## ChemComm

## **Chemical Communications**

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## IN THIS ISSUE

ISSN 1359-7345 CODEN CHCOFS (45) 5857-6060 (2008)



**Cover** See Timothy C. Lillestolen and Richard J. Wheatley pp. 5909–5911. Using a simple new algorithm, molecules can be divided into atoms with chemically intuitive charges and shapes. The image was generated with the kind assistance of Dr Samantha Tang. Image reproduced by permission of Timothy C. Lillestolen and Richard J. Wheatley from *Chem. Commun.*, 2008, 5909.



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#### Inside cover

See Graeme Cooke *et al.* pp. 5912–5914. The synthesis, solid-state and preliminary solution properties of a flavin-based [2]catenane. Image reproduced by permission of Stuart T. Caldwell, Graeme Cooke, Brian Fitzpatrick, De-Liang Long, Gouher Rabani and Vincent M. Rotello from *Chem. Commun.*, 2008, 5912.

## CHEMICAL BIOLOGY

#### **B89**

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**

## December 2008/Volume 3/Issue 12

www.rsc.org/chembiology

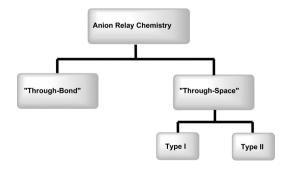
## FEATURE ARTICLES

#### 5883

## Evolution of multi-component anion relay chemistry (ARC): construction of architecturally complex natural and unnatural products

#### Amos B. Smith, III\* and William M. Wuest

Efficient construction of architecturally complex natural and unnatural products is the hallmark of organic chemistry. Anion relay chemistry has the potential to provide the chemist with a powerful synthetic tactic, enabling efficient, rapid elaboration of structurally complex scaffolds in a single operation with precise stereochemical control.



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Chemical Communications (print: ISSN 1359-7345; electronic: ISSN 1364-548X) is published 48 times a year by the Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge, UK CB4 0WF. All orders, with cheques made payable to the Royal Society of Chemistry, should be sent to RSC Distribution Services, c/o Portland Customer Services, Commerce Way, Colchester, Essex, UK CO2 8HP. Tel +44 (0)1206 226050; E-mail sales@rscdistribution.org

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## FEATURE ARTICLES

#### 5896

## Coordination-driven self-assembly of functionalized supramolecular metallacycles

## Brian H. Northrop,\* Hai-Bo Yang and Peter J. Stang

Coordination-driven self-assembly of ditopic Pt(II) metal acceptors and bis-pyridyl organic donors, either or both of which contain covalently linked functional groups, provides facile access to novel polyfunctional supramolecular materials wherein the stoichiometry and location of functional groups as well as the size and shape of the assembly can be precisely controlled.

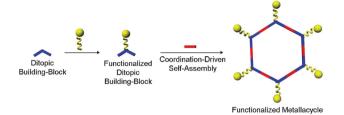
#### COMMUNICATIONS

#### 5909

## Redefining the atom: atomic charge densities produced by an iterative stockholder approach

Timothy C. Lillestolen and Richard J. Wheatley\*

Atomic charge densities of formamide generated using an iterative stockholder approach. This new computational method allows molecular electron densities to be divided into atoms having intuitively correct shapes and charges.



## H(2) N H(3) H(1) H(1)

5912

#### A flavin-based [2]catenane

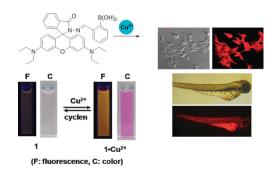
Stuart T. Caldwell, Graeme Cooke,\* Brian Fitzpatrick, De-Liang Long, Gouher Rabani and Vincent M. Rotello We report the synthesis, solid-state and preliminary solution properties of a flavin-based [2]catenane.

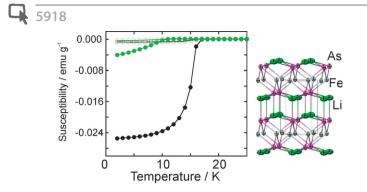
## 5915

## Boronic acid-linked fluorescent and colorimetric probes for copper ions

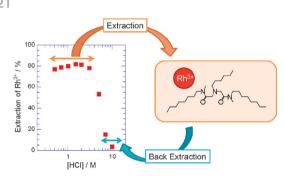
K. M. K. Swamy, Sung-Kyun Ko, Soo Kyung Kwon, Ha Na Lee, Chun Mao, Joung-Min Kim, Keun-Hyeung Lee, Jinheung Kim, Injae Shin\* and Juyoung Yoon\*

The first examples of boronic acid-linked fluorescent and colorimetric chemosensors for copper ions are reported.

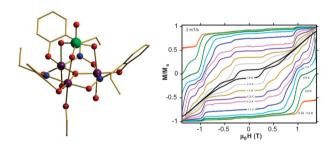








## 5924



#### Structure and superconductivity of LiFeAs

Michael J. Pitcher, Dinah R. Parker, Paul Adamson, Sebastian J. C. Herkelrath, Andrew T. Boothroyd, Richard M. Ibberson, Michela Brunelli and Simon J. Clarke\*

Superconductivity in LiFeAs samples demonstrates that superconducting anti-PbO-type [FeAs]<sup>-</sup> anionic layers occur with a wide range of As–Fe–As bond angles.

## The first effective extractant for trivalent rhodium in hydrochloric acid solution

Hirokazu Narita,\* Kazuko Morisaku and Mikiya Tanaka

The tertiary amine compound containing two N-disubstituted amide groups, N-n-hexyl-bis(N-methyl-N-n-octylethylamide)amine (HBMOEAA), can effectively extract and back-extract Rh<sup>3+</sup> from hydrochloric acid solution.

## Enhancing SMM properties *via* axial distortion of $Mn^{III}_{3}$ clusters

Ross Inglis, Leigh F. Jones, Georgios Karotsis, Anna Collins, Simon Parsons, Spyros P. Perlepes, Wolfgang Wernsdorfer\* and Euan K. Brechin\*

Replacement of carboxylate and solvent with facially capping tripodal ligands helps to enhance the SMM properties of ferromagnetic [Mn<sup>III</sup><sub>3</sub>] triangles.





## Enzyme catalyzed site-specific protein labeling and cell imaging with quantum dots

Murat Sunbul, Michelle Yen, Yekui Zou and Jun Yin\*

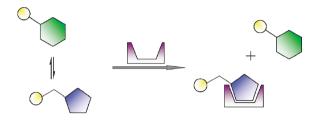
We have developed an efficient method for one-step covalent labeling of cell surface proteins with quantum dots based on enzyme catalyzed site-specific modification of short peptide tags.

## 5930

## Disaccharide recognition by binuclear copper(II) complexes

## Susanne Striegler\* and Moses G. Gichinga

In spite of comparable binding strengths and intermetallic Cu–Cu distances, disaccharides bind with different overall geometry to similar binuclear copper( $\pi$ ) complexes in aqueous solution.



laln[OP(p-Anis)a]o

400

 $C_{\odot}(^{115}\text{In}) = 200.0 \text{ MHz}$ 

0

## 5933

## Solid-state <sup>115</sup>In NMR study of indium coordination complexes

Fu Chen, Guibin Ma, Ronald G. Cavell, Victor V. Terskikh and Roderick E. Wasylishen\*

The feasibility of solid-state <sup>115</sup>In NMR is demonstrated by an examination of four representative indium coordination complexes.

## 5936

## Carbon coated microshells containing nanosized Gd(III) oxidic phases for multiple bio-medical applications

Aldo Arrais, Mauro Botta, Stefano Avedano, Giovanni Battista Giovenzana, Eliana Gianolio, Enrico Boccaleri, Pier Luigi Stanghellini\* and Silvio Aime\*

A novel material containing Gd( $\Pi$ ) oxidic phases irreversibly confined in encapsulating sp<sup>2</sup> carbon coating shells are potential candidates for multiple diagnostic and therapeutic bio-medical applications.

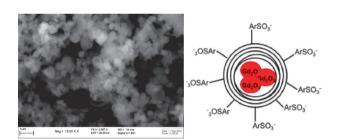
## 5939

## The effect of complex stoichiometry in supramolecular chirality transfer to zinc bisporphyrin systems

Juan Etxebarria, Anton Vidal-Ferran\* and Pablo Ballester\*

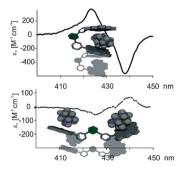
The self-assembly of Zn–bisporphyrin tweezers induced by coordination to enantiopure 1,2-diaminocyclohexane features supramolecular chirality induction and inversion processes that are exclusively controlled by the stoichiometry of the assembled complexes.

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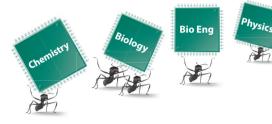
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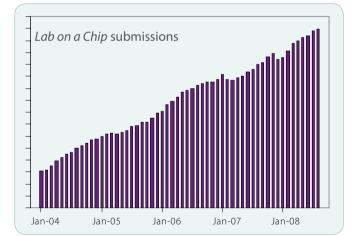


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## 5942

#### Dispersion polymerisation in supercritical CO<sub>2</sub> using macro-RAFT agents

Mengmeng Zong, Kristofer J. Thurecht\* and Steven M. Howdle\*

Fluorinated macro-RAFT agents can act as in situ stabilisers while exhibiting good control over block copolymers formed by dispersion polymerisation in supercritical  $\dot{CO}_2$  to yield well-defined spherical particles with a fluorinated "halo".

## 5945

#### CuS nanotubes for ultrasensitive nonenzymatic glucose sensors

Xiaojun Zhang,\* Guangfeng Wang, Aixia Gu, Yan Wei and Bin Fang

CuS nanotubes made up of nanoparticles were successfully prepared in large quantities in an O/W microemulsion system under low temperature. The as-prepared CuS nanotube modified electrode was used as an enzyme-free glucose sensor.

## 5948

#### Low toxic, thermoresponsive dendrimers based on oligoethylene glycols with sharp and fully reversible phase transitions

Wen Li, Afang Zhang,\* Yong Chen, Kirill Feldman, Hua Wu and A. Dieter Schlüter\*

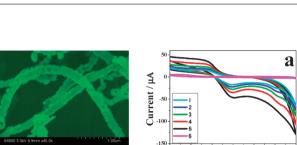
First and second generation dendrimers based on three-fold branched oligoethylene glycol dendrons have been efficiently synthesized; the latter show characteristic thermoresponsive behavior and negligible cytotoxicity.

#### 5951

#### Cell adhesive hydrogels synthesised by copolymerisation of arg-protected Gly-Arg-Gly-Asp-Ser methacrylate monomers and enzymatic deprotection

Lynne Perlin, Sheila MacNeil\* and Stephen Rimmer\*

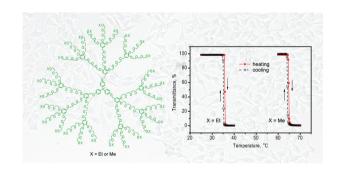
Cell adhesion promoting peptide monomers containing arginine protected with an aryl sulfonamide are polymerised to form a hydrogel. The protected group is removed by glutathione-S-transferase to yield cell adhesive hydrogels.

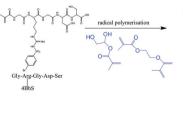


-0.4

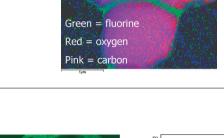
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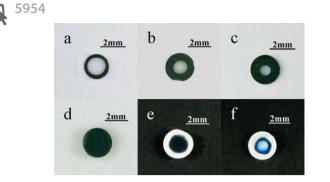
0.2 0.4 Potential/V(vs.SCE)







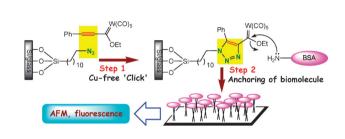




**5**957

5960

C-terr



Cd1 •

Ha1

Zn1

N-term

Cd2 🖕

## New method for the preparation of nonuniform distributed $Co/SiO_2$ catalysts

Jingwei Li, Yunjie Ding,\* Xianming Li, Guiping Jiao, Tao Wang, Weimiao Chen and Hongyuan Luo

Egg-shell, egg-yolk and egg-white types of  $Co/SiO_2$  catalysts were prepared by reducing the capillary pressure driving force in the impregnation process and utilizing the entrapped air to inhibit the entrance of impregnation or leaching solution into the cores of catalyst pellets during the preparation procedure.

## A new bio-active surface for protein immobilisation *via* copper-free 'click' between azido SAM and alkynyl Fischer carbene complex

Sudeshna Sawoo, Piyali Dutta, Amarnath Chakraborty, Rupa Mukhopadhyay, Othman Bouloussa and Amitabha Sarkar\*

A Fischer carbene complex grafted on an azido-terminated monolayer by copper-free 'click' reaction (step 1) permits a convenient, instantaneous and covalent anchoring of BSA (step 2) to SAMs.

## Structural probing of Zn(11), Cd(11) and Hg(11) binding to human ubiquitin

Giuseppe Falini,\* Simona Fermani, Giovanna Tosi, Fabio Arnesano and Giovanni Natile

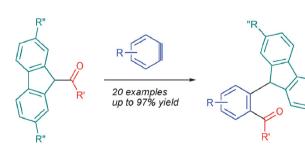
A structural investigation performed on adducts of human ubiquitin with group-12 metal ions reveals two preferential anchoring sites, His68 and Met1. The protein aggregation stereochemistry appears to be driven by the clustering of deshielded backbone hydrogen-bond patches, and metal ions foster this process.

Fluorenes as new molecular scaffolds for carbon–carbon  $\sigma$ -bond cleavage reaction: acylfluorenylation of arynes

Hiroto Yoshida,\* Takeshi Kishida, Masahiko Watanabe and Joji Ohshita

Synchronous installation of acyl and fluorenyl moieties into adjacent positions of aromatic skeletons has been achieved. The ease of formation of fluorenyl anions, being attributable to their aromatic stabilization, is the key to the successful reaction.

**5**963



Cd3

## 5966

Heterolytic dihydrogen activation with the 1,8-bis(diphenylphosphino)naphthalene/B( $C_6F_5$ )<sub>3</sub> pair and its application for metal-free catalytic hydrogenation of silvl enol ethers

Huadong Wang, Roland Fröhlich, Gerald Kehr and Gerhard Erker\*

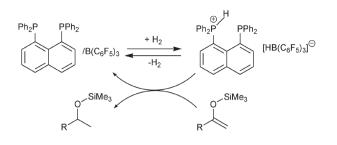
1.8-Bis(diphenylphosphino)naphthalene forms an "antagonistic/frustrated Lewis pair" with  $B(C_6F_5)_3$ that activates dihydrogen reversibly and catalyzes the hydrogenation of silyl enol ethers.

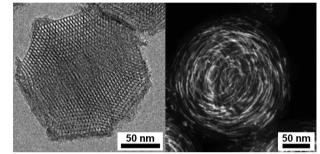
## 5969

## 2D-Rectangular c2mm mesoporous silica nanoparticles with tunable elliptical channels and lattice dimensions

Chia-Min Yang,\* Ching-Yi Lin, Yasuhiro Sakamoto, Wei-Chia Huang and Li-Ling Chang

Mesoporous silica nanoparticles with a two-dimensional center-rectangular (plane group c2mm) lattice and coiled elliptical channels have been synthesized.



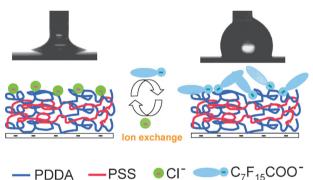


## 5972

## Tunable wettability by counterion exchange at the surface of electrostatic self-assembled multilayers

Liming Wang, Yuan Lin, Bo Peng and Zhaohui Su\*

A novel method to tune surface wettability rapidly and reversibly has been developed by ion exchange of the counterions at the surface of a multilayer film assembled via electrostatic interaction.

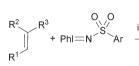


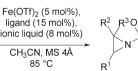
## 5975

## Iron-catalysed aziridination reactions promoted by an ionic liquid

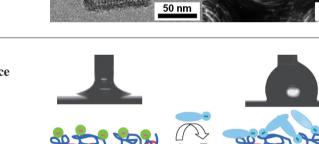
Agathe C. Mayer, Anne-Frédérique Salit and Carsten Bolm\*

Olefin aziridinations have been achieved using a simple catalytic system on the basis of iron(II) triflate, quinaldic acid, an ionic liquid and a preformed iminoiodinane bearing a pyridine backbone.





11 examples, up to >95%





## **42nd IUPAC CONGRESS** Chemistry Solutions 2–7 August 2009 | SECC | Glasgow | Scotland | UK

On behalf of IUPAC, the RSC is delighted to host the 42nd Congress (IUPAC 2009), the history of which goes back to 1894. RSC and IUPAC members, groups and networks have contributed a wealth of ideas to make this the biggest UK chemistry conference for several years.

As well as a programme including more than 50 symposia, a large poster session and a scientific exhibition, we are planning a series of social and satellite events to enhance networking and discussion opportunities.

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## 5978

G

#### Chaetoglobins A and B, two unusual alkaloids from endophytic Chaetomium globosum culture

Hui Ming Ge, Wei Yun Zhang, Gang Ding, Patchareenart Saparpakorn, Yong Chun Song, Supa Hannongbua and Ren Xiang Tan\*

Chaetoglobins A (1) and B (2), two azaphilone alkaloid dimers with an unprecedented skeleton, were characterized from an endophytic fungus Chaetomium globosum with the former valuable for anti-tumor drug discovery.



#### Revealing molecular self-assembly and geometry of non-covalent halogen bonding by solid-state NMR spectroscopy

Markus Weingarth, Noureddine Raouafi, Benjamin Jouvelet, Luminita Duma, Geoffrey Bodenhausen, Khaled Boujlel, Bernd Schöllhorn\* and Piotr Tekely\*

We report a new spectroscopic fingerprint of halogen bond-driven self-assembling aggregates.

## 5984

#### 8-Nitroguanosines as chemical probes of the protein S-guanylation

Yohei Saito, Hirobumi Taguchi, Shigemoto Fujii, Tomohiro Sawa, Eriko Kida, Chizuko Kabuto, Takaaki Akaike\* and Hirokazu Arimoto\*

The importance of a cyclic phosphate moiety of NO<sub>2</sub>-cGMP in upregulation of heme oxygenase-1 via protein S-guanylation was examined. Fluorescence detection of S-guanylated proteins by a nitroguanosine-based probe is also described.

## 5987

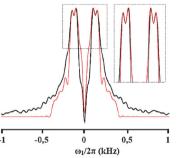
#### Resin-assisted solvothermal synthesis of metal-organic frameworks

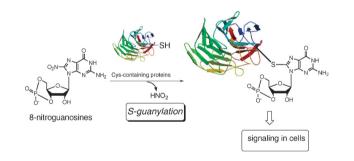
Yi Du, Amber L. Thompson and Dermot O'Hare\*

Transition metal-exchanged polymer resin beads have been used as a heterogeneous controlled-release source of metal cations in high yielding, phase pure solvothermal syntheses of novel transition metal-organic frameworks.









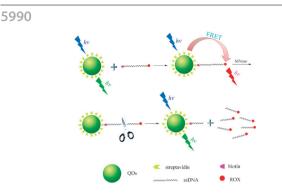
#### Fe<sup>2\*</sup>-exchanged sulfonated styrene-divinylbenzene resin



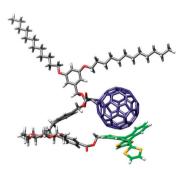


Fe<sup>2+</sup>-MOF

= Fe



5993



## A high sensitive and specific QDs FRET bioprobe for MNase

Shan Huang, Qi Xiao, Zhi Ke He,\* Yi Liu, Philip Tinnefeld, Xiong Rui Su and Xiao Niu Peng

A simple and rapid method to detect MNase with high sensitivity and specificity based on the new QD-FRET bioprobe has been developed, which can be extended to the realistic diagnostic assay conditions.

## Cooperativity between $\pi$ - $\pi$ and H-bonding interactions-a supramolecular complex formed by $C_{60}$ and exTTF

José Santos, Bruno Grimm, Beatriz M. Illescas, Dirk M. Guldi\* and Nazario Martín\*

Cooperative  $\pi$ - $\pi$  and H-bonding interactions afford a supramolecular complex from C<sub>60</sub> and exTTF exhibiting exceptional stability ( $K_a \approx 10^6 \text{ M}^{-1}$ ); upon photoexcitation, a short living radical-ion pair ( $\tau = 9.3 \text{ ps}$ ) is formed.

## Highly selective detection of 5-methylcytosine using photochemical ligation

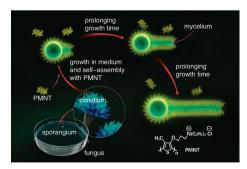
Masayuki Ogino, Yuuta Taya and Kenzo Fujimoto\*

The authors report the nonenzymatic detection of 5-methylcytosine by using template-directed photoligation through 5-cyanovinyl-2'-deoxyuridine ( $^{C}$ U) with high selectivity. A new methylation detection method using a photoligation-based DNA chip assay is presented.

**1** 5999

5996

target DNA



photoligation wash

probe DNA

detection

## Microorganism-based assemblies of luminescent conjugated polyelectrolytes

Libing Liu, Xinrui Duan, Huibiao Liu, Shu Wang\* and Yuliang Li

A novel approach was developed for the assembly of fluorescent conjugated polyelectrolytes into tubes on the micrometre scale of tunable length using fungi as living templates.

## 6002

#### Chromogenic detection of nerve agent mimics

Ana M. Costero,\* Salvador Gil, Margarita Parra, Pedro M. E. Mancini, Ramón Martínez-Máñez,\* Félix Sancenón and Santiago Royo

A new chromogenic reagent for the detection of warfare agent simulants in vapour and neutral mixed aqueous environments is reported.

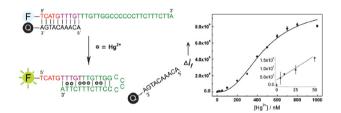


6005

## Highly sensitive "turn-on" fluorescent sensor for Hg<sup>2+</sup> in aqueous solution based on structure-switching DNA

Zidong Wang, Jung Heon Lee and Yi Lu\*

A simple design of "turn-on" fluorescent sensor for mercury was demonstrated based on structure-switching DNA with a low detection limit of 3.2 nM and high selectivity.



## 6008

## A facile route to bulk high-Z polymer composites for gamma ray scintillation

Yong Sheng Zhao, Zhibin Yu, Ali Douraghy, Arion F. Chatziioannou, Yueqi Mo and Qibing Pei\*

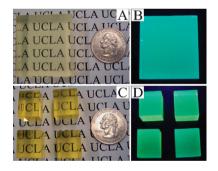
Bulk transparent polymer composites for gamma ray detection were prepared from liquid solution formulations. The composites exhibit fluorescence resonance energy transfer from the high-Z compounds to a conjugated polymer also admixed in the composites.

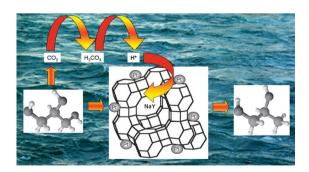
#### 6011

## Catalytic glycerol conversion into 1,2-propanediol in absence of added hydrogen

Els D'Hondt, Stijn Van de Vyver, Bert F. Sels and Pierre A. Jacobs\*

Conversion of glycerol into high yields of 1,2-propanediol in absence of added hydrogen is possible with Pt impregnated NaY zeolite characterized by extra-zeolitic metal particles combined with zeolite Brønsted acidity.





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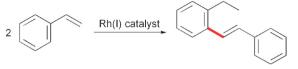
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## 6013

## Rhodium-catalysed anomalous dimerization of styrenes involving the cleavage of the *ortho* C–H bond

Mamoru Tobisu,\* Isao Hyodo, Masahiro Onoe and Naoto Chatani\*

The dimerization of styrene derivatives in the presence of a rhodium catalyst proceeds to give stilbene derivatives, in which the *ortho* C–H bond of styrenes is cleaved and functionalized.



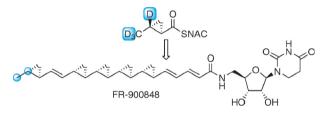


## 6016

## Unprecedented biological cyclopropanation in the biosynthesis of FR-900848

Tetsuo Tokiwano,\* Hiroaki Watanabe, Takashi Seo and Hideaki Oikawa\*

We were able to show the predominant incorporation of a single enantiomer and intact incorporation of multiply labelled synthetic diketide precursors, which established the intermediacy of cyclopropanated diketide in the biosynthesis of FR-900848.



#### 6019

## The effects of pressure on valence tautomeric transitions of dinuclear cobalt complexes

Bao Li, Feng-Lei Yang, Jun Tao,\* Osamu Sato, Rong-Bin Huang and Lan-Sun Zheng

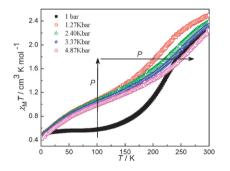
The effects of pressure on valence tautomeric transition of two complexes,  $[{Co(tpa)}_2(dhbq)] \cdot (PF_6)_3$  (I  $\cdot (PF_6)_3$ ) and  $[{Co(dpqa)}_2(dhbq)] \cdot (PF_6)_3$  (II  $\cdot (PF_6)_3$ ) were investigated. The results show that external pressure makes the SC + ET transition process of the two complexes into a general SC process only.

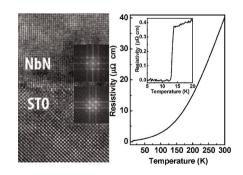
#### 6022

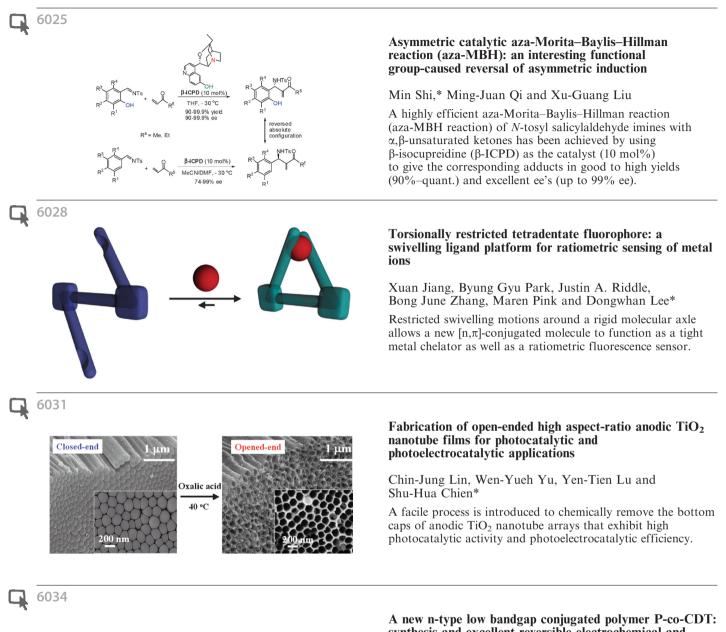
## Ultrathin epitaxial superconducting niobium nitride films grown by a chemical solution technique

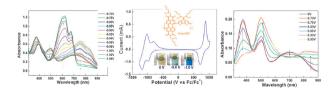
Guifu Zou,\* Menka Jain, Honghui Zhou, Hongmei Luo, Scott A. Baily, Leonardo Civale, Eve Bauer, T. Mark McCleskey, Anthony K. Burrell and Quanxi Jia\*

Ultrathin epitaxial superconducting NbN (18 nm) films, exhibiting a superconducting transition temperature of 14 K, were grown on  $SrTiO_3$  (STO) by a chemical solution technique, polymer assisted deposition (PAD).









#### A new n-type low bandgap conjugated polymer P-co-CD1: synthesis and excellent reversible electrochemical and electrochromic properties

Jianhui Hou,\* Shaoqing Zhang, Teresa L. Chen and Yang Yang\*

A n-type low bandgap conjugated polymer based on perylene diimide and cyclopenta[2,1-*b*:3,4-*b*']dithiophene, which exhibits excellent reversible electrochemical properties in both n-doping/dedoping and p-doping/dedoping processes, was designed, synthesized and characterized.

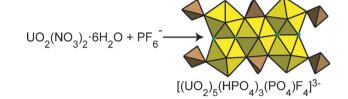
## 6037

G

 $\mathrm{PF_6}^-$  Hydrolysis as a route to unique uranium phosphate materials

Nicholas P. Deifel, K. Travis Holman and Christopher L. Cahill\*

The *in situ* formation of  $PO_4^{3-}$  through the hydrolysis of hexafluorophosphate anions ( $PF_6^{-}$ ) is utilized as a route to a new uranium phosphate fluoride with a unique pentameric secondary building unit.

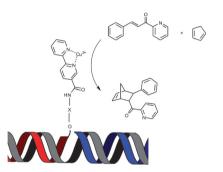


## 6039

#### Modular assembly of novel DNA-based catalysts

Núria Sancho Oltra and Gerard Roelfes\*

A novel modular strategy towards the assembly of DNA-based catalysts containing a covalently anchored metal complex is presented.



## 6042

#### Addition of H<sub>2</sub> to distannynes under ambient conditions

Yang Peng, Marcin Brynda, Bobby D. Ellis, James C. Fettinger, Eric Rivard and Philip P. Power\*

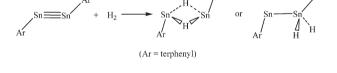
 $H_2$  reacts with a series of distannynes at *ca*. 25 °C and 1 atmosphere pressure to give  $Sn_2H_2Ar_2$  products whose structures depend on the type of terphenyl ligand employed.

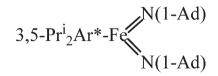
#### 6045

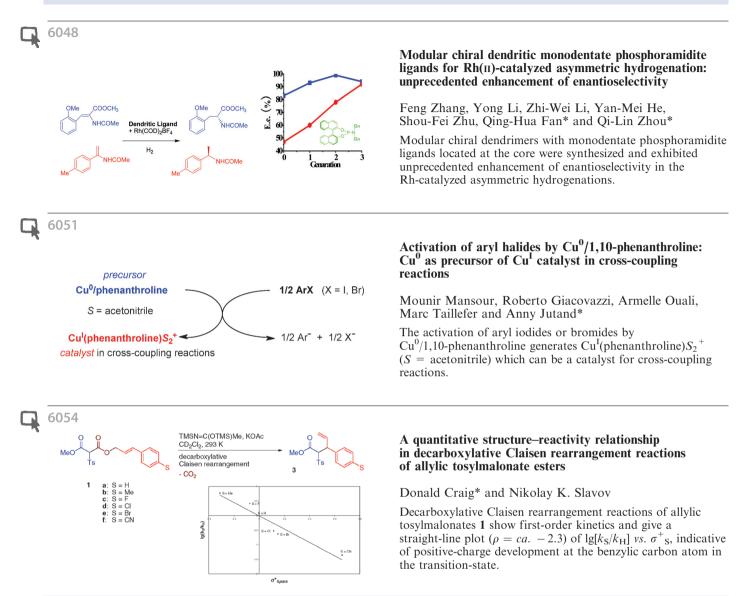
## Reaction of a sterically encumbered iron(1) aryl/arene with organoazides: formation of an iron(v) bis(imide)

Chengbao Ni, James C. Fettinger, Gary J. Long, Marcin Brynda and Philip P. Power\*

The synthesis, structural and spectroscopic characterization of a stable Fe(v) imido complex is reported.







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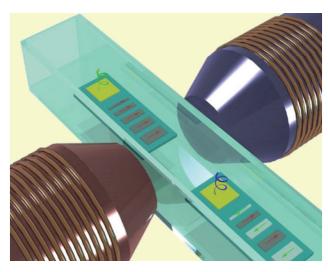
# Chemical Biology

## Miniature magnetic tags used to track DNA samples in chip systems **The barcode and the bioassay**

Barcodes have been used to track many things, from airline luggage to parcels. Now they are being used to label and track samples in microfluidic, high-throughput systems.

Jong-Ryul Jeong's group at the University of Cambridge, UK, is working towards one of the big goals in biological science: a DNA sequencing technology that can sequence the human genome in one day. But to achieve this they need to create new microfluidic systems and realised they required a labelling technique to track samples through the small devices. Their solution was tiny magnetic barcodes that can be attached to the samples and tracked.

The magnetic barcodes consist of a small strip of plastic, smaller than the average human cell, onto which strips of cobalt are attached. The cobalt can be magnetised in two different directions, to give either a plus one or minus one signal, much like the black and white strips of



a conventional barcode. These barcodes can then be read quickly as labelled samples pass a detector, just like being swiped at the checkout.

Jeong explains that the main advantages of this technology are that the tags can be coded after they have been applied to a Barcoded DNA samples can be scanned much like food at the supermarket checkout sample, reducing the likelihood of mislabelling. They can also be coded remotely and even rewritten if needed, he adds.

Samuel Sia of Columbia University, New York, US, works on creating low cost lab-on-a-chip diagnostic devices. He says that the technique is a 'potentially useful concept' that could be used in highthroughput biological assays.

Jeong has recently set up a spin-out company to explore the opportunities that the technology presents and to develop it further. He admits that there are challenges ahead, both in improving the barcode detection speed and in developing high-throughput assays to exploit the technique. Nevertheless, he points out, the concept 'is generic enough to be applied to a variety of biological assays.'

Laura Howes

ChemComm

Molecular

BioSystems

Reference J-R Jeong *et al, Lab Chip*, 2008, **8**, 1883 (DOI: 10.1039/b807632d)

Lab on a Chip

## In this issue

## Quadruplex binding clicks into place

Ureas shun the double helix to bind quadruplex DNA

## **Fired up about fungi**

Russell Cox discusses his fiery introduction to chemistry, polyketide biosynthesis and Bristol's ChemLabS programme

## The path of least resistance

Instant insight: If targeting a virus directly promotes drug resistance, why not take a different approach?

## Life at the extremes

Instant insight: There are miniature natural product libraries to be found in the most unexpected places...



NPR

## **Research highlights**

# Solid-state NMR spectroscopy used to probe cause of spider silk's strength **INADEQUATE coverage of silky sheets**

Spider silk has a unique combination of mechanical properties that make it one of the toughest materials known. Now US chemists have used solidstate NMR spectroscopy to probe the structural features responsible for the silk's strength in an approach that could be applied to a range of biopolymers.

Spider dragline silk is made from two proteins. Its strength is thought

to come from sections of protein in a  $\beta$ -sheet conformation, while the elasticity comes from helical regions. Knowing the relative proportions of these conformations, and how this correlates to the amino acid sequence, is important for understanding the silk's mechanical properties and for developing

 $\beta\mbox{-sheets}$  are thought to give spider dragline silk its strength

**Reference** G P Holland *et al, Chem.* 

Commun., 2008, 5568 (DOI: 10.1039/b812928b) synthetic silk. Normally, spider silk produces broad unresolved NMR signals.

When the silk is treated with water, the fibres swell in diameter and shorten by approximately 50 per cent. Gregory Holland and Jeffery Yarger at Arizona State University in Tempe, and their colleagues were studying this supercontraction when they noticed that water affected the NMR response of the helical regions.

Holland explains the process: 'Water penetrates the helical domains and causes them to become mobile, resulting in a sharpening of their NMR resonances and an increase in resolution. In contrast, water does not penetrate the  $\beta$ -sheet domains so they remain rigid on NMR timescales and the resonances resemble those of dry silk.' The team used an incredible natural abundance double quantum transfer experiment (INADEQUATE) NMR method to

analyse spider silk. By exploiting the difference between the NMR spectra of wet and dry silk they could differentiate the signals from the helical and sheet structures and quantify the amino acid levels in each. They concentrated on the amino acids glycine and alanine, which make up 60–70 per cent of spider silk, and found that 28 per cent of the silk's glycines and 82 per cent of the alanines are in the  $\beta$ -sheet conformation.

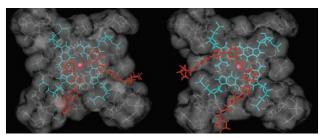
Holland and Yarger say that fully understanding the properties of spider dragline silk requires characterising the rest of its structure and the interactions between the two proteins. They are continuing to investigate these areas. *Michael Townsend* 

## Ureas shun the double helix to bind quadruplex DNA **Quadruplex binding clicks into place**

Small molecules selectively targeting four-stranded DNA could lead to anticancer drugs without the toxic side-effects, say scientists in the UK.

Quadruplex DNA is a fourstrand form of the biomolecule and is associated with cancer cell replication. Stephen Neidle and William Drewe at the University of London designed a series of diphenyl urea-based structures that bind strongly to quadruplex DNA but have low affinity for duplex DNA – the two strand double helix. This selectivity means the molecules aren't toxic to healthy cells, and could specifically knock out cancer cell growth, says Neidle.

Guanine-rich DNA quadruplexes (G4s) can be found in many telomeres, end sections of chromosomes which in healthy tissue gradually degrade until the cell can no longer divide. But in cancer cells, telomeres are continually maintained by telomerase – an enzyme switched off in most healthy adult tissue – effectively



Molecular modelling studies suggested that diphenyl ureas would bind to guanine-rich DNA quadruplexes

Reference

W C Drewe and S Neidle, Chem. Commun., 2008, 5295 (DOI: 10.1039/b814576h) making cancer cells immortal. Neidle and Drewe's molecules are designed to disrupt telomerase from binding to the quadruplex.

'The defining characteristic of most drugs is that they are toxic to most cells, including healthy ones,' says Neidle. 'We're looking for molecules that don't kill cells, but have a telomerase blocking mechanism.' While a number of molecules have been found to bind G4 DNA, these molecules have typically been unselective, and too large to be useful as drug molecules. 'The idea was to move away from polycyclics and develop a much more drug-like framework,' he adds.

Neidle and Drewe used click chemistry to link a biaryl urea core to two azide side chains, which modelling studies had suggested would bind strongly to G4 DNA. This synthetic strategy uses reliable reactions to join small units together, meaning that a variety of related compounds could be synthesised quickly for testing.

'Designing a drug-like quadruplex binder that really doesn't bind to duplex DNA is a pretty big step forward,' says Mark Searcey, who studies DNA quadruplex binding at the University of East Anglia, Norwich, UK. 'You're trying to target one DNA quadruplex among hundreds of thousands of duplexes, so you need very high selectivity,' he adds.

Having shown that the compounds selectively bind G4 DNA, and are not toxic to cells, Neidle is currently testing the compounds' ability to curb cancer cell growth. James Mitchell Crow

# Order-of-magnitude improvement for ion channel studies **Chip measures channel currents**

The disposable chip

allows non-invasive

electrophysiological

measurements

By allowing ions into and out of cells, ion channels play a crucial role in cell metabolism by regulating ion concentrations. Whilst this makes them key drug targets, these membranespanning pores respond so rapidly to changes in ion concentration that studying them can be difficult. Now, Elodie Dahan at the Swiss Federal Institute of Technology in Lausanne, and colleagues have addressed the problem using lab-on-a-chip technology.

Electrophysiologists evaluate ion channel reactions to drug candidates by measuring resulting changes in the channels' response times. These measurements are often made using the two electrode voltage clamp method, in which the cell is pierced with two microelectrodes to record the membrane cell potentials. Although automated versions are available, the impaling is time-consuming and may harm the cell. Also the measurements can be limited by the time it takes to replace the solution surrounding the cell. If these are much longer than the response time the cell will have already responded before the measurement can be taken.

The Swiss team's answer is a disposable chip for noninvasive electrophysiological measurements. Two different solutions flow into the chip mixing at the centre of a Yjunction. The mixed solution then flows towards a cell held inside the chip and the ion current across the cell membrane is measured. The chip design enables the user to change the solution flowing to the cell whilst maintaining a continuous flow, avoiding abrupt changes in shear force and stress effects on the cell membrane.

The team modified frog egg cells to express ENaC, a human sodium channel, which is involved in sodium transport in the kidneys and airways, and linked to conditions such as cystic fibrosis and hypertension.

> They then monitored the channel's response to sodium ion concentration by placing the egg cells in the chip and rapidly

exchanging a sodium-free solution for a sodium ion solution and recording the current across the membrane over time. The device showed an order of magnitude improvement over conventional techniques.

Daniel Irimia of Massachusetts General Hospital, Boston, US, who develops microfluidic devices for biological and clinical sciences, says the device is a 'wonderful example of how emerging technologies based on microfluidic principles enable more precise, quantitative measurements in biology.'

Dahan explains that the chip's design should allow other, more complicated experiments to investigate other ion channels. 'The possibility of investigating fast kinetic events of drug receptors with increased throughput overcomes classical bottlenecks and will open the way for such systems to be used in pharmacological laboratories,' she says. *Vikki Chapman* 

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## **News in brief**

#### This month in Chemical Science

#### A total mismatch

In this month's interview, Penny Brothers, associate professor at the University of Auckland, New Zealand, tells Michael Brown about porphyrins and their potential role in neutron capture therapy.

## Which came first, the nanotube or the egg?

Egg whites have found a novel use as a template for making inorganic nanotubes, thanks to Chinese scientists.

## Underperforming yeasts opt out of life

Suicide-committing yeasts are assisting German scientists striving towards the perfect enzyme for catalysing asymmetric organic reactions.

See www.rsc.org/chemicalscience for full versions of these articles.

#### This month in Chemical Technology

## Sweet solution for on-card reagent storage

Low-cost disposable cards for storing dry reagents could be used for point-of-care diagnostics in the developing world, claim US scientists.

## Microfluidics joins fight against bioweapon

US scientists have developed a new sensor capable of detecting trace levels of lethal neurotoxin botulinum toxin A.

See www.rsc.org/chemicaltechnology for full versions of these articles.

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## In the current issue of Research Articles...



**Scrapheap challenge and the single cell** Rupak Doshi and Philip J R Day, *Lab Chip*, 2008, **8**, 1774 (DOI: 10.1039/b811692j)

Affinity assays for detection of cellular communication and biomarkers

Christelle Guillo and Michael G Roper, *Analyst*, 2008, **133**, 1481 (DOI: 10.1039/b808735k)

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**Tissue engineering with nano-fibrous scaffolds** Laura A Smith *et al, Soft Matter,* 2008, **4**, 2144 (DOI: 10.1039/b807088c)

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Chemopreventive effects of natural dietary compounds on cancer development

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## Interview

# **Fired up about fungi**

Russell Cox discusses with Nina Notman his fiery introduction to chemistry, his work on polyketide biosynthesis and Bristol's ChemLabS programme



## **Russell Cox**

Russell Cox is a reader in organic and biological chemistry at the University of Bristol, UK, and a Bristol ChemLabS University Teacher Fellow. He is currently investigating programming in fungal iterative polyketide synthase, by applying molecular genetics, enzymology and synthetic chemistry.

#### Do you remember your first experiment?

As a young child, while living in Southampton, I remember filling an air-raid shelter in a friend's garden half an inch deep with methylated spirits and setting fire to it [Ed: we don't recommend you try this!]. This was definitely an experiment, but more designed to see whether the friend's mother would notice, or not. She didn't!

## What attracted you to research in biological chemistry?

Being in the right place at the right time. It was David O'Hagan who attracted me towards biological chemistry. I started a PhD with him combining synthesis and fungal biology and was hooked from then. I have always been grateful to have studied chemistry – the ability to synthesise and analyse compounds has underpinned all the advances in my area of research, but the questions of biology remain the biggest.

#### What are you working on at the moment?

Our biggest project is investigating programming in fungal iterative polyketide synthases. These enzyme systems are responsible for the biosynthesis of a huge range of biologically active compounds. The enzymes responsible are true nano-machines that are programmed to perform a choreographed sequence of reactions. We can change the reactions – but not yet rationally. We are applying molecular genetics, enzymology and synthetic chemistry to investigate this problem. At the moment we are attempting to shuffle genes encoding proteins with closely related programmes in order to dissect the programmes and discover which parts of the proteins are involved.

## What are the wider aims of Bristol's new ChemLabS other than the teaching of the university's undergraduates?

ChemLabS is a truly innovative programme. We were lucky enough to win funding from the Higher Education Funding Council for England to set up a centre of excellence in teaching and learning focussed on practical chemistry. We have invested in our teaching labs to make them world-class, and have brought the level of infrastructure and equipment up to industrial standards. Simultaneously, we have rebuilt all of our practical teaching material and developed a fully integrated digital system (called the Dynamic Laboratory Manual, DLM) to support all of our practical teaching. Students now are encouraged to use simulations of techniques, equipment and individual experiments before they go into the labs. We now use this methodology at all levels in the School of Chemistry at Bristol, but we are expanding with commercial partners, to make a DLM for AS and A level study.

#### What advice would you give to a young researcher who wants to forge a career in biological chemistry research?

Move to Germany or the US! The UK has a truly great history of scientific discoveries, especially in biological chemistry, and some great scientists, but we make life difficult for ourselves. Researchers in British universities have to fit research interests in around a full schedule of teaching and administration so time is at a premium, and the funding situation for chemistry is pretty tough in the UK at the moment.

#### You are a keen and successful teacher of undergraduates (having recently won the Faculty of Science Teaching Prize at Bristol), and were heavily involved in the launch of ChemLabS. What do you view as the necessary ingredients to be a good teacher?

The ability to see problems from different perspectives – our students vary tremendously in their backgrounds and approaches to learning. I am lucky to be working with a very skilled and experienced team at Bristol, and I have learned as much, or more, by being a teacher as any other aspect of my career.

#### What do you like to do in your spare time?

I've given up setting fire to air-raid shelters, but I still like knocking things down. I am currently working on my house in the Mendips, knocking bits down and building new bits. I recently sawed a huge oak beam out of the loft to create space for a new room, and I enjoy plumbing, wiring and carpentry. I have two young sons and we spend a lot of time together, fishing, sailing and even doing the odd scientific experiment.

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

I'd be a gardener. Chemistry and gardening have much in common: one has to have a plan and vision and see far ahead. Gardens require patience, nurture and constant attention, and the results are very rewarding – but you don't need to write grant applications!

# Instant insight The path of least resistance

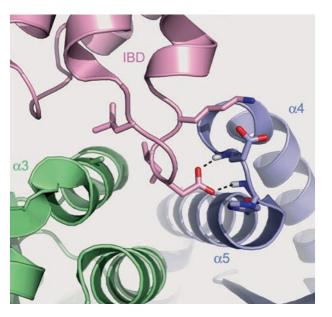
If targeting a virus directly promotes drug resistance, why not take a different approach? Zeger Debyser and colleagues at the Catholic University of Leuven, Flanders, Belgium, suggest an alternative

Until very recently, the prospect of using small molecules to block specific protein-protein interactions was viewed with much skepticism. But protein-protein interactions play a key role in most biological processes and therefore are an important class of therapeutic targets. These interactions were overlooked for a long time, since developing drugs against the traditional targets such as enzymes and receptors was more cost effective. Since the cost of developing these classical drugs is increasing rapidly and pipelines are running dry, research into proteinprotein interactions is becoming feasible and warranted.

This idea can be applied to the human immunodeficiency virus type 1 (HIV-1). The virus relies on several cellular proteins to replicate, proteins referred to as cofactors. Not only does understanding the interaction between HIV proteins and cellular cofactors shed light on the virus's effects but it provides new strategies for antiviral therapy.

Developing drugs to target cellular cofactors constitutes a paradigm shift in antiviral research as present day antivirals typically target viral proteins. In the case of chronic viral infection this specificity for the viral target comes at a cost since viruses, with their high mutation rate, can become resistant to the antiviral drugs. The answer could be to develop drugs that target specific virus protein– cofactor interactions.

The conserved nature of cellular proteins may provide a critical advantage in the struggle against antiviral resistance. The virus may find more difficulties in developing



Targeting protein-protein interactions such as that between HIV-1 integrase (green and blue) and the cellular cofactor LEDGF/ p75 (purple) could lead to new antiviral drugs

Reference

h810306h

K Busschots et al. Mol.

BioSyst., 2008, DOI: 10.1039/

resistance against drugs targeting interactions between invariable cellular proteins and conserved viral protein domains. Also, since a specific protein–protein interaction is targeted and not the cellular protein per se, this should circumvent cellular toxicity. Moreover, outside the field of infectious diseases, drugs can target cellular targets in a nontoxic way.

One of the major obstacles to finding small molecule protein– protein interaction inhibitors (SMPPIIs) is the flat nature of the protein–protein interface. X-ray structures have shown that a large part of the interaction area is buried, with atoms closely packed together, implying a lack of available cavities for small molecule binding. Yet, it has become clear that some protein– protein interfaces have a welldefined compact area, commonly referred to as a hot spot, which plays a major role in the interaction. These hot spots define potential targets for SMPPII development.

Returning again to the HIV example, our group discovered the cellular cofactor LEDGF/p75 which plays a crucial role in HIV replication. The cofactor is essential to the viral enzyme HIV integrase, which helps incorporate the viral DNA into regions of the host cell where it will be transcribed. LEDGF/p75 had previously been reported as a cellular stress response factor and a variant, p52, as a transcriptional coactivator but the link with HIV was unexpected. The interaction with integrase is specific for the p75 form; LEDGF/p52 lacks the integrase binding domain (IBD).

A crystal structure of the dimeric catalytic core domain of HIV-1 integrase complexed to the IBD of LEDGF is available (see figure). An interhelical loop of the IBD protrudes into a pocket at the interface of the integrase core. This pocket classifies as a hot spot for interaction and a suitable drug target. We have established an assay to detect SMPPIIs for the integrase-IBD interaction. Early hits with micromolar activity in vitro and in cell culture have raised our hopes that we can effectively and safely block this protein-protein interaction in HIV infected patients in the future.

Read more in Debyser et al's review 'In search of small molecules blocking interactions between HIV proteins and intracellular cofactors' in Molecular BioSystems.

# Instant insight Life at the extremes

There are miniature natural product libraries to be found in the most unexpected places. Zoe Wilson and Margaret Brimble of the University of Auckland, New Zealand, delve deeper

A microorganism that survives extreme environments can be classified as either extremetolerant, if it grows best under more moderate conditions, or extremophilic, if it grows optimally under these extraordinary conditions. In order to survive in such settings, microorganisms have developed unique defences, and this has frequently led them to produce novel molecules. This has made them a mine for natural product chemists. But whilst the first extremophilic organism was isolated in the 1860s, it took over a century for scientists to realise that the number of these organisms is significant, leading to a rapid growth in research in this area.

Traditionally, the extremes of life are considered to be high and low temperature (inhabited by thermophiles and psychrophiles respectively), high pressure (piezophiles/barophiles), high and low pH (alkaliphiles and acidophiles), and high salt (halophiles). Many extremophiles actually thrive in environments which are extreme in two or more aspects. For example, the Shewanella violacea strain DSS12, which produces a novel violet pigment, was isolated from the Ryukyu trench in the Philippine Sea, at a depth of 5110m. This bacterium is a barohalopsychrophile - growing optimally at 30MPa, 8°C and in the presence of 3 per cent sodium chloride.

To date the largest number of novel molecules from extreme dwelling microorganisms have been isolated from thermophiles. Several of these molecules are thought to play a role in survival at extreme temperatures, such as ether linked lipids, modified nucleosides and a variety of



Geysers and geothermal sites are just two of the many unlikely environments where microorganisms have been found

Reference

Z E Wilson and M A Brimble.

Nat. Prod. Rep., 2009, DOI:

10.1039/b800164m

polyamines which are thought to stabilise DNA at high temperatures by reducing flexibility.

The term psychrophile was first used in 1902. Representatives of all the major taxa have been found inhabiting temperatures below 0°C, making this is one of the more diverse branches of the extremophiles. To date however the only novel molecules first isolated from psychrophilic or psychrotolerant microorganisms are secondary metabolites, which are largely based on modified peptides. These include mixirins A-C, three cyclic peptides isolated from the psychrotolerant Bacillus sp. strain MIX-62, which have been shown to inhibit human colon tumour cell growth.

Piezophiles (barophiles) are typically isolated from the bottom of the ocean and the majority of secondary metabolites isolated from these extremophiles are cyclic. Notably, a series of cyclic secondary metabolites that halt cell replication in mouse tsFT210 cells were isolated from *Aspergillus fumigatus* strain BM939, a fungus isolated from the sea bottom of the Oi river, Sizuoka prefecture, Japan.

Halophiles have to survive osmotic stress. One survival mechanism they use is to accumulate small molecules known as osmolytes, with eight novel osmolytes being first isolated from halophilic or halotolerant microorganisms.

Enzymes from alkaliphilic or alkali-tolerant microorganisms have made a large impact due to their industrial applications in biological detergents. But, to date, relatively few novel molecules have been isolated from these microorganisms. Among them are novel carbohydrates and an unusual lipid from bacteria of the *Halomonas* species.

Microorganisms capable of surviving low pH have been isolated from a range of sources around the world, both natural, for example acidic hot springs, and man-made, such as Berkeley Pit Lake (an abandoned copper mine which filled with acidic water). These microorganisms produce diverse secondary metabolites with a range of biological activities. For example, thirteen of the molecules isolated from Berkeley Pit Lake microorganisms inhibit proteincleaving enzymes caspase-1 and matrix metalloproteinase-3.

When the large number of reported extremophiles is considered, very few have been screened for novel secondary metabolite production. Despite nearly 150 years in the public domain, this rich source of novel molecules remains largely untapped.

*Read more in 'Molecules derived from the extremes of life' in issue 1, 2009, of Natural Product Reports.* 

# **Essential elements**

## **Board member wins Nobel Prize**

The Nobel Prize in Chemistry 2008 has been awarded to Roger Tsien (below right), University of California, San Diego, US, a member of the editorial board for the upcoming RSC journal *Integrative Biology* (to be launched in January 2009), and colleagues for their work in the development of the gene marker green fluorescent protein (GFP).

Harp Minhas, editor of Integrative Biology, says: 'Congratulations to Professor Tsien, from all of us at the RSC. We are all immensely pleased that 2008 Nobel Prize winner Roger Tsien is an editorial board member for Integrative Biology; his work typifies the quality of material we are seeking in the development of biology through new tools and technologies.'

Derivatives of GFP are used in experiments to observe

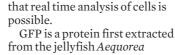
## Integrative Biology



cell dynamics and behaviour – their

fluorescent glow allows scientists to visualise processes inside cells. Furthermore, as it

is non-toxic to cells it can be used in live



cell (in vitro) studies meaning

victoria in the 1960s by Osamu Shimomura, who was jointly awarded this year's prize with Tsien and Martin Chalfie. Variants of GFP can fluoresce in different colours, allowing several different proteins

in a cell to be studied simultaneously.

Find out more about our new journal Integrative Biology at www.rsc.org/ ibiology

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## Announcing Lab on a Chip prize winners

Lab on a Chip, the miniaturisation journal for chemistry, biology and bioengineering, has yet again shown extensive community support by sponsoring some of the most prestigious prizes in the miniaturisation field. At this year's µ-TAS meeting in San Diego the journal, together with Corning Inc., awarded the 'Pioneers in Miniaturisation Prize' to Patrick Dovle. professor at the department of chemical engineering at MIT, US. Jean-Louis Viovy from the Institute Curie comments on Doyle's

Chemical Biology (ISSN: 1747-1605) is published monthly by the Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge UK CB4 0WF. It is distributed free with Chemical Communications, Organic & Biomolecular Chemistry, Molecular BioSystems, Natural Product Reports, Dalton Transactions and Photochemical & Photobiological Sciences. Chemical Biology can also be purchased separately. 2008 annual subscription rate: £199; US \$396. All orders accompanied by payment should be sent to Sales and Customer Services, RSC (address above). Tel +44 (0) 1223 432360, Fax +44 (0) 1223 426017. Email: sales@rsc.org work: '[Patrick] developed the "stop-flow lithography" technological platform, which I consider a major breakthrough in microfluidics.'

Lab on a Chip also awarded the 'Widmer Young Researcher Poster Award' to Maged Fouad for best poster and presentation. Among 589 candidates, this poster titled 'Nanotechnology meets plant biotechnology: carbon nanotubes deliver DNA and incorporate into the plant cell structure' caught the judges' eyes.

A new award named 'Art in

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Science' recognised the aesthetic value in scientific illustrations. 'The winner, Yu Wen Huang (Texas A & M University) clearly understood the principles of this award and produced an image that was reminiscent of a tall city building seen in an early morning fog. The picture is an optical effect generated by concentrated double-stranded DNA in the vicinity of a 50 micrometre wide electrode inside a microchannel.' comments Harp Minhas, editor of Lab on a Chip, who proudly presented all awards to the winners.

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