relapse. Recently researchers at Duke University, North Carolina, have found that an enzyme usually present in the brain, PKC- $\zeta$ , appears in increased concentrations in cocainesensitised rats, suggesting that it plays a role in this memory process.

Jiyong Hong and colleagues at Duke University and the Korea Research Institute of Chemical Technology, Daejeon, intend to develop therapeutic compounds that target this enzyme to help people 'forget' their drug dependence. 'A patient has some memory of using a drug,' explains Hong, 'and we aim to erase that memory by inhibiting PKC-ζ.' This



poses a significant challenge, says Hong, since compounds that can selectively target specific forms of PKC are rare.

Undeterred by this, and passionate about the social impact of this work, the team tested over 1000 different compounds for their ability to inhibit PKC- $\zeta$  function and found three suitable

Benzopyranone compounds have been identified as possible therapeutics for drug dependency

Reference L Yuan *et al, Mol. BioSyst.*, 2009, DOI: 10.1039/ b903036k benzopyranone candidates. They then used computer modelling to determine the interactions behind the compounds' inhibitory activity. With this knowledge, Hong aims to subject these compounds to a process of directed evolution: creating a library of compounds based upon this scaffold and selecting those compounds which show enhanced activity as the bases of new libraries.

Nathanael Gray, an expert in PKC function at Harvard University, Massachusetts, US, agrees that these results represent a promising start. However, he emphasises the need to 'know about cellular activity and the broader selectivity profile versus other enzymes given that this scaffold is capable of having numerous other activities.'

Hong is also well aware of this. 'We now want to expand the enzyme panel to see just how selective the compounds are and to optimise the potency and selectivity before, ultimately, performing an in vivo study,' he says. *Philip Robinson* 

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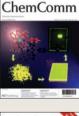
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This month's Instant insight examines how antidepressants reach their target

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









# **Research highlights**

Cell membranes removed to probe their physical properties **Pulling membranes off cells** 

German scientists are ripping cells apart to study their elasticity.

Elasticity allows a cell to perform many fundamental processes, such as migration, adhesion and interaction. Investigating how a cell's individual components contribute to its overall elasticity is therefore of vital interest for scientists trying to understand how these processes work. However, gauging the membranes' contribution has proved to be difficult, in particular at smaller than micrometre length scales.

Andreas Janshoff at the University of Gottingen and colleagues have now developed a method to trap cell membranes so that their elastic properties can be mapped. The researchers attach epithelial cells to a surface before placing a polymercoated porous chip on top of the cells. On lifting off the chip, the membranes stick to its poly-D-lysine coating, leaving behind the rest of the cell. The group can then perform atomic force microscopy experiments on the



Gauging the membrane's contribution to elasticity has proved challenging

membranes to obtain quantitative stress-strain measurements.

Importantly, the membrane fragments are from the apical side of the cells. Since epithelial cells are polar, the two membrane segments apical and basolateral - may behave differently. But whilst in earlier work the researchers were able to isolate membranes from the basolateral side. this is the first time they have been able to study the apical membrane away from the rest of the cell.

T Fine et al, Soft Matter, 2009, DOI: 10.1039/b901714c

Reference

Janshoff suggests that the method is an improvement over existing

elasticity measuring techniques. 'To assess the properties of lipid bilayers, mainly non-local methods have been used,' he says. These include indentation and aspiration of giant liposomes, a method in which cell membrane models are poked to measure their response. 'Now, mechanical information can be accessed from cell membrane fragments on nanometre length scales,' Janshoff explains.

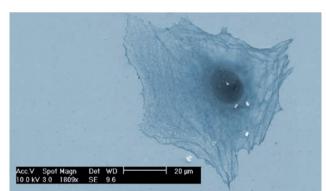
Markus Deserno, associate professor of physics at Carnegie Mellon University, Pittsburgh, US, agrees that this is a step forward. 'Cell membranes are fascinating objects that keep surprising us," he says. 'This work shows how suspected links between chemistry, thermodynamics and elasticity can be probed quantitatively. Such experiments are challenging, both in terms of execution and analysis, but they promise deeper and more quantitative insights than existing indentation tests.' Edward Morgan

# Stainless steel film brings bonus beneficial effect on cell growth Implant coating with potential

Researchers in Canada have found that a way to make medical implants last longer makes them more biocompatible than at first thought.

Stainless steel is often used in, for example, joint replacements, because it is cheap and corrosion resistant. Nevertheless its implants are not as long-lived in the body as those made of other materials, such as titanium or titanium alloys, so researchers have looked at modifying implant surfaces to make them more biocompatible.

Previously, Sasha Omanovic and coworkers at McGill University, Montreal, have shown that electrically modifying the surface of stainless steel implants can increase their lifespan. Using a form of cyclic voltammetry known as cyclic potentiodynamic passivation (CPP) the researchers can produce a film laver on the surface of stainless steel which is resistant to corrosion under



**Cells are better attached** and more spread out on **CPP-modified surfaces** 

Reference

A Shahryari et al, Phys. Chem. Chem. Phys., 2009, DOI: 10.1039/b902881a

physiological conditions. In their latest work, they have found the technique has further advantages. Omanovic explains that 'CPP influences the surface concentration and structure of the cell-binding protein fibronectin which leads to a healthier morphology of boneforming cells.'

The heart disease applications are

particularly important. Often after heart surgery an artery that has been widened can narrow again, a process called restenosis. For coronary stents, which are used to keep open these arteries, stainless steel is the preferred material. Omanovic suggests that CPP 'could be used to treat the surface of the stents currently in use, and thus decrease the restenosis rate and the need for re-implantation.'

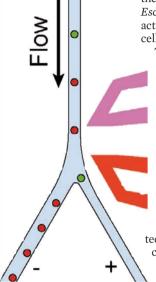
Omanovic points out that fundamental challenges remain to be tackled. 'The origin of the improved protein-cell-surface interactions we report is not completely understood,' he says. 'This requires further studies, especially on the influence of the surface properties, such as charge, wettability, and topography, on fibronectin's conformation, and how this influences the interactions of various cells with the surface.' Colin Batchelor

# Enzyme activity assists microfluidic droplet sorter to separate cells **Cell sorting sorted**

Catching cells in droplets has enabled scientists to make a highly efficient microchip for cell sorting.

Andrew Griffiths, at the University of Strasbourg. and colleagues in the US and France have improved on an established technique for sorting cells. Fluorescence-activated cell sorting (FACS) separates mixtures of cells into different containers based on the tagging of cell-surface proteins. Griffiths' microfluidic system uses a similar approach but in the new fluorescence-activated droplet sorting (FADS) method, each cell is trapped in an individual aqueous droplet, instead of being in a continuous stream of liquid as in FACS. The droplets then flow over the microfluidic chip, which sorts each one according to the enzyme activity of the cell inside.

To show the technique's potential,



Fluorescent droplets are deflected at a junction

the researchers used a mixture of Escherichia coli cells expressing an active galactosidase enzyme and cells expressing an inactive enzyme.

The cells were captured in

droplets containing a substrate that fluoresces when acted on by the active enzyme. This meant that only the active cells became fluorescent and that their corresponding droplets could be identified. A highspeed computer is programmed to recognise the fluorescent droplets, feeding back to the chip, which collects them and so the cells containing the active enzyme - separately. The technique is simple, inexpensive and can be used for high-throughput applications.

This is the first time the droplet and microfluidic approaches have been combined for this use. Charles Baroud, an expert in multiphase flows in microfluidic devices at the Polytechnic School in Palaiseau, France, commends this approach. While the individual basic operations have already been demonstrated, their integration has added tremendous complexity. Studies such as this are instrumental in the development of truly useful droplet-based lab-on-a-chip devices,' he savs.

Griffiths says that in future work the team will try to put different microfluidic operations on the same chip to select cells with multiple optimised properties. 'This would enable cell selections that are currently impossible to do,' he comments. He says he hopes that this will allow the chips to be useful for industrial and biomedical applications. Roxane Owen

Reference

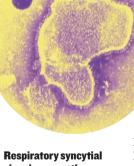
J-C Baret et al, Lab Chip, 2009, DOI: 10.1039/ b902504a

# Sensitive approach allows naked eye detection of respiratory virus A beacon of hope for childhood infection

Although treatable, respiratory syncytial virus (RSV) results in the deaths of over one million children annually as its late detection renders antivirals ineffective. Now US researchers have created a tool to detect small amounts of the virus simply and quickly.

David Wright's group at Vanderbilt University, Nashville, has developed a probe that can detect RSV RNA in infected cells with approximately 200 times greater sensitivity than existing techniques, potentially making early diagnosis of infection possible.

Wright's method is adapted from existing filament-based antibody recognition (FARA) assay technology. FARA uses probes consisting of a polyester filament with antibodies for specific pathogens bound to its surface. When the filament is exposed to infected cell lysates, the antibodies bind to pathogens in the sample. The filament-pathogen complexes can then be analysed using fluorescent



virus is among the four most common respiratory viruses in humans

#### Reference

J W Perez, F R Haselton and D W Wright, Analyst, 2009, DOI: 10.1039/b904191e

reporters, allowing pathogen detection. Wright's probe avoids the need for the separate analysis step by incorporating its own fluorescent reporter.

Unlike FARA filaments, the new probe's filament is gold clad and, rather than antibodies, is attached to one end of a length of DNA that has a fluorophore at the other end.

The DNA is complementary to a repeated sequence found in RSV RNA. In the absence of this RNA, the DNA adopts a hairpin conformation, which brings the fluorophore and the gold filament close together. The gold acts as a quencher, preventing the fluorophore fluorescing. When the probe is exposed to RSV RNA in infected cell lysates, it opens into a straight conformation to bind to the RNA. This creates distance between the fluorophore and the gold filament quencher, resulting in fluorescence.

Wright suggests that advantages over existing viral detection

methods could make widespread implementation of the beacon a real possibility. 'Most gold standard approaches [for example culturing the virus or amplifying its DNA] take anywhere from one to four days in a clinical setting,' he says. 'We are hoping that the proven processing capability of this technology will significantly reduce this time. Additionally, the results demonstrate a sensitivity and ease of use that one day may make the platform amenable to point of care applications.'

Jenny Handforth, a general paediatric consultant and expert in infectious diseases, at the Mayday Hospital, Croydon, UK, agrees. 'If the potential for simplification is realised, then coupled with the sensitivity data this could be an exciting tool,' she says. 'Of course, its usefulness needs to be shown in clinical samples,' she adds. 'If such results are demonstrated then it could become an important adjunct in RSV infection diagnosis.' Katie Dryden-Holt

# Microfluidics separates bacteria to make detecting slow-growing species easier **Culturing rare microbes**

Getting microbes such as *Escherichia coli* to grow may be 'easy' enough, but what if you want to amplify the rarer, slower-growing species within a microbe mixture? US biochemists are using microfluidics to do just this.

Microbe mixtures occur widely in nature, from soils and oceans to animals, making studying them of interest in several scientific fields. Led by Rustem Ismagilov, a team at the University of Chicago has developed an approach to analyse such mixtures. The method involves mixing an aqueous cell suspension with an organic solvent. This mixture is passed through a series of tubes that splits the aqueous suspension into successively smaller droplets within the solvent, ultimately producing droplets containing just one cell. It is then possible, says Ismagilov, to isolate just those droplets containing the rarer cells. These can then be grown in cultures.

Ismagilov's approach allows the researchers to characterise live microbes. Although there are some other live microbe approaches, they can be complicated by difficulties in the culturing process – mixtures are often dominated by fast-growing species, making it difficult to study the slower-growing ones. A previous solution has been to dilute the mixture to separate the individual cells. However, such dilution makes detecting the cells and the chemicals they produce

much more difficult, says Ismagilov. Ismagilov adds that their approach 'allows sampling directly from the environment, even from soil slurry.' This, he explains, allows them to cultivate microbes that rely strongly on the chemicals present in the Isolating Paenibacillus curdlanolyticus in droplets means the rare bacterium can be detected in mixtures original sample for growth.

The researchers tested their method on a mixture containing *E. coli* and a rare microbe, the slow-growing *Paenibacillus curdlanolyticus*. They found that they could separate and culture cells of the rare species even from mixtures containing the cells in ratios as low as 1 to 40. Using a conventional method, colonies of the rare microbe could be detected only at ratios higher than 1 to 15.

Doug Weibel, an expert in microbial biochemistry from the University of Wisconsin, Madison, US, describes the method as 'a clever and practical approach.' He adds that the droplet-based technique makes it possible to probe bacteria using a number of assays that may be mutually incompatible.

Ismagilov suggests that the single-cell processing approach has applications in environmental and human microbiology, and that it could also be applied to other cell types, including mammalian cells, for use in disease diagnostics. David Barden

Reference W Liu *et al, Lab Chip*, 2009, DOI: 10.1039/ b904958d

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Chung-Yi Wu et al, Org. Biomol. Chem., 2009, **7**, 2247 (DOI: 10.1039/b902510n)

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Craig E Wheelock *et al, Mol. BioSyst.*, 2009, **5**, 588 (DOI: 10.1039/b902356a)

Vibrational spectroscopy: a clinical tool for cancer diagnostics Catherine Kendall *et al*, *Analyst*, 2009, **134**, 1029 (DOI: 10.1039/b822130h)

**Revival of deuterium-labeled reagents for protein quantitation** Dexing Zeng and Shuwei Li, *Chem. Commun.*, 2009, 3369 (DOI: 10.1039/b906335h)

**Microfluidic culture of single human embryonic stem cell colonies** Luis Gerardo Villa-Diaz *et al, Lab Chip*, 2009, **9**, 1749 (DOI: 10.1039/b820380f) Miniaturized thermocontrol devices enable analysis of biomolecular behavior on their timescales, second to millisecond

Hideyuki F Arata and Hiroyuki Fujita, *Integr. Biol.*, 2009, **1**, 363 (DOI: 10.1039/b901902b)

#### Gold nanoparticles in nanomedicine: preparations, imaging, diagnostics, therapies and toxicity

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### Uptake pathways of anionic and cationic photosensitizers into bacteria

Saji George *et al, Photochem. Photobiol. Sci.*, 2009, **8**, 788 (DOI: 10.1039/b809624d)

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# Interview

# The frontiers of medicine

Wilfred van der Donk tells Rachel Cooper about investigating enzymes and the choice between history and science



#### Wilfred van der Donk

Wilfred van der Donk is an investigator at the Howard Hughes Medical Institute, Chevy Chase, US, and the Richard E Heckert Professor of Chemistry at the University of Illinois, Urbana, US, and has recently joined the *Chemical Communications* editorial board. He uses a combination of synthetic and protein chemistry to address problems at the interface of chemistry and biology. He is also the winner of the 2009 OBC Lecture Award.

#### What inspired you to become a scientist?

I am afraid it was not a dream from very early on as for some of my colleagues. I never had a chemistry set at home nor did I read about science beyond the textbooks at school. My parents have their own small business and when I was not helping there, I was usually playing soccer with my friends. The way the Dutch school system worked, I had to make a choice between liberal arts and science when I was 14. Because science courses were more challenging to me, I chose the science track. I have come to cherish that choice, although I very much regretted then that I had to drop history, which I always loved from a very early age. Once on the science track, I chose chemistry as my major in college because of its cool laboratories.

#### What motivated you when choosing chemical biology?

More than anything my motivation came from a Robert A Welch foundation conference entitled Chemistry at the Frontiers of Medicine in Houston in 1991. At that time, I was a second year graduate student studying organometallic chemistry at Rice University [US] with a masters degree in inorganic chemistry. The line-up of that Welch meeting was spectacular and the talks very inspiring. Seeing what chemists can do to understand and manipulate biology prompted me to seek a postdoc position in a laboratory where I could learn the tools of molecular biology and biochemistry.

I was fortunate to receive that opportunity with JoAnne Stubbe at MIT [US]. There I became intrigued by the power of enzymatic transformations. Our current research is still driven by a desire to both understand enzyme catalysis and use that knowledge for improving human health.

### What is your favourite result from all of your investigations so far?

Probably solving the problems of getting lantibiotic biosynthetic enzymes to work in vitro. Although we have done more important work since then, it was such a tough road for my students in the early years of my laboratory, that the day we had our first in vitro activity is still the most exciting day of my independent career.

### And what do you find most exciting in your current research?

The use of genomic information to discover new natural products. These compounds are in my opinion still the best lead source for antimicrobial agents, but most pharmaceutical companies have shut down their natural product discovery efforts because of diminishing success. An enormous reservoir of novel scaffolds remains untapped and I am optimistic that genomic approaches will provide access to them. However, for this approach to become economically attractive new methodology needs to be developed and a number of groups, including our own, are trying to develop those methods.

#### You have won a variety of awards including being appointed Howard Hughes Medical Investigator in 2008, and winning the 2009 OBC Lecture Award. What do you think is the secret to being a successful scientist?

I am not sure there is a secret. Scientists are successful using very different approaches. Everyone has to find his/her own style of managing a group successfully, something that is very much influenced by who you are and where you are.

I have been fortunate to start my career at the University of Illinois where I have been blessed with a superb group of coworkers. I don't think that awards are the best criteria to define success. Any scientist that solves a problem is successful.

To receive widespread recognition, however, at least two factors are essential. You have to work on problems that are of high scientific interest and that have broader impact.

#### What do you enjoy doing outside of work?

Right now, I enjoy spending time with my kids of four and six years old. Kids are so amazing; every day I learn new things simply by observing them and every day you recognise aspects of their character that are scarily similar to how you were yourself as a child. When I am not exhausted from playing with them, I love to read historical novels and follow the Illinois sports teams.

### And finally, if you weren't a scientist, what would you be?

I mentioned my love for history. I would have been very happy to do historical research and write books on various topics that I am interested in. But, I already have the best possible job right now!

# A new journal from RSC Publishing for 2009

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# Instant insight

**Recognising antidepressants** 

A small change in an antidepressant can dramatically change its target in the brain. Understanding this, say Kristian Strømgaard and colleagues at the University of Copenhagen, Denmark, is the key to developing more effective drugs<sup>1</sup>

Neurotransmitters are continually at work in our bodies, controlling when we wake up and when we feel hungry and even affecting our emotional state. Given their importance in regulating so many human brain functions it is hardly surprising that dysfunctions in neurotransmitter systems have been implicated in mental and behavioural disorders, from depression to anorexia and drug addiction.

Neurotransmitters transmit signals from neuron (nerve cell) to neuron via junctions called synapses and work by interacting with receptor proteins in the cell membranes. Levels of the monoamine neurotransmitters serotonin (5-hydroxytryptamine), norepinephrine (or noradrenaline) and dopamine are tightly regulated outside the cells by three unique, but closely related transporter proteins: SERT (serotonin), NET (norepinephrine) and DAT (dopamine). These proteins are found in the membranes of the presynaptic neurons - the cells that send the signals - where they are responsible for moving the neurotransmitters into the neurons from the extracellular space.

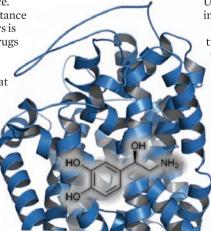
The transporters' importance in treating mental disorders is highlighted by the many drugs currently used to target SERT, NET and DAT, including those used to treat anxiety and attentiondeficit hyperactivity disorder. Moreover, drugs of abuse, such as cocaine and amphetamines such as 3,4-methylenedioxy-*N*-methylamphetamine (MDMA or ecstasy), also bind to these transporters. SERT

HO NH2

5-Hydroxytryptamine and norepinephrine are the natural substrates for transporter proteins SERT (above) and NET (below)

References 1 J Andersen et al, Chem.

Commun., 2009, DOI: 10.1039/b903035m 2 A Yamashita et al, Nature, 2005, **437**, 215



and NET blockers, which increase extracellular serotonin and norepinephrine levels, have found unparalleled use in treating clinical depression and related disorders.

Tricyclic antidepressants (TCAs) formed the first generation of monoamine transporter inhibitors developed as antidepressants and represented a major therapeutic breakthrough in the 1950s. However, their broad activity across a variety of receptors results in some severe side-effects. As TCAs' clinical effect began

to be attributed to their activity at monoamine transporters, the 1960s and 1970s saw medicinal chemists focus their efforts on developing a new generation of inhibitors with selectivity for these proteins. This resulted in the selective serotonin reuptake inhibitors (SSRIs), which are the most prescribed class of antidepressants today. One of the first developed and best known of these is fluoxetine (Prozac), which was approved for use by the US Food and Drug Administration in 1987.

Considering that monoamine transporter drugs have now been used for over four decades, it is surprising how little is known about how they work at the molecular level and how the various drug types can bind and block transporters selectively. Several structure-activity

relationship studies of SSRIs have shown that even very subtle modifications of these compounds can change their pharmacological profile. Fluoxetine, which has SERT selectivity, is a prominent example: replacing its *para*-trifluoromethyl group with an *ortho*-methoxy group leads to a compound that is very selective for NET. One would expect such similar molecules to bind in a similar way in the SERT and NET binding pockets, suggesting that their subtle structural differences reflect corresponding differences in the binding pockets.

A major obstacle to understanding how monoamine transporter drugs work has been a complete lack of structural details of the antidepressant binding sites in the transporters. However, breakthroughs have been made. Specific amino acids in SERT and NET have been identified as important for antidepressant recognition. Another turning point was the resolution of the x-ray crystal structure of a bacterial homologue of the human transporters, a leucine transporter (LeuT) from the thermophile Aquifex aeolicus.<sup>2</sup> LeuT's structure provides a starting point for constructing 3D models of the inhibitor binding sites in monoamine transporters. It can also be used to help understand existing structureactivity data for antidepressants.

The information generated from these studies should help us towards understanding how these important drugs bind to their target. In turn, this should allow a much more rational approach to the development of future inhibitors of monoamine transporters, and so might lead to new and more effective drugs.

Read more in the feature article 'Recent advances in the understanding of the interaction of antidepressant drugs with serotonin and norepinephrine transporters' in issue 25, 2009 of Chemical Communications.

# **Essential elements**

# New journal: Polymer Chemistry

On 1 June, RSC Publishing announced that Polymer Chemistry - a new journal encompassing all aspects of synthetic and biological macromolecules, and related emerging areas - will be the latest title to join its journal portfolio.

Launching early in 2010, the journal will provide a showcase for the ongoing efforts driving polymer chemistry, highlighting the creativity of the field and previously inaccessible applications. Monthly issues will contain a full mix of research articles including communications, reviews and full papers. The journal will have a broad scope, covering areas of polymer chemistry of interest to materials scientists and bioscientists, as well as all traditional areas of the field.

# Polymer Chemistry



Editor-in-chief of Polymer Chemistry is David Haddleton of the University of Warwick, UK. In outlining his vision for Polymer Chemistry, he describes how the new journal 'will report on the best polymer chemistry from

around the globe and will become a high impact factor journal that all polymer chemists will be proud to have on their CV.'

Polymer Chemistry joins an exclusive group of journals launched by RSC Publishing in the past 12 months. Metallomics and Integrative Biology both published their first issues in January 2009, with new journals Nanoscale and Analytical Methods due to follow later this year.

The current issue of *Polymer* Chemistry will be freely available to everyone on the website from launch until the end of 2011 Free online institutional access to previous issue content during 2010 and 2011 is also available following a simple registration process.

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# **Community embraces RSC-ChemSpider**

Hailed by some as 'a scientific "marriage" made in

heaven,' news about RSC's recent acquisition of ChemSpider spread fast through the blogosphere and other channels.

ChemSpider, a free online service providing access to almost 21.5 million unique chemical entities sourced from over 200 different data sources and integration to a multitude of other online services, is the richest single source of structure-based chemistry information. Its acquisition

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to providing access to premium resources of chemistry data and information. This complements RSC's existing leading role in online chemistry, including award-winning

semantic mark-up technology and the release of the InChI resolver, recently launched in partnership with ChemSpider.

Antony Williams, the original host of ChemSpider, is excited by the new possibilities. 'What originally started as a hobby

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project to give back something to the chemistry community has become one of the primary internet resources for chemistry. And this from home built computers in a basement, with no funding and a team of volunteers,' he says. 'With the resources, reputation and vision of the RSC to support ChemSpider, our long term goal is to deliver the primary online platform where chemists will resource information and collaborate with a worldwide community of scientists.'

The ChemSpider website will be re-launched later in the year. Visit www.chemspider.com

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