Organic & Biomolecular Chemistry

An international journal of synthetic, physical and biomolecular organic chemistry

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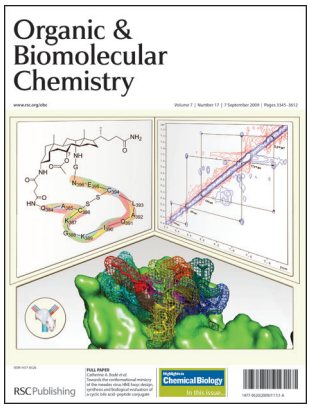

Cover

See Catherine A. Bodé *et al.*, pp. 3391–3399.
The haemagglutinin noose epitope (HNE) of the H-protein of measles virus and the mouse monoclonal antibodies specifically binding this epitope acted as tools to develop a novel construct of the HNE-peptide bound to a bile-acid scaffold. The H-protein (pbd code 2ZB6) illustration was performed with Pymol.

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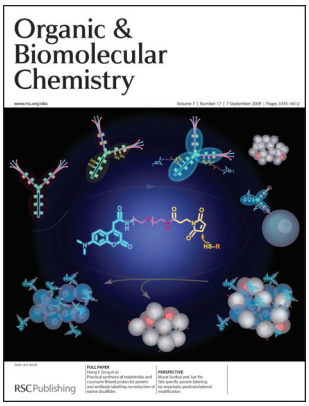

Inside cover

See Hong Y. Song *et al.*, pp. 3400–3406.
Reduction of disulfides within antibodies and cysteine-based fluorescent tagging with a water-soluble maleimide reagent allows for a convenient way to sort cells and label proteins.

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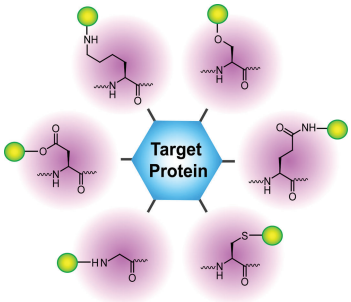

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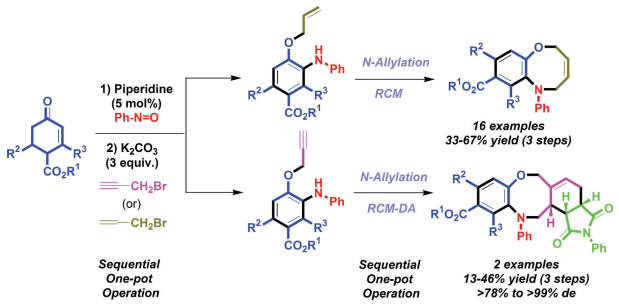
3372

High-yielding synthesis of Nefopam analogues (functionalized benzoxazocines) by sequential one-pot cascade operations

Dhevalapally B. Ramachary,* Vidadala V. Narayana, M. Shiva Prasad and Kinthada Ramakumar

An efficient process for the synthesis of Nefopam analogues was achieved through combinations of cascade enamine amination/iso-aromatization/*O*-allylation and diene or enyne metathesis as key steps starting from functionalized Hagemann's esters *via* amine-/ruthenium-catalysis.

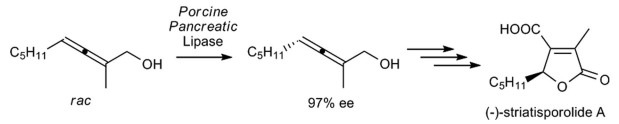


3379

Enzymatic kinetic resolution of primary allenic alcohols. Application to the total synthesis and stereochemical assignment of striatisporolide A

Jan Deska and Jan-E. Bäckvall*

Porcine pancreatic lipase catalyzes the kinetic resolution of axially chiral allenols with high enantioselectivity. This approach towards optically active allenes was applied to the total synthesis of the fungal metabolite (–)-striatisporolide A.

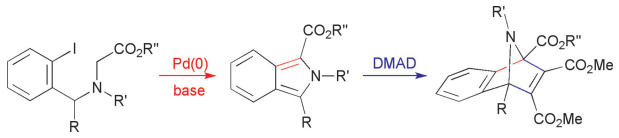


3382

Palladium-catalysed synthesis of 1-isoindolecarboxylic acid esters and sequential Diels–Alder reactions: access to bridged- and fused-ring heterocycles

Daniel Solé* and Olga Serrano

The Pd-catalysed intramolecular α-arylation of α-amino acid esters provides a useful methodology for the synthesis of substituted isoindole derivatives, which have been used in Diels–Alder reactions to access diverse skeletal frameworks.

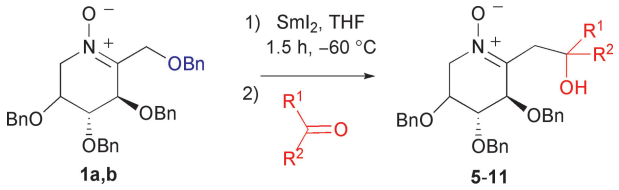


3385

Tandem SmI_2-induced nitrone β-elimination/aldol-type reaction

Emilie Racine and Sandrine Py*

Upon treatment with SmI_2, the carbohydrate-derived nitrones **1a,b** undergo a *β*-elimination of the benzyloxy group at C-1, forming original samarium(III) oxy-enamine intermediates. The latter can be reacted with carbonyl compounds to produce aldol-type adducts. The tandem process results in the transformation of a C–O bond into a C–C bond.



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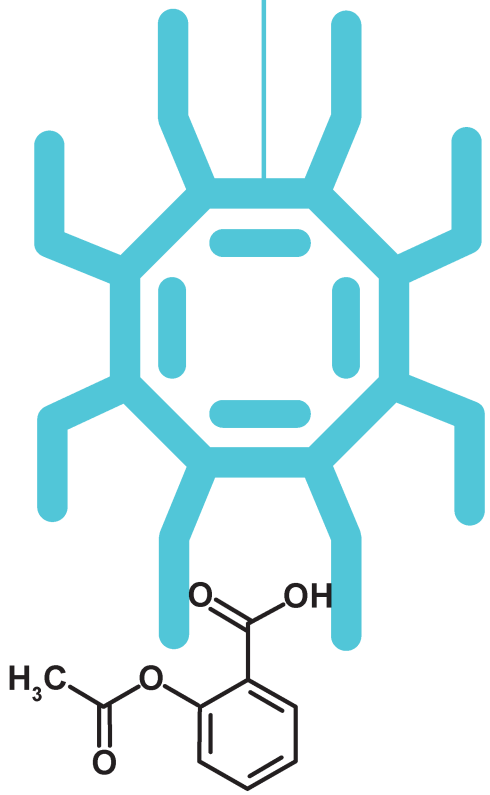

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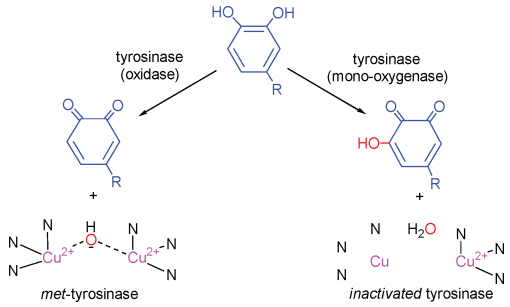
The influence of catechol structure on the suicide-inactivation of tyrosinase

Christopher A. Ramsden,* Michael R. L. Stratford and Patrick A. Riley

3,6-Difluorocatechol, which cannot act as a monooxygenase tyrosinase substrate, is an oxidase substrate, and, in contrast to other catechols, oxidation does not lead to suicide-inactivation, providing experimental evidence for an inactivation mechanism involving reductive elimination of Cu^0 from the active site.



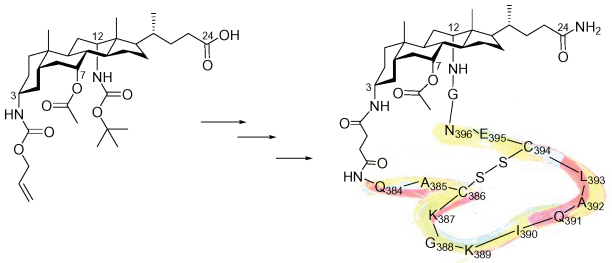
PAPERS

3391

Towards the conformational mimicry of the measles virus HNE loop: design, synthesis and biological evaluation of a cyclic bile acid–peptide conjugate

Catherine A. Bodé, Tom Bechet, Emmanuel Prodhomme, Katelijne Gheysen, Pieter Gregoir, José C. Martins, Claude P. Muller and Annemieke Madder*

A cyclic bile acid–peptide conjugate as a mimic of the loop-like structure of the measles virus HNE epitope was synthesised. This macrocycle displayed increased biostability and good HNE antibody binding and thus has potential in a peptide-based vaccine.

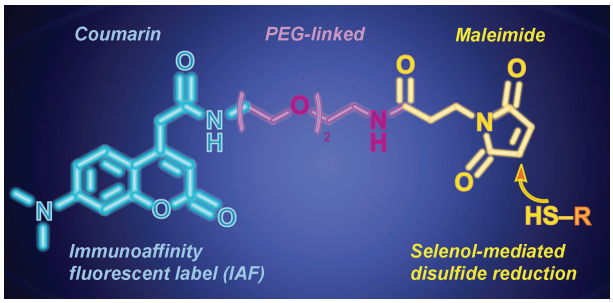


3400

Practical synthesis of maleimides and coumarin-linked probes for protein and antibody labelling *via* reduction of native disulfides

Hong Y. Song, Mun H. Ngai, Zhen Y. Song, Paul A. MacAry, Jonathan Hobley and Martin J. Lear*

Reduction of disulfides within antibodies and cysteine-based fluorescent tagging with a readily made, water-soluble maleimide reagent allows for a convenient way to sort cells and label proteins.

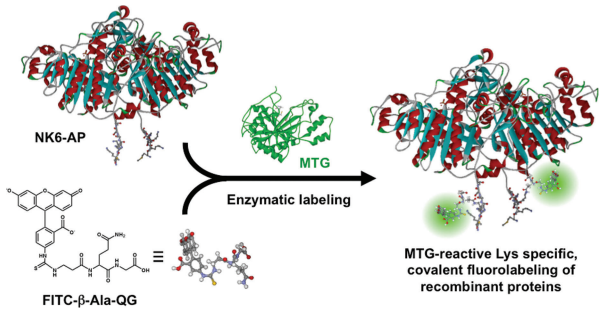


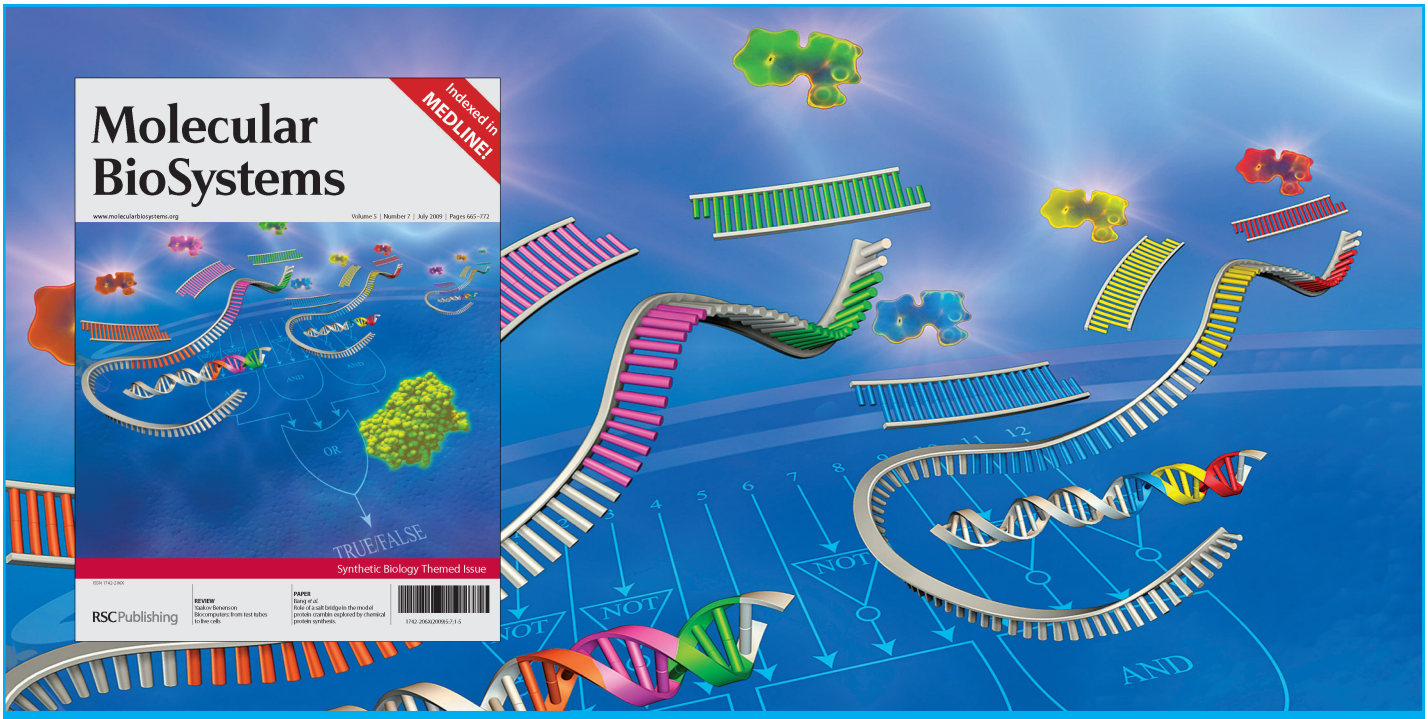
3407

Fluorescent substrates for covalent protein labeling catalyzed by microbial transglutaminase

Noriho Kamiya,* Hiroki Abe, Masahiro Goto, Yukiko Tsuji and Hiroyuki Jikuya

Novel small substrates with a variety of fluorophores were designed for site-specific and covalent labeling of recombinant proteins catalyzed by microbial transglutaminase.





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Molecular BioSystems issue 7, 2009, is a themed issue on **Synthetic Biology** coordinated by Editorial Board members Hagan Bayley (Professor of Chemical Biology, Oxford University, UK) and Sachdev Sidhu (Assistant Professor, Banting and Best Department of Medical Research, University of Toronto, Canada).

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Darwinian chemistry: Towards the synthesis of a simple cell
Phil Holliger and David Loakes

Synthetic Chemistry Used to Make, Study the Folding, and Determine the X-ray Structure of a Unique Protein Analogue, [V15A]Crambin-α carboxamide
Stephen Kent, Duhee Bang, Anthony A Kossiakoff, Valentina Tereshko

Biocomputers: from test tubes to live cells
Yaakov Benenson (also provided the cover image)

A Synthetic Metabolite-Based Mammalian Inter-cell Signaling System
Martin Fussenegger, Nicholas Denervaud, Marco Schütz, Wilfried Weber

Engineering and Exploiting Protein Assemblies in Synthetic Biology
Stefan Howorka and David Papapostolou

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Pam Silver and Christina Agapakis.


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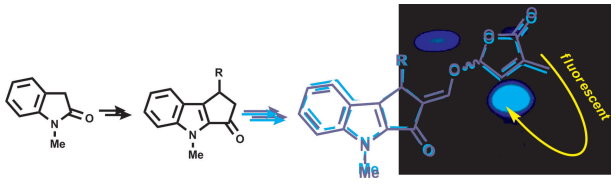

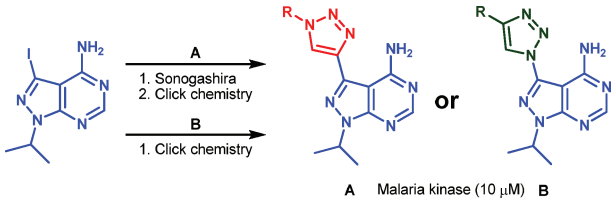

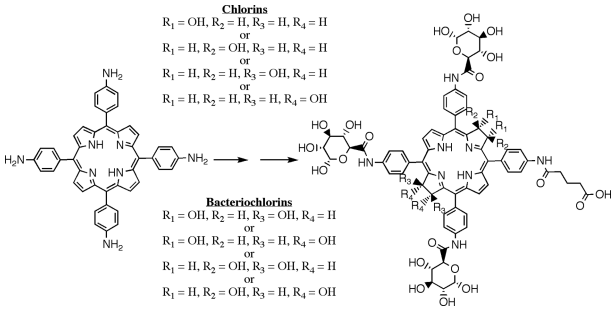

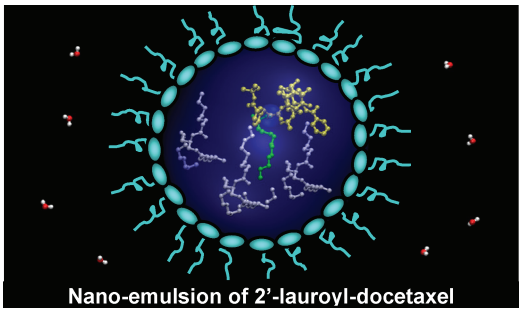

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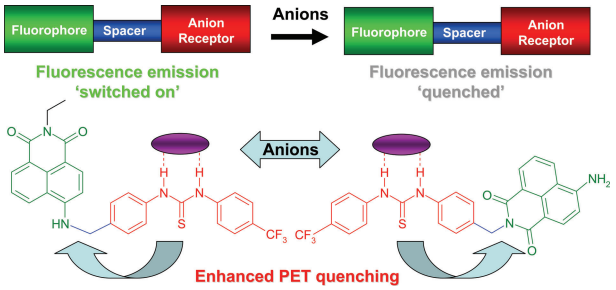
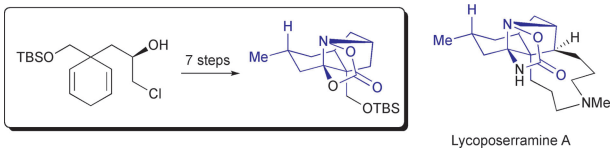


Demonstration of bidirectional photoinduced electron transfer (PET) sensing in 4-amino-1,8-naphthalimide based thiourea anion sensors

Emma B. Veale, Gillian M. Tocci, Frederick M. Pfeffer, Paul E. Kruger and Thorfinnur Gunnlaugsson*

The fluorescence emission of the PET anion sensors **1–5** is quenched in DMSO solution, upon binding of acetate, phosphate and fluoride to the di-aryl thiourea receptors, which are located either at the 4-amino moiety or at the imide site.

3455

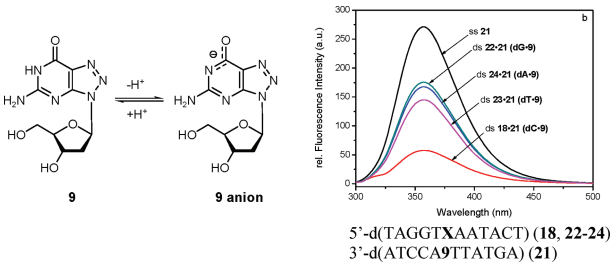


Studies towards the total synthesis of lycoposerramine A. Synthesis of a model for the tetracyclic core

Mark C. Elliott* and James S. Paine

A model compound for the tetracyclic core of lycoposerramine A has been prepared in seven steps, including a free-radical desymmetrisation of a cyclohexa-1,4-diene and a novel spirocyclisation.

3463



8-Aza-2′-deoxyguanosine: Base pairing, mismatch discrimination and nucleobase anion fluorescence sensing in single-stranded and duplex DNA

Frank Seela,* Dawei Jiang and Kuiying Xu

Oligodeoxyribonucleotides containing 8-aza-2′-deoxyguanosine (**9**) were synthesized. The fluorescence of **9** is sensitive to pH changes and its anion is strongly fluorescent. DNA mismatch studies show (X = dA, dG, dT, dC) that quenching is strongest when **9** is part of a Watson–Crick base pair.

3474

Acetylenic tetrathiafulvalene-dicyanovinyl donor-acceptor chromophores

Asbjørn Sune Andersson, François Diederich and Mogens Brøndsted Nielsen*

Novel donor-acceptor chromophores based on tetrathiafulvalene and cyanoethynylethenes were synthesised and characterised by cyclic voltammetry and UV-Vis absorption spectroscopy.

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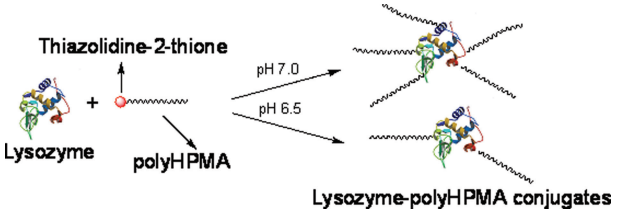

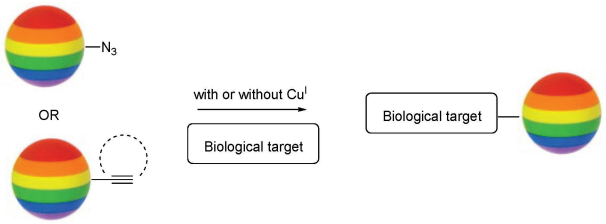

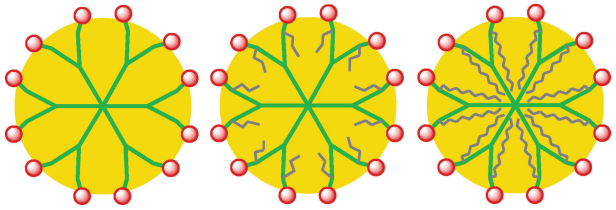

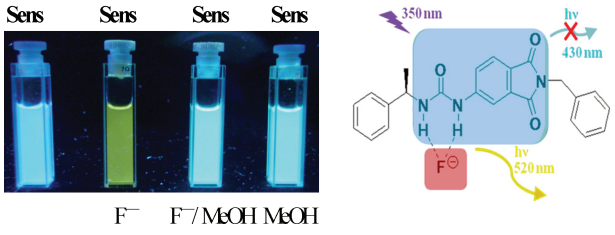

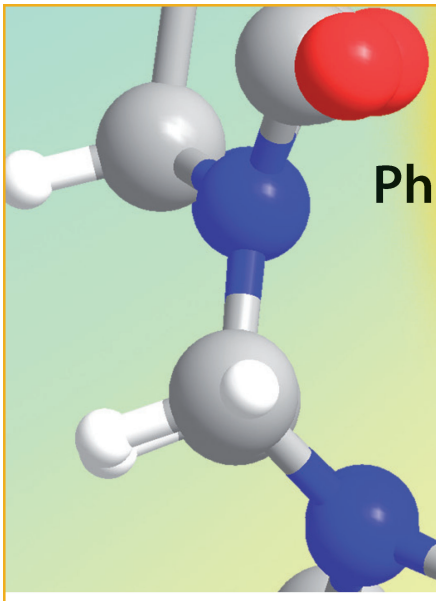

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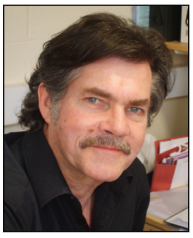

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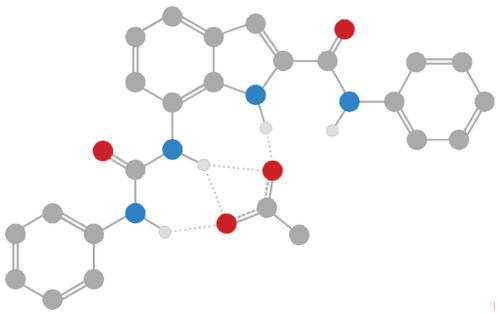

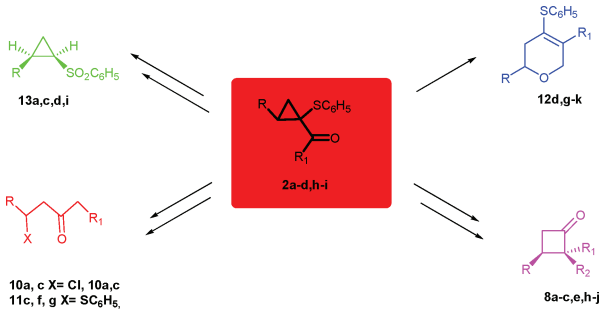

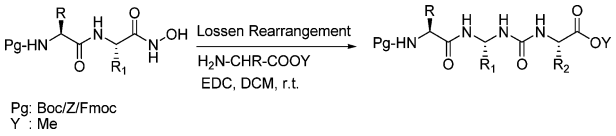

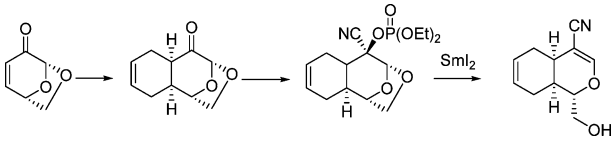

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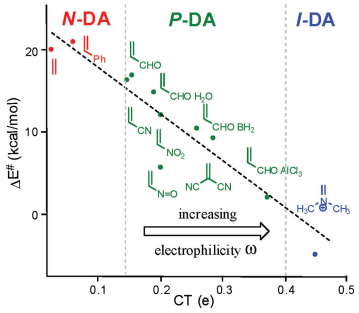

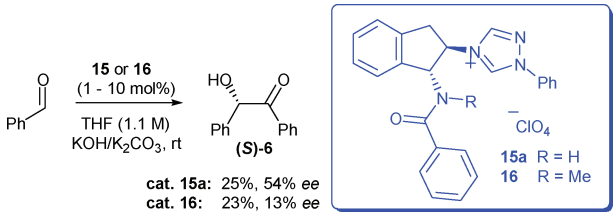

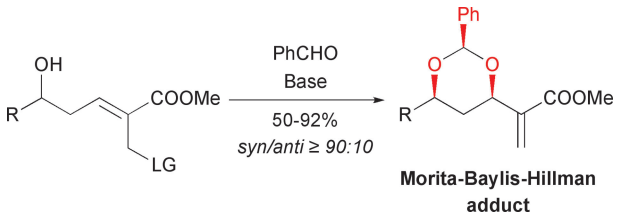

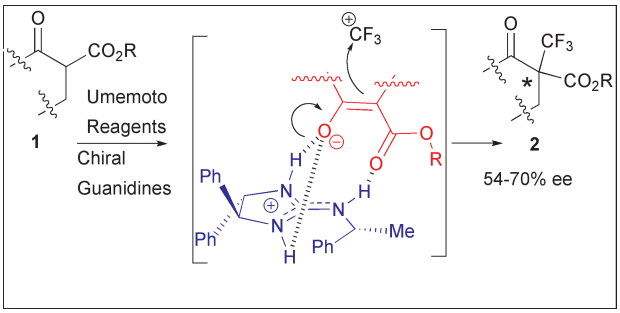

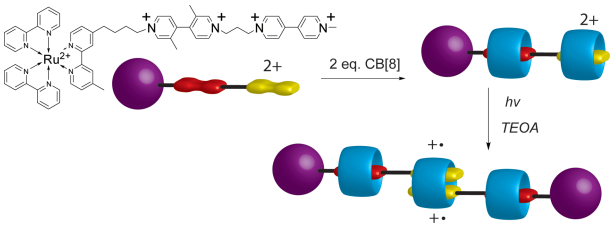

Light driven formation of a supramolecular system with three CB[8]s locked between redox-active Ru(bpy)$_3$ complexes

Samir Andersson, Dapeng Zou, Rong Zhang, Shiguo Sun and Licheng Sun*

Three CB[8]s have been reversibly locked between two Ru(bpy)$_3$–viologen complexes by light driven electron transfer reactions.

AUTHOR INDEX

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Highlights in
Chemical Biology

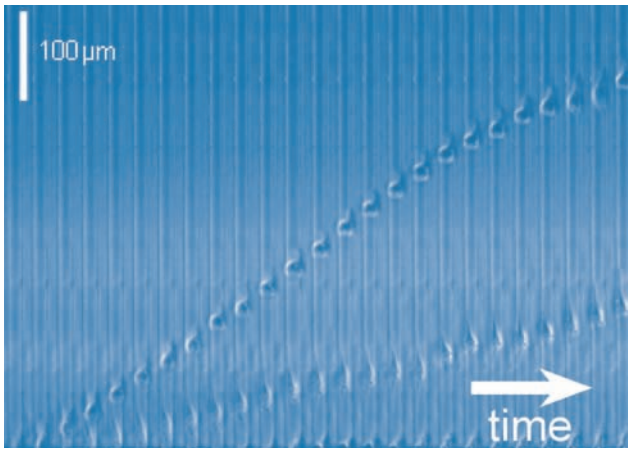
Metastasis mechanism revised as cancer cells move spontaneously

Watching cancer cells spread

A simple channel is all it takes to challenge established beliefs about cancer cell migration and offer a solution.

If you're unlucky enough to be diagnosed with a malignant form of cancer one of the first things the doctor will test are your lymph nodes. The outcome of this test dramatically changes your prognosis and the treatments used, as cancer cells can spread from the lymph nodes throughout the body, a process known as metastasis. Now, work by Daniel Irimia and Mehmet Toner at Harvard Medical School in Boston, US, suggests the mechanism of metastasis may be different to previously thought.

Until now the hypothesis has been that for cancer cells to spread they need a concentration gradient to direct their motion. Irimia's work, however, shows that the gradient is not necessary and that when they are constrained within a small channel cancer cells will spontaneously move in one direction.



Cancer cells migrate in one direction along microchannels

Irimia and Toner initially designed their microchannel system to investigate guided cancer cell migration, to mimic the process occurring along vessels and fibres in the body. However, Irimia says they were surprised to find that the cells could travel continuously in one direction for hours without a chemical gradient being applied.

Reference
D Irimia and M Toner, *Integr. Biol.*, 2009, DOI: 10.1039/b908595e

They noted that some cells could still migrate after being exposed to the anticancer drug Taxol, something Irimia describes as 'scary'.

Peter Friedl, an expert in cell migration from the Nijmegen Centre for Molecular Life Sciences in the Netherlands, suggests that the researcher's system could also be used to study cancer treatments. 'The device complements existing migration assays,' he says. 'It allows the study of 3D migration in a defined environment that is amenable for [high-throughput] research, particularly for screening for anticancer drugs.'

The pair say that this is their next step as they plan to investigate how the cell migration can be stopped. They aim to perform screens by placing the devices into a 96 well plate, a standard piece of lab kit. 'My feeling is that if we are able to stop the cells [in the microchannels] it will have some relevance,' says Irimia. 'But that's just my intuition at the moment.' *Laura Howes*

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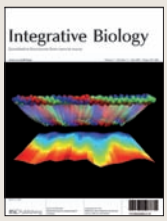

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Research highlights

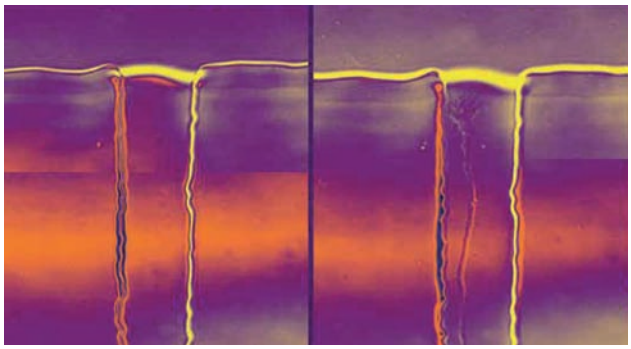
Developments in brain injury studies as laser hits a nerve

Déjà vu for axon regrowth

Damaged brain cells retrace their steps when they repair themselves, say US scientists.

A microfluidic device has enabled the American team to study single mammalian axons – projections sent out by nerve cells – as they regenerate after laser-induced injury. Digant Davé and colleagues at the University of Texas, Arlington, say their method could provide insights into the effects of injury on the nervous system including the events that occur after spinal trauma. 'So much of regenerative neurobiology remains largely unknown,' declares Davé.

The new device has three components: a microfluidic chip to isolate single axons, a laser for highly localised injury and a custom-built incubator, all on an inverted microscope. Using these tools, Davé's group can cut hundreds of individual axons reproducibly and at precise locations. In this way the team can monitor the axons as they regenerate and observe their growth over distances of several millimetres, which until now has not been possible using conventional tools.



After axons are cut, the nerve cell projections can regrow (left to right)

Reference
Y Kim *et al*, *Lab Chip*, 2009, DOI: 10.1039/b903720a

The researchers have made many surprising observations using the device. 'Very interestingly, we found that neurons [from the brain cortex] closely follow the same track they had before injury after regeneration,' says Davé. In contrast, neurons found in the spinal nerve follow a new path.

'Neuronal repair studies are important for improving our understanding of the mechanisms that enable functional recovery from traumatic injury to the nervous system,' explains Larry Millet, an expert in neurobiology and microfluidics at the University of Illinois at Urbana-Champaign, US. Microfluidic devices are indispensable to control and manipulate the microenvironment in these studies, he adds.

Davé's team has also used the platform to create a neuronal circuit model to study how injury affects connections between axons and muscles. 'It's simply amazing to see how dynamic these neurons are,' says Davé. *Nicola Cogan*

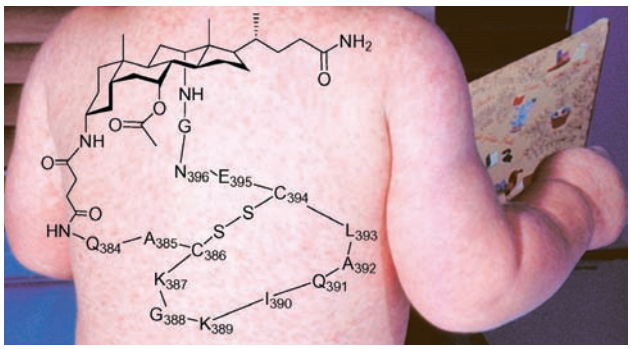
Liver compound and measles protein fragment combined for potential vaccine

A structured approach to measles

European scientists are one step closer to a new measles vaccine, which they say may be suitable for very young infants among the most at risk from the disease.

Annemieke Madder, from Ghent University, and colleagues in Belgium and Luxembourg have made a molecule that combines a fragment of a measles virus protein with a derivative of cholic acid – a bile acid made naturally in the liver. The acid derivative is attached to the protein fragment in a cyclic fashion, so that it acts as a scaffold to maintain the fragment's helical shape. The structure stabilises the protein fragment in biological fluids. The aim is to prevent the body from breaking it down until it has invoked an immunological response.

Madder says that 'such a construct could find application in modern vaccine technology, which has been evolving towards the inclusion of only the most essential virus parts or derivatives in new formulations for the prevention and treatment of a great number of diseases.' The team has already demonstrated that antibodies known to bind to the measles virus also successfully bind to the construct.



By joining it to a bile acid derivative Madder's measles virus fragment maintains its shape and antibody-binding

Reference
C A Bodé *et al*, *Org. Biomol. Chem.*, 2009, DOI: 10.1039/b907395g

Measles is a highly infectious disease, killing 197 000 people in 2007. Currently a live-attenuated vaccine – a weakened version of the live virus – is used to prevent the disease. But this vaccine is usually given to babies only after around 6–9 months as at an earlier age it can be destroyed by vaccine-neutralising maternal antibodies. Maternal antibodies also destroy the disease itself, but these antibodies, particularly in babies in developing countries, can wane at an early age, leaving infants vulnerable to the disease. Vaccines based on virus fragments can overcome these problems as they avoid detection by maternal antibodies but are still able to stimulate antibody formation. Madder says that such vaccines could be given at a much younger age.

'This work showcases an elegant solution to the problem of conformational control in peptides,' says Anthony Davis, an expert in bile acid scaffolds from the University of Bristol, UK. 'Bile acids have been used as functionalised scaffolds in a number of other areas, but this extension into vaccine design is novel and seems very promising,' he says.

To move this project forward Madder's team will next be looking into applying well-known reactions – such as click chemistry – to make the cyclic peptide conjugates. *Jennifer Newton*

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

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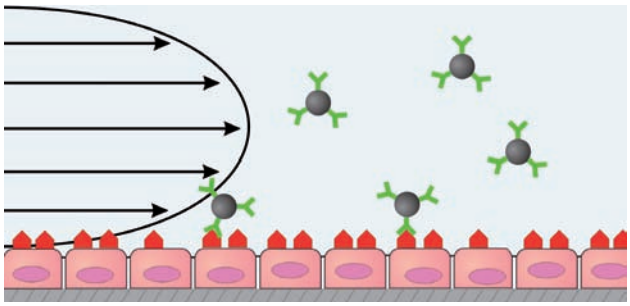
Microfluidic chip mimics physiological flow conditions

Nano-earthquake to shake up drug screening

A thumbnail-sized chip is mimicking the turbulent conditions a drug experiences on its journey through the body. Franz Gabor, at the University of Vienna, and colleagues in Austria and Germany developed the sound-driven biochip that can be used to study how moving fluids affect cell–particle interactions.

Nanoparticles with tailored properties are promising vehicles for drug delivery. But to develop these systems, researchers need to better understand how the body affects the particles' route to their target. This means that they must simulate the physiological environment in the lab. Gabor's team has developed a fully biocompatible system that mimics a range of flow conditions, such as those that would be found in the circulatory system, on a microfluidic chip.

'At the heart of our flow system is the surface acoustic wave pump which is only as big as pinhead,' says Christian Fillafer, a member of the European team. 'When the pump is activated, it generates a nano-earthquake on the chip surface and liquid can be streamed by placing it into the epicentre.' Using a liquid containing a cell and nanoparticle mixture, the researchers can monitor how stress affects the particles' interactions with the cells.



Bioadhesive proteins help nanoparticles to stick to cells in flow conditions

'Using this set up we observed that flow completely inhibits nanoparticle binding to cells, unless the particle surface is modified with a bioadhesive protein,' says Fillafer. 'This bears implications for drug delivery, since flow is omnipresent in the body from the urinary tract to the cardiovascular system.'

Michael Köhler, an expert in miniaturisation biotechnology at the Ilmenau University of Technology, Germany, agrees that the findings may have consequences for drug delivery. He suggests that 'further investigation could address the behaviour of other cell types and classes of particles.' In particular, he adds that 'studying interactions of lymphocytes [key to the immune system] with bacteria, viruses and cancer cells could be of particular interest.'

The pump's small size and lack of tubes and connectors makes it ideal for use in highly miniaturised devices. Gabor's team is now developing a platform that can generate identical flow conditions in several independent microchannels. They suggest that, as well as for fundamental research into cell–particle binding, the device could be used for drug screening studies that are not possible with large scale conventional systems. *Philippa Ross*

Reference
C Fillafer *et al*, *Lab Chip*, 2009, DOI: 10.1039/b906006e

Cell boosting peptide could help diabetics

Blood cells get active

American scientists have shown that a peptide produced in the body could potentially be used to treat type 2 diabetes.

C-peptide is released into the bloodstream at the same time as insulin and is often measured in diabetic patients to determine the levels of insulin that they produce. Recently, C-peptide treatment has been found to have beneficiary effects for type 1 diabetes; however, it doesn't affect type 2 blood cells as it cannot bind to their membranes. Now, a team led by Dana Spence at Michigan State University, East Lansing, US, has found that C-peptide can be activated with zinc to increase binding.

Spence explains that the membranes of the diabetic red blood cells are more negatively charged than healthy ones as negative phoshphatidyl serine groups flip from the inner to the outer cell membrane.

Peptide treatment could make diabetic blood cells healthier

'At physiological pH, C-peptide is negatively charged as well so they're probably not going to interact very much,' he says. 'We think that the positively charged metal facilitates the interactions between the peptide and the membrane.'

Spence's team found that the zinc–peptide species improved type 2 blood cells' activity, which is typically lower than that of normal cells. They measured the activity by monitoring the adenosine triphosphate (ATP) released from the red blood cells as they deform on travelling through small blood vessels. The group also explored the effect of metformin, a drug often prescribed to type 2 diabetic patients, on C-peptide. They found that, when they administered zinc-activated C-peptide with metformin, the type 2 diabetic red blood cells released ATP at levels comparable to healthy ones. Diabetic red blood cells are more rigid and so normally release less ATP than normal cells.

As metformin is positively charged at physiological pH, Spence suggests the metformin neutralises the phosphatidyl serine groups on the outer cell membrane, making it less negative and more able to interact with the C-peptide.

Claus Jacob, an expert in metalloproteins and drug design, from Saarland State University, Germany, says the findings 'provide a fine explanation of the modes of action of C-peptide and metformin towards these [red blood] cells. They also pave the way for the development of novel therapeutics in the field of type 2 diabetes.' *Elizabeth Davies*

Reference
J A Meyer *et al*, *Mol. BioSyst.*, 2009, DOI: 10.1039/b908241g

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Conducting cell scaffold could signal advances in regenerative medicine

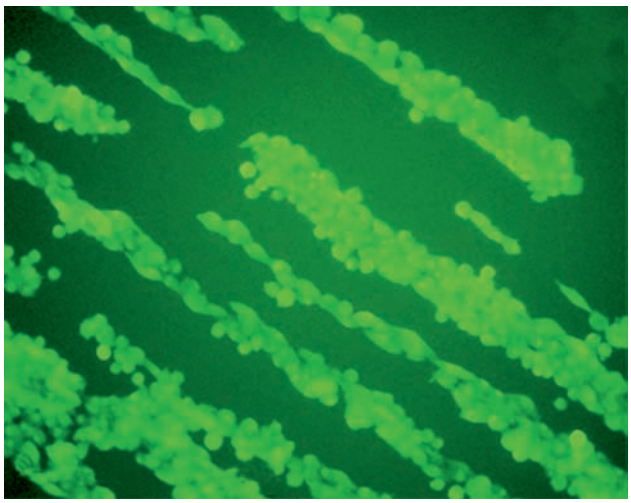
Jelly sparks innovation for tissue repair

A food additive is finding an alternative use in electrically-conducting hydrogels with potential in tissue engineering.

Marc in het Panhuis and Cameron Ferris at the University of Wollongong, Australia, used gellan gum, a common additive in yogurts, jellies and toothpaste, to prepare a scaffold that jellifies at body temperature. The researchers say that the gel's formation under mild and physiological conditions suggests medical applications. For example, cell-doped gels could be developed as injectable scaffolds to repair tissues non-invasively, such as heart or muscle.

The team investigated cell growth on their gellan gum gel. 'Because it's a hydrogel, we can mould it into any shape we like,' says in het Panhuis. To demonstrate this, the researchers used vinyl records as a template, spreading the gel in a thin film on the surface to create a subtly ridged pattern. When the team added cells to the gel, the cells adhered in valleys within the pattern, demonstrating that they could be prompted to grow in a desired arrangement.

The researchers also added highly conducting carbon nanotube fillers to their gellan gum gels and investigated how electrical signals propagated through the composites. The duo found that the nanotubes form an interconnected network within the hydrogel, which aids conductivity.



Cells grow readily on hydrogel surfaces moulded using vinyl records

Phillip Messersmith, an authority on biomaterials for tissue engineering at Northwestern University, Evanston, US, points out that whilst there are many examples of carbon nanotubes in hydrogels, 'the electrical conductivity measurement is a nice accomplishment.'

'Electrical stimulation of cells is one of the cues used by the human body,' says in het Panhuis, explaining his motivation for developing the conducting gels. 'It is used to trigger wound healing and many other biological functions.' However, the researchers avoided patterning cells on the gels containing carbon nanotubes due to the intense speculation surrounding their biocompatibility. 'Now that we've made the materials, a major challenge is to look at the electrical stimulation of cells using common materials other than carbon nanotubes,' says in het Panhuis.

Mark Bradley, an expert in biomaterials at the University of Edinburgh, UK, says that it would also be interesting for the researchers to look at other cell types. 'If you take stem cells, for example, and apply an electrical stimulus, they can be directed to differentiate in a specific direction,' he adds, suggesting that the study could have widespread implications in many other fields of biomaterials research.

Lois Alexander

Reference
C J Ferris and M in het Panhuis, *Soft Matter*, 2009, DOI: 10.1039/b909795c

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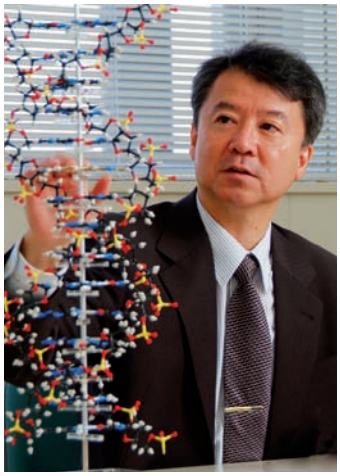
Interview

Genetic alphabets

Ichiro Hirao talks about nucleic acid research, expanding the genetic code and the possibility of creating new life. Kathleen Too asks the questions



Ichiri Hirao

Ichiro Hirao is a team leader at the RIKEN System and Structural Biology Center, Yokohama, Japan. He is interested in the creation of unnatural base pairs towards the expansion of the genetic code and re-engineering DNA/RNA materials.

What inspired you to become a scientist?

From a very young age, I have been fascinated by science. When I was in elementary school I devised my own experiments. At the age of 11, I attempted the electrolysis of water to make hydrogen and oxygen gas on my own.

What motivated you to study the chemistry of nucleic acids?

I used to attend a technical college combining high school and university and came to be interested in organic chemistry. When I was 19 years old, one of my professors gave me a book called *The Double Helix* by James D Watson. I was very impressed by it and at the time I really wanted to create artificial genetic compounds by employing synthetic chemistry. Since then, I have used synthetic chemistry and applied it to nucleic acids research. In the US, I worked with Professor Andrew Ellington in Indiana, where we focussed on nucleic acid aptamers to study evolution. We wanted to synthesise new compounds to incorporate into DNA, RNA and proteins. At the time, Dr Shigeyuki Yokoyama at RIKEN started a project in conjunction with the Japan Science and Technology Agency to expand the genetic code, and called me back to Japan to lead the project.

You are currently working on unnatural base pairs for the expansion of the genetic alphabet. Can you explain why this is important?

If we create new base pairs besides the A–T and G–C pairs, we can add new compounds into nucleic acids and proteins. All creatures have only 4 bases: A, T, C and G. I often ask: why is this the case and can I challenge it? Can new bases be added into a new creature? For that purpose I want to test the expanded genetic system in a test tube. So, we managed to create a new base pair, different from the usual A, T, C and G. In 2002, we reported our first new pair, by which a non-standard amino acid can be incorporated into a protein using a chemically synthesised gene containing the new pair.[1]

What is going to be the next biggest development in your field?

In 1989 Steven Benner reported the first novel unnatural bases.[2] Since then a lot of unnatural bases have been made. However, precise replication is often too difficult for these unnatural base pairs. My second aim was to make sure that the unnatural base pairs can replicate as this is the most important function.

After several years of struggle, we at last developed the other new pair and published this in 2006.[3] The results, thus far, were obtained in a test tube and the next aim is to discover if the unnatural base pair works in the cell. I have also founded a venture company, TagCyx Biotechnologies, for applying the unnatural base pair technology.

What is the most rewarding achievement in your career?

Sometimes we find new things by serendipity. I consider working with my colleagues very rewarding. Often ideas and new methods arise from different people in the group and from foolish ideas but precise experiments. By working together, we aim to achieve a common goal and I am ever so grateful to have my own research group.

What is the secret to running a successful research group?

We have to make sure that the correct control experiments are done and that all the data are reproducible. Obtaining reproducible and precise data is very important for the success and credibility of a research group. During the research process, we try not to miss very subtle things which could be of importance.

If you were not a scientist, what would you be?

I am a computer and board-game geek, so maybe I would be a game designer. I also like to play the classical guitar, so a guitarist would be another option.

Which scientists do you most admire and why?

I admire all the researchers that I have ever met and have known through literature. They are always inspiring me to come up with solutions.

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2 C Switzer, S E Moroney and S A Benner, *J. Am. Chem. Soc.*, 1989, **111**, 8322 (DOI: 10.1021/ja00203a067)

3 I Hirao *et al*, *Nat. Methods*, 2006, **3**, 729 (DOI: 10.1038/nmeth915)

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Instant insight

Untangling Alzheimer's

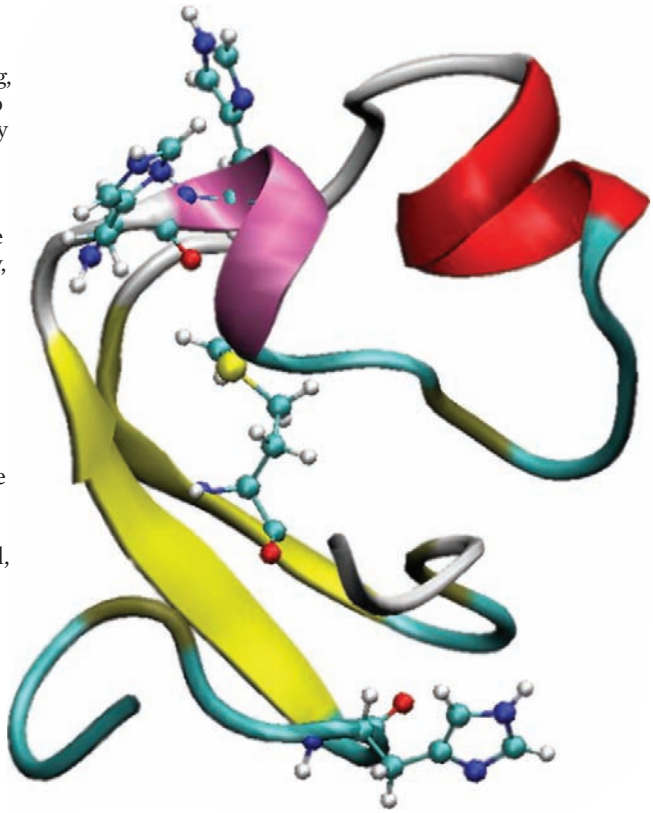
Cures for Alzheimer's may come from understanding its chemistry. Arvi Rauk of the University of Calgary, Canada, examines the disease at the molecular level

Alzheimer's disease is a devastating, fatal, neurological disorder with no known cause and no cure. Primarily a disease of old age, it has become a very serious problem as general life-expectancy has increased. The afflicted person suffers progressive loss of memory and thinking ability, mood swings, personality changes, and loss of independence.

Physically, Alzheimer's is characterised by massive loss of neurons and disrupted signalling between cells in the brain. The disease can be diagnosed post mortem by observing tangles inside and senile plaques outside cells throughout the brain. The major component of the plaques is a small, 40- or 42-amino acid peptide: amyloid beta (Aβ). That Aβ is a causative agent in Alzheimer's was first suggested as the amyloid hypothesis about 15 years ago and is now widely accepted. Uncovering the chemistry associated with Aβ is crucial to understanding Alzheimer's progression and may shed light on the cause or causes.

Aβ is an elusive entity whose chemical and biological actions have been difficult to fathom. It does not crystallise, is not very soluble, and has a highly changeable structure in solution. On incubation, it does form ordered fibrils that can be analysed by nuclear magnetic resonance analysis. Whilst the structure of the toxic species has not been established, the peptide is known to be at its most damaging in aggregates of two or more. Therefore the fibril structures can provide clues about the nature of the toxic aggregates.

Aβ binds strongly to copper(II) ions in the body through its three histidines and the resulting copper–Aβ complex is a moderately strong oxidising agent. It is readily reduced to the copper(I) form by vitamins C and E and other reducing agents, possibly including the peptide's single methionine group. In the reduced form, the copper–Aβ complex can generate destructive species such as hydrogen peroxide, hydroxyl radicals, and other reactive oxygen compounds. Since Aβ is generated from a transmembrane protein it – and its copper complexes – inherits an affinity for cell membranes from its parent. Therefore the copper(I)–Aβ complex may generate radicals near the highly unsaturated lipid bilayers that make up membranes in the brain, resulting in extensive membrane damage through lipid peroxidation. In addition, Aβ aggregates can form membrane-penetrating holes that allow ions to pass into and out of brain cells unregulated, including across the protective blood–brain barrier.



Amyloid beta peptide is widely accepted as a cause of Alzheimer's

In addition to copper and itself, Aβ binds to numerous other proteins, all with deleterious consequences. For instance, interaction with nervous system protein tau results in nerve cell collapse; binding to catalase causes the enzyme to lose its hydrogen peroxide clearing function; interaction with apolipoprotein E accelerates the aggregation of Aβ itself into toxic species. When Aβ interacts with insulin receptors in nerve cells it causes reversible memory loss and diabetes symptoms.

So, are there any drugs available that can prevent Alzheimer's? The answer is not yet, but luckily, the likelihood of contracting Alzheimer's can be reduced by some statins and non-steroidal anti-inflammatory drugs. Antioxidants such as those found in red wine may also be effective. Since Aβ is the culprit, some pharmaceutical companies are seeking to block the enzymes responsible for forming the peptide or to promote enzymes that can degrade Aβ into smaller harmless pieces. Others are seeking compounds that can prevent its aggregation process, or reverse it.

The past decade has seen significant advances in our understanding of Aβ neurotoxicity mechanisms and this has spawned a new generation of drug candidates that should lead to prevention of the disease. In my optimistic opinion, these approaches will meet with success sooner rather than later.

Read more in the critical review 'The chemistry of Alzheimer's disease' in Chemical Society Reviews.

Reference
A Rauk, *Chem. Soc. Rev.*, 2009, DOI: 10.1039/b807980n

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Essential elements

IUPAC 2009

The RSC hosted the 42nd IUPAC Congress at the SECC, Glasgow, UK, and enjoyed meeting over 2000 delegates from 72 countries and 64 chemical societies. The programme featured seven themes: Analysis & Detection, Chemistry for Health, Education & Communication, Industry & Innovation, Materials, and Synthesis & Mechanism. RSC journals sponsored a variety of sessions within the 50 symposia taking place. Speakers presented key research topics demonstrating the impact of the chemical sciences, and highlighting exciting innovations with an overall focus on 'Chemistry Solutions'.

Following the RSC's acquisition of ChemSpider, Graham McCann, Business Manager for ChemSpider, joined Antony Williams, ChemSpider Vice President of Strategic Development, on the ChemSpider stand to share future plans on what the collaboration will bring to scientists. The new website, demonstrated on the stand, gave delegates the opportunity to navigate around the website to see the new functionality it offers to users.

The RSC stand was also very well attended, and showcased hot new titles including the very latest news on *Analytical Methods* and *Nanoscale*, the new journals to be launched later this year, and *Polymer Chemistry*, a new journal for 2010.

This year's IUPAC conference also saw the successful launch of RSC's highly interactive social networking tool, MyRSC.

MyRSC allows chemical scientists to network with one another across the globe, share information about themselves and their research, receive details of career opportunities and join specialist groups. *Visit http://my.rsc.org for the very latest information on this exciting new development, and to find out details on how to join.*

Don't miss out on the next IUPAC Congress in Puerto Rico in 2011! (www.iupac2011.org)

Working together

What do a free online source of structure-based chemical information, Twitter and a roadmap have in common?

They are all ways in which the RSC is working with the global scientific community – and they all feature in Issue 2, 2009 of *Fusion*, RSC Publishing's newsletter, which has a distinct technology theme. We, as members of the community, have a vast range of new and emerging technologies at our disposal. We can alert you to an article immediately it is published online, and provide links to open online resources to help you enhance your knowledge.

You can share your experiences with other scientists via virtual discussion groups, and allow a global audience to view details of your work on videos.

There are many other ways in which technology has facilitated international networking and dissemination of the latest scientific advances. Gone are the days when a researcher waited for a print journal to arrive on the desk to see the latest developments, or relied on the occasional overseas trip to a scientific conference to catch up with like-minded researchers!

So can these new technologies help us to work together to overcome some of the global challenges that are facing scientists? We'd like to think so.

Find out more on our website: www.rsc.org/publishing/fusion

ChemSpider sensation

August marks a milestone in ChemSpider's 2009 calendar. Just two months after announcing RSC's new partnership, we unveiled to the world at the 42nd IUPAC Congress in Glasgow a refreshed looking ChemSpider, now hosted on powerful RSC servers.

The ChemSpider booth at the event was abuzz: delegates searched for chemicals they didn't expect ChemSpider to have...and found them! They deposited and curated data live. People who'd never heard of ChemSpider rushed to tell others. We heard comments like, 'This is the best thing I have seen all day' and 'Do you realise how much this will do for the world of chemistry?'

Delegates were impressed by the fast text and structure searching capabilities, the size and diversity of the database (including videos, reactions and blog posts). They were also complimentary about the new ChemSpider look and feel delivered through the logo, exhibition booth and literature, and excited about ChemSpider's vision for the future.

The ChemSpider team thanks everyone for their support.

Search, share and help refine the data at www.chemspider.com

ChemSpider
Building community for chemists

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